DEAR READER

The leading cause of death among people with HIV in the US is liver failure. When did this happen? Well, it's been this way for a few years now. Sometime just after opportunistic infection rates plummeted with the widespread use of potent antiretroviral therapy (1996–1997) and just before federal funding for HIV/AIDS began to wither (circa 2002), the AIDS community began to feel a sense of uneasiness. Treatment did not work for everyone; people fell through the cracks. Death rates may have fallen, but that did not mean an end to losing friends or colleagues. The funerals and memorials still happen, only less frequently for most of us. Liver failure, cardiovascular events, cancers, and other maladies show us that even avoiding "full-blown AIDS" does not necessarily guarantee escape from other perils, some of which are related to or even exacerbated by having HIV disease.

But what's causing liver disease to be the leading cause of death in people with HIV in the US and other developed nations? The answer is hepatitis co-infection, and mainly co-infection with hepatitis C. This blood-borne disease has only been widely recognized within the last 10 to 15 years, and the worldwide epidemic is staggering. The global estimate of almost 200 million hepatitis C infections far outnumbers the estimated cases of AIDS worldwide. But while AIDS untreated can progress fairly rapidly, especially in resource-poor areas where nutrition deficiencies and endemic diseases alone can shorten lifespan, hepatitis C may not cause fulminant disease and death until years after infection—in some cases as many as 20 years or longer.

As presented in this issue of RI*TA!*, much has been learned about the hepatitis C virus (HCV) and treatments have even been developed that can clear the infection in some individuals. Yes, remission—some even call it a cure—is possible with HCV, but HIV co-infection complicates matters and reduces an already less than ideal success rate. In addition, there are significant obstacles to HCV treatment access given the expense of treatment, and the current therapies carry with them substantial side effects and toxicities.

But perhaps most disturbing of all is what the hepatitis C epidemic in the US tells us about our society. Hepatitis C, like HIV/AIDS, carries with it a stigma and thrives in populations that are mostly unwanted, marginalized, or ignored by society at large. Homeless people, injection drug users, sexual minorities (including people with many sex partners), and yes, racial minorities, all have greater prevalence rates of HCV infection. In the journal *Clinical Infectious Diseases* (36, pp. 368-69, 2003), Camilla S. Graham wrote, "HCV antibody status may be serving as a marker for poorer access to care and competing problems with addiction that lead to delays in care or failure to implement the standard of care. . . . If we are to improve the health status of patients with HIV/HCV co-infection, perhaps we should focus on these issues as well as the presence of the 2 viruses."

As US government domestic funding for HIV/AIDS dwindles in the face of a steady epidemic (with its highest rates now in minority and underserved populations), I cannot help but wonder—is our society, in particular our political leadership, more at ease with denying basic care and support to people with HIV/AIDS who have less power and status than 10 or 20 years ago? Perhaps the same may be true for hepatitis C. Unabated rates of co-infection with both viruses may very well represent where our society has failed us.

Very truly yours,
The Center for AIDS:
Hope & Remembrance Project

Thomas Gegeny, MS, ELS
Senior Editor

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Co-infection with HIV and hepatitis C: An overview

By Jennifer Newcomb-Fernandez, PhD

This report provides an overview of hepatitis C infection and special issues regarding co-infection with HIV. However, it was not possible to cover all aspects of this topic in depth. For a thorough review, RITA! recommends referring to the recent Treatment Action Group report by Tracy Swan and Daniel Raymond, "Hepatitis C Virus (HCV) and HIV/HCV Coinfection: A Critical Review of Research and Treatment" available online at ***aidsinfonyc.org/tag/coinf/hcv2004****.*

EPIDEMIOLOGY OF HCV AND HIV/HCV CO-INFECTION

For many people infected with HIV, co-infection with hepatitis C virus (HCV) is a very real problem. These 2 viruses share many features, as both are blood-borne pathogens, share certain routes of transmission, are refractory to complete eradication by currently available treatments, and have extremely high replication rates. HCV is the most common blood-borne infection and is the leading cause of chronic liver disease in the US.[1] There are an estimated 170 million people worldwide infected with HCV, about 3% of the world's population.[2] (See Figure 1.) The NHANES III study (the third National Health and Nutrition Examination Survey conducted by the National Center for Health Statistics, Centers for Disease Control and Prevention), studied samples from 21,241 subjects for antibody to HCV (anti-HCV) and reported an overall prevalence of 1.8%, corresponding to an estimated 3.9 million US residents who have been infected with HCV (including some who clear the infection spontaneously).[1] In addition, 74% of this study population was positive for HCV RNA, suggesting that about 2.7 million people in the US are chronically infected with HCV (ie, those who do not spontaneously clear infection). In this large sampling, 65% of those positive for anti-HCV were between 30 to 49 years of age. HCV infection was more prevalent in male subjects and African-Americans. However, the estimate of 1.8% deduced in the NHANES III may be somewhat conservative as incarcerated and homeless people, 2 populations with high HCV prevalence rates, were not included. In prisons worldwide, HCV prevalence is reported to be anywhere from 31% to 50%. In the US, 30% to 40% of the 1.8 million inmates are infected with HCV.[3]

Figure 1. Hepatitis C infection worldwide: an estimated 170 to 200 million cases

World Health Organization (WHO) estimates, 1999.

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HCV is a small, enveloped RNA virus that is part of the *Flaviviridae* family. Humans are the only known hosts of HCV, but the virus can be transmitted experimentally in chimpanzees.[2] HCV is structurally unrelated to hepatitis A or hepatitis B and was initially referred to as "non-A, non-B hepatitis." Like HIV, HCV has significant genetic diversity.[4] There are 6 genotypes (genotypes 1 through 6) and about 100 subtypes (a, b, c, etc.). Genotypes 1 through 3 are found worldwide, genotypes 4 and 5 are found predominantly in Africa, and genotype 6 is found primarily in Asia.[2] Genotype 1 is the most prevalent genotype in the US.[1,4-6] Unfortunately, genotypes 1, 4, and 5 are not as sensitive to currently available HCV treatments and result in poorer response rates depending on genotype.

Of the approximately 800,000 people living with HIV/AIDS in the US,[7] an estimated 200,000 persons are co-infected with HCV.[8] Though different research cohorts report somewhat disparate rates of co-infection, the consensus is that approximately 25% to 30% of the HIV-positive population in the US is co-infected with HCV.[7,9,10] Nonetheless, the risk of acquiring HCV varies widely according to a patient's risk factors and thus depends on the makeup of the particular patient population. A 2002 study from the US Adult AIDS Clinical Trials Group estimated an overall co-infection rate of 16.1%, but this rate varied greatly according a patient's risk factors. For example, 72.7% of the "high-risk" subjects were HCV positive, while only 3.5% of the "low-risk" patients were positive.[6] Moreover, some believe that injection drug users, a group seriously at risk for contracting HCV, were underrepresented in this study and therefore the co-infection rate is much higher.[8] Indeed, the co-infection rate in Europe also appears to be closer to 30%, according to unpublished data from the EuroSIDA study.[8]

ROUTES OF HCV TRANSMISSION

HCV is transmitted through direct contact with blood from an infected person (see Figure 2). The sharing of injection equipment during injection drug use (IDU) is by far the most common way to contract HCV. Receipt of previously unscreened blood, blood products, or organs was a risk factor, but extensive screening and viral inactivation procedures in developed countries have minimized this risk in the past 2 decades. Other potential routes of transmission include sexual contact with an HCV positive partner, mother-to-infant transmission, exposure to contaminated needles or sharps (usually in healthcare settings), or use of inadequately sterilized instruments during medical or dental procedures.[2,11,12] In 9% of cases, the source of infection cannot be identified.[11] Many of these risk factors are escalated in developing countries (particularly exposure to infected blood or blood products, or contaminated needles or sharps) as screening procedures may not be in place or enforced. Other sources of transmission include scarification, tattooing, and ear and body piercing when equipment is not properly sterilized.[2] HCV is not transmitted through casual contact or through kissing, hugging, sneezing, coughing, or sharing food utensils or drinking glasses.[11]

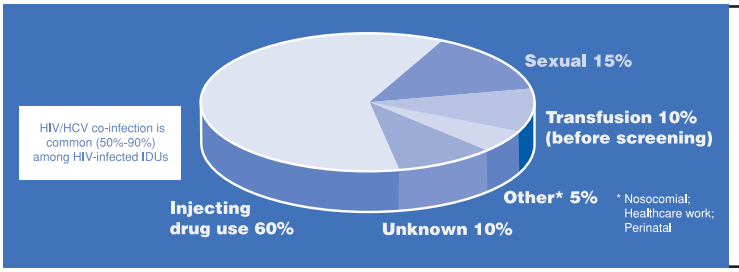

Figure 2. Sources of hepatitis C infection in the US

Sentinel counties data, Centers for Disease Control and Prevention (CDC)

Injection drug use

There is little doubt that IDU bears with it a significant risk of transmitting HCV. IDU is responsible for the largest proportion of HCV infections;[2,11] 20% to 40% of injection drug users will be infected within the first year of having used needles, increasing to over 50% for those with 1 to 5 years of use, and reaching up to 92% for those with greater than 5 years of use.[2] A recent study of 428 injection drug users in London reported an HCV incidence of 41.8%.[13] In US and European cities, 50% to 90% of persons who contracted HIV infection from IDU were already infected with HCV.[8] A history of intranasal cocaine use may also be a risk factor, but this has not been proven.[11]

Contaminated blood products

In the US, HCV transmission attributable to blood transfusion is very low, with a risk of 0.004% to 0.0004% per unit transferred. The risk can be significantly higher in developing countries where inconsistent screening policies may be in place or absent altogether.[2] Prior to 1990, the risk of transmission through blood transfusions was about 10%.[11] Unfortunately, before the introduction of virus-inactivating procedures in 1984, many hemophiliacs received contaminated clotting factor and were infected with HCV, in addition to HIV and hepatitis B.[14-16]

Mother-to-infant transmission

Mother-to-infant transmission (MTIT) of HCV does occur, but the risk is probably less than 5%.[2] Indeed, an extensive review of studies examining MTIT estimated that the rate of MTIT was between 1% and 5% in women who were positive for anti-HCV.[12] Factors that increase the rate of MTIT are maternal co-infection with HIV, maternal use of injection drugs, and higher maternal HCV RNA levels.[2,12] Regardless of these low percentages, MTIT transmission can still be a significant worldwide predicament. Yeung and colleagues[12] note that if 35% of the 170 million people infected worldwide are women of child-bearing age and have an annual fertility rate of 2%, 10,000 to 60,000 infants will be infected with HCV each year. Unlike with MTIT of HIV, specific procedures to reduce HCV transmission from mother to child have not been discovered. Rates of HCV transmission are similar regardless of mode of infant delivery (vaginal versus cesarean) and whether the infant is breast-fed.[2,12] Although no cases of HCV transmission via breast-feeding have been reported, HCV RNA has been detected in breast milk.[12] Obviously, bleeding nipples as a result of breast-feeding could increase the risk of HCV transmission to an infant.

Other potential risk factors

Transmission of HCV in healthcare settings via exposure to contaminated needles or sharps can occur, but is relatively rare with a rate of approximately 4% in healthcare workers frequently exposed to blood.[11] Documented cases show that HCV has been transmitted through medical procedures using contaminated equipment and unsafe injection practices (ie, re-use of disposable needles/syringes and contamination of multiple-dose medication vials). In developed countries, the risk of contracting HCV during surgery or dental procedures,[1] tattooing, acupuncture, or ear piercing is very low.[2,11] HCV can be transmitted percutaneously through shared use of razors or other objects that might be exposed to blood, but this risk is most likely limited.[2] In one study of HCV-positive hemophiliacs and their families, only one case out of 228 household contacts was detected.[14]

Sexual transmission of HCV

HCV transmission via sexual contact is not as efficient as HIV and hepatitis B.[14,16,17] Nevertheless, the actual risk of HCV transmission through sexual contact is a subject under great debate.[18] The high prevalence of HCV transmission among sex workers, men who have sex with men (MSM), persons with multiple sex partners, partners of HCV-infected persons, and patients who visit sexually transmitted disease clinics cannot be ignored and

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suggests that sexual transmission may occur.[18-20] Moreover, according to the US Centers for Disease Control and Prevention (CDC), approximately 18% of cases occur in persons with no other risk factors other than exposure to an infected sexual partner or exposure to multiple sex partners.[11] However, studies investigating female sexual partners of male hemophiliacs report HCV transmission rates of 2.6%[17] and 2.7%,[21] rates similar to the worldwide rate of 3%.[2] Other studies report no evidence of sexual transmission,[16] and the majority of HCV serodiscordant couples have unprotected sex without ever transmitting HCV.[22]

The consensus seems to be that there is a real risk of HCV transmission through sexual contact, but that this risk is low.[17,18,20,23-26] Further, HCV RNA has been detected in normal cervical smears from HCV-positive women[19] as well as in semen samples from HCV-positive men[24] and HIV/HCV co-infected men.[22] These HCV viral loads were detected in only some of the patients[19,22,24] and were low in semen samples,[24] thus possibly explaining why the risk of HCV transmission through sexual contact is low, but still present. Factors that might affect HCV transmission are the stage of a person's HCV disease, duration of infection, HCV viral load, HIV status, and period of exposure.[18]

EFFECT OF HIV ON HCV TRANSMISSION

Though the connection between sexual activity and HCV transmission is debatable, there is some evidence that co-infection with HIV may increase the likelihood of HCV transmission by acting as a "cofactor."[17,25,26] A correlation between HIV seropositivity and HCV transmission has been reported, whereby there was a significantly greater likelihood of HCV seropositivity in MSM who were HIV-positive, compared with men who were HIV-negative.[27] In addition, a study of female sexual partners of male hemophiliacs reported that the frequency of HCV transmission was 5 times higher when HIV was also transmitted.[17] However, other studies have failed to detect this relationship and have dismissed the idea that HIV could act as a cofactor in facilitating HCV transmission.[16,21] Nevertheless, pre-existing infection with other agents, such as hepatitis B, gonorrhea, anogenital herpes, and syphilis is associated with an increased risk of HCV transmission.[1,26,27] But these studies do not specify whether certain sexual behaviors or practices could have contributed to this increased risk of transmission.

Increased HIV RNA levels have also been linked to the presence of HCV RNA. In fact, for each unit increase in log HIV RNA level, the chances of having a positive HCV RNA test increased 86%.[6] Some researchers speculate that changes to the immune system, rather than the sexual transmission route, is responsible for this association sometimes detected between HIV and HCV transmission.[8,27] One hypothesis is that the immune suppression caused by HIV aids the transmission of HCV. For example, among subjects considered to be at high risk for transmitting HCV, 100% of those with CD4 T cell counts less than or equal to 100 cells/mm^3 were HCV positive, while only 68.6% of those with CD4 T cell counts greater than 100 cells/mm^3 were positive for HCV.[6] Other reports of unusually high HCV transmission rates in patients with hematologic malignancies and severe aplastic anemia (conditions associated with compromised immune systems), despite strict blood-screening procedures, provide further evidence that HCV transmission may be enhanced among immunosuppressed patients.[28] In support of an association, there is some preliminary evidence that HCV can replicate extrahepatically under conditions of immunodeficiency.[29]

CLINICAL ASPECTS OF HCV INFECTION

Diagnosis of HCV infection

According to the CDC website (***cdc.gov***), testing should be routinely offered to persons most likely to be infected with HCV. Abnormalities in levels of liver enzymes, specifically alanine transaminase (ALT), may suggest a diagnosis of HCV. Patients infected with HCV typically develop antibodies to HCV within 6 weeks to 6 months; however, some individuals will not generate antibodies until much later.[30] The third-generation enzyme immunoassay (EIA-3) is currently recommended as a first-line method for detecting HCV antibodies, but false-positive results can occur.[2,31] Therefore, all positive EIA results should be confirmed with an HCV RNA test, as chronic HCV is diagnosed by the presence of HCV RNA in serum. In addition, patients who test negative for HCV antibody, but who are at high risk for HCV infection, should also undergo testing to detect HCV RNA.[31] Persons at risk who test negative for HCV antibody and who have undetectable HCV RNA should be re-tested 6 months after initial testing, as this is the only way to confirm or rule out chronic HCV infection.

Diagnosis of HCV infection is similar in HIV-positive patients. However, immunosuppressed individuals (including organ transplant recipients and HIV-positive patients, especially those with CD4 T cell counts below 200 cells/mm^3) should also undergo HCV RNA testing as many fail to generate antibodies to HCV, and HIV infection itself can impair antibody responses to HCV.[8,30] In fact, some studies have reported that up to 6% of co-infected patients are actually anti-HCV negative.[8] Testing for HCV in HIV-positive patients is not routinely performed,[6] though current guidelines from the CDC suggest that HIV-positive individuals would benefit from testing. Also, the National Institutes of Health (NIH) *Consensus Statement on Management of Hepatitis C: 2002* (***consensus.nih.gov/cons/116/116cdc_intro.htm***) recommends that all persons with HIV be tested for HCV. The advantages are clear in HIV-positive patients with additional risk factors (ie, injection drug users and hemophiliacs); however, it is not clear if universal screening of low-risk, HIV-positive patients would be beneficial.[6]

Clinical course of HCV infection

Acute HCV infection is relatively mild and asymptomatic with only about 20% to 30% of individuals experiencing symptoms. Spontaneous recovery from HCV infection occurs in approximately 15% to 30% of HIV-negative people.[2,8] (In co-infected patients, the spontaneous clearance rate drops to only 5% to 10%, dropping even further in patients with lower CD4 T cell counts.[8,32]) Widespread hepatocyte involvement is a characteristic of chronic HCV infection,[33] and the major site of viral replication is the liver;[8] though HCV replication has also been reported in monocytes and lymphocytes.[8,19] Thus far, it is unknown if HCV replicates in organs other than the liver or in the central nervous system.[34] HCV RNA has been detected in semen from HCV-infected men[24] and HIV/HCV co-infected men,[22] as well as in normal cervical smears from HCV-infected women.[19] Moreover, preliminary evidence indicates that under conditions of immunodeficiency, HCV can replicate extrahepatically. Specifically, HCV was detected in peripheral blood mononuclear cells, and in the lymph nodes, pancreas, and adrenal glands of HIV/HCV co-infected patients.[29]

In individuals infected with HCV alone, infection can follow an indolent course for decades before causing liver cirrhosis, which can lead to hepatocellular carcinoma (HCC) and liver failure, but outcomes vary widely.[2] Conditions affecting systems outside the liver include cutaneous manifestations (sporadic porphyria cutanea tarda and lichen planus), ocular lesions (Mooren's ulcers), sialadenitis, and B-cell lymphoma.[2] Factors that influence the rate of progression to these more serious hepat-

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ic conditions are heavy alcohol use,[2,32,35,36] age,[2,35,37] duration of infection,[2] severity of liver histology at initial biopsy,[2] and possibly other factors such as HCV viral load and co-infection with hepatitis B or HIV (see page 13).[2] Studies assessing the pathogenesis of one HCV genotype versus another are conflicting.[5,37,38] One report demonstrated that HCV genotype 1b was associated with more advanced histologic deterioration in the liver compared with genotype 2,[38] while other studies have failed to detect a relationship between genotype and stage or severity of liver disease.[5,37] In fact, infections caused by all of the HCV genotypes can progress to HCC.[37] In addition, fatigue and depression are the most common symptoms of HCV infection.

Treatment of HCV Infection

According to the NIH *Consensus Statement on Management of Hepatitis C: 2002*, HCV treatment is recommended for patients with an increased risk of developing cirrhosis, specifically those patients with detectable HCV RNA levels higher than 50 IU/mL, a liver biopsy showing portal or bridging fibrosis, and at least moderate liver inflammation and necrosis. Other factors include HCV genotype, patient motivation, patient age, HCV symptoms, and the presence of comorbid illnesses. A liver biopsy is the most reliable way to assess liver damage and to determine the need for HCV treatment. Liver enzymes are regularly monitored, as many chronically infected patients have elevated ALT levels. However, these tests cannot be used to accurately assess disease stage or progression. For instance, 30% of HCV-infected patients have normal ALT levels and another 40% have ALT levels less than 2 times the upper limit of normal.

In the HCV-infected patient, treatment typically lasts for 24 or 48 weeks, depending on the HCV genotype. Patients infected with genotypes 2 or 3 usually require 24 weeks of treatment, while those infected with genotypes 1 or 4 require longer treatment (which may still not be effective).[2] At one time, the standard treatment for HCV-infected patients was interferon plus ribavirin. The development of a pegylated version of interferon (peginterferon) has made this formulation, combined with ribavirin, the new standard treatment for HCV infection.[39] The pegylated version has a longer half-life and allows for weekly dosing by injection, compared to standard interferon, which requires injections 3 times a week. The combination of peginterferon α-2b plus ribavirin produces a sustained viral response (SVR) rate in many patients, but is not as effective in patients with genotype 1 virus (see Table). In contrast, patients with genotype 2 or 3 respond well to this treatment.[39] While results tend to be disappointing in patients infected with genotype 1, the pegylated formulation has improved the SVR rate (42% versus 33% with standard interferon[39]).

Table. Sustained virologic response (SVR) rates from HCV treatment trials by HIV status and HCV genotype

Author	Population	Sample Size	% SVR, Overall	% SVR, Genotype 1	% SVR, Genotype 2 or 3
Manns et al.[39]	HCV	N=511	54%	42%	82%
Fried et al.[40]	HCV	N=453	58%	44%	70%*
Hadziyannis et al.[41]	HCV	N=424	61%	51%	80%
Torriani et al.[42]	HIV/HCV	N=289	40%	29%	62%
Chung et al.[43]	HIV/HCV	N=66	27%	15%	44%
Perrone et al.[44]	HIV/HCV	N=205	27%	15%	44%

Special thanks to Tracy Swan for assembling this table.

*This includes genotypes 4, 5, & 6.

Side effects from HCV treatment are frequent and sometimes severe. The most common side effect of ribavirin is anemia. Side effects common to peginterferon and standard interferon are injection site reactions, a flu-like syndrome (asthenia, fatigue, pyrexia, rigors, myalgia, and headache), arthralgia, chest pain, nausea, vomiting, diarrhea, anorexia, neutropenia, lymphopenia, thrombocytopenia, infection, alopecia, thyroid dysfunction, dizziness, and insomnia.[39,45] In addition to the above side effects, standard interferon and peginterferon treatment can cause psychiatric side effects including irritability, relapse of drug use, drug overdose, depression, suicidal ideation, and suicide. Considering the severity of these side effects, a psychiatric evaluation may be warranted before commencing treatment. The adverse event profile is similar for standard interferon and peginterferon, though comparison studies have reported that patients receiving peginterferon experienced injection site reactions, flu-like syndrome, neutropenia, and thrombocytopenia more frequently than standard interferon.[39,42,46] Despite the side effect profiles of these medications, many patients have been able to successfully complete therapy and achieve improved clinical status.

In most instances, the benefits of HCV treatment counterbalance the risks. However, patients and their physicians must weigh the likelihood and severity of adverse events from HCV medications with the likelihood of a response to these medications and the risk of progression of liver disease. Several studies suggest that patients (both mono- and co-infected) who do not experience a significant decrease in HCV RNA (early viral response or EVR) within 12 or 24 weeks of starting treatment will probably not achieve viral clearance after the course of treatment and may want to discontinue treatment if they have minimal or no fibrosis.[39,42,47] The absence of an EVR at week 12 strongly predicts that treatment will not be successful and may be stopped. However, patients, especially those with more serious liver fibrosis, may still benefit from HCV treatment even if they do not achieve an SVR. In fact, responses have been detected histologically in patients who do not achieve a viral response, indicating that HCV maintenance strategies may be beneficial as a way to slow the progression of fibrosis, particularly in co-infected patients with moderate to advanced fibrosis.[47]

Obviously, more effective treatments are necessary for both HCV-infection and HIV/HCV co-infection. Peginterferon plus ribavirin produces sustained HCV responses in a number of HIV/HCV co-infected patients, but many are still not responding to this therapy, particularly those infected with HCV genotypes other than 2 and 3 (see Table). Potential new treatments are being developed and are discussed in detail in this issue of RI*TA!* (see page 21).

SPECIAL CONSIDERATIONS FOR TREATING HIV/HCV CO-INFECTION

In both mono- and co-infected patients, the major treatment objective has been the prevention of cirrhosis, end-stage liver disease, and HCC. For HIV/HCV co-infected patients, HCV treatment is generally considered in patients with stable HIV viral load and CD4 T cell counts over 500 cells/mm^3 because the efficacy of HCV treatment is questionable in immunosuppressed patients with higher HIV viral loads.[48] However, successful treatment has been achieved in patients with lower CD4 T cell counts,[49] though clinicians must take into consideration the increased risk of end-stage liver disease in patients with decreasing CD4 T cell counts. The medical management of patients co-infected with HIV and HCV is extremely challenging for various reasons, most notably the complexity of both infections, the potential for drug interactions, and a lack of published information regarding how best to treat this patient population. Currently, there are no FDA-approved medications for this specific indication, although Roche Pharmaceuticals is currently seeking approval of their product for an indication in co-infected patients.

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Unfortunately, studies to determine the tolerability and efficacy of HCV treatments in HIV-positive people have lagged behind those conducted in people with HCV alone. The strategy thus far has been to take treatments that work in HCV-infected patients and apply these to HIV/HCV co-infected patients. Regardless of treatment options, co-infected patients must be advised on ways to prevent or to minimize liver damage and HCV transmission, and to abstain from drinking alcohol. In addition, these patients should be evaluated for chronic liver disease, as well as tested for and vaccinated against hepatitis A (to avoid fulminant liver failure and death) and hepatitis B (which can increase the severity of HCV).[8,11] However, these vaccines can be less immunogenic in persons infected with HIV (especially in patients with CD4 T cell counts less than 200 cells/mm^3) and therefore may not protect the patient against these viruses. Measuring response to these vaccines may be necessary.

Several randomized studies have recently investigated the activity of peginterferon α-2a[42,47] and peginterferon α-2b[46] combined with ribavirin in co-infected patients, the majority of whom were taking antiretroviral medications (also see Table). HCV treatment with these drug combinations was associated with higher rates of SVR compared with standard interferon, but rates were still lower than those observed in HCV-infected patients and ranged from 27% to 44%. SVR rates varied depending on the specific study but were generally worse for patients infected with HCV genotype 1, with rates ranging from 14% to 38% (although the 38% rate was for a group that also included patients with genotype 4[46]), compared to 53% to 73% for patients co-infected with other genotypes. Of note, HCV treatment did not have a negative effect on HIV disease progression, as shown by unchanged[46,47] or even reduced HIV RNA levels in patients who had detectable HIV viral loads at baseline.[42] However, interferon can produce transient decreases in CD4 T cell counts, which usually return to baseline values after completion of treatment. Possible reasons for variability in SVR rates include differences in study design, patient population, and ribavirin dose, as well as administration of 2 different types of peginterferon (peginterferon α-2a versus peginterferon α-2b). Differences in patient population in terms of severity of liver damage could further explain the variability in results. For example, the level of fibrosis did affect SVR, as patients with more advanced fibrosis did not experience SVR as frequently.[46]

Co-infected patients typically experience similar side effects to HCV treatment as do patients infected with HCV alone.[42,46,47] In addition, a recent report suggests that peginterferon α-2b can also cause ophthalmic problems in HIV/HCV co-infected patients and recommends increased monitoring of patients being treated with this drug.[50] Thirty-five percent of the study patients developed ophthalmic adverse events that included cotton wool spots, cataracts, and decreased color vision. Also, HCV and HIV medications share several common side effects (eg, diarrhea, nausea, vomiting, various cytopenias, etc.). Clinicians need to be aware of the potential for additive side effects and toxicities and that patients may require supportive care agents, such as growth factors, anti-emetics, anti-diarrheal agents, etc.

Of note, drug interactions can occur between HCV medications and antiretrovirals used to treat HIV. In particular, ribavirin may interact with nucleoside reverse transcriptase inhibitors as it is a guanosine nucleoside analog. When ribavirin is combined with antiretrovirals (specifically nucleoside reverse transcriptase inhibitors) to treat HIV, mitochondrial toxicity can be a complication. In fact, one case report documents 2 HIV/HCV co-infected patients receiving concurrent HCV treatment and antiretroviral treatment who experienced mitochondrial toxicity, multi-organ dysfunction, and lactic academia.[51] In addition, ribavirin can be antago-

nistic to the antiretroviral activity of stavudine (Zerit, d4T) and zidovudine (Retrovir, AZT). The combination of didanosine (Videx, ddI) and ribavirin can also lead to pancreatitis and lactic acidosis and is therefore not recommended. Additionally, because zidovudine can also cause anemia, this agent should not be taken concomitantly with ribavirin. Finally, because all antiretrovirals are potentially hepatotoxic, liver enzymes must be carefully monitored regularly when patients are also taking ribavirin.

CHALLENGES TO TREATING CO-INFECTED PATIENTS

Poor responses to HCV treatment in co-infected patients

Why do HCV treatments work less effectively in co-infected patients as compared with patients infected with HCV alone? Researchers speculate that the higher levels of HCV RNA detected in co-infected patients[6,31,52,53] may be responsible, as could an altered immune system that may prevent co-infected patients from clearing HCV. In general, an HCV viral load less than 2 million copies is considered a favorable prognostic factor. Soriano and colleagues[54] hypothesize that HIV infection may alter HCV viral kinetics, particularly under drug pressure. Furthermore, post-treatment relapses (where HCV again becomes detectable) occur almost twice as often in co-infected patients as they do in HCV mono-infected patients within 6 months of discontinuing treatment.[54] As far as which patients relapse, there seems to be no significant difference in terms of HCV treatment (standard interferon versus peginterferon), HCV genotype, CD4 T cell count, use of antiretroviral therapy, HIV viral load, or any other baseline characteristic.

Several reports examining HCV treatment in co-infected patients have speculated on ways to improve the response rate. One idea is to alter the doses of HCV medications, particularly ribavirin, by either increasing the dose in a step-wise manner or administering "dose-optimized" (weight-based) ribavirin.[47] Anemia is a common side effect of ribavirin and can be treatment limiting. This can be managed by concomitant use of epoetin (Epogen), a ribavirin dose reduction, or both. Extending the treatment period beyond 48 weeks is another strategy that may improve response to therapy.[54] Some patients have experienced success with this approach (see page 28 in this issue of RI*TA!*). Though patients with HCV genotype 2 or 3 are typically treated for only 24 weeks, researchers recommend the full 48 weeks of treatment for HIV/HCV co-infected patients, even those infected with these HCV genotypes.[42] Liver transplantation is a potential treatment for co-infected patients with advanced cirrhosis, but this is still considered investigational (see page 17 in this issue of RI*TA!*).

Other issues

An important question is whether HIV and HCV affect each other's disease progression. Despite a great deal of study in this area, no concrete answers to this question have been found. Evidence suggests that HIV alters the natural history of HCV and negatively affects HCV disease progression, though it is not clear if liver damage is a result of HIV co-infection or drug-related toxicity. As discussed above, standard HCV treatments are not as effective in the HIV/HCV co-infected population.[42,46,47] Moreover, the presence of HIV results in increased HCV persistence and HCV RNA levels.[6,31,52,53] In addition, by comparing HCV-positive patients who were seropositive for HIV with those who were seronegative, investigations have demonstrated that co-infected patients experience accelerated progression to cirrhosis,[36,55] and liver failure.[15] Others have specifically reported that HIV co-infection accelerates HCV-related liver fibrosis progression.[35] Though HCV disease progression is accelerated in co-infected patients, cirrhosis still takes many years to develop. In fact, one study reported that the median duration from HCV infection to cirrhosis was 26 years in co-infected patients, compared with 38 years in HCV mono-

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infected patients.[35] Regardless of this prolonged time frame, co-infected individuals have a higher rate of mortality from liver-related disease.[56] In fact, liver failure is the leading cause of death in the HIV-infected population in the US.

Evidence supporting a negative effect of HCV on HIV disease progression is not as strong as that for the inverse relationship. However, several studies have reported evidence that HCV negatively affects the course of HIV infection. Accelerated clinical progression has been observed in HIV/HCV co-infected patients compared with HIV-positive, HCV-negative patients, implicating HCV as a prognostic factor for disease progression in these patients.[57] Moreover, one study reported that HCV appeared to accelerate HIV infection, as co-infected patients were 3 times as likely to experience a new AIDS-defining event or death.[58] These findings are in agreement with another study by Anderson and colleagues, which demonstrated that HIV/HCV co-infected patients have a decreased survival time from the point of HIV or AIDS diagnosis.[9] Although, other life factors associated with poorer outcomes (homelessness, disparities in health care, drug inadherence, etc.) must also be considered in populations with a high prevalence of HCV. In addition, a recent investigation found that HIV/HCV co-infected patients tend to perform worse cognitively and are more likely to be diagnosed with HIV-associated dementia, findings that could not be explained by the presence of liver disease.[34] Nonetheless, other studies report no effect of HCV on HIV disease progression.[59-62] Specifically, these studies found that HCV did not influence progression to AIDS[59,61,62] or survival time.[60-62]

One possible explanation for these disparate results focuses on the time in which these studies were conducted, specifically before or after the introduction of highly active antiretroviral therapy (HAART). The widespread availability of HAART has changed the landscape of HIV disease, and while it has obviously benefited HIV-positive patients, the increased survival afforded by HAART has also allowed certain conditions to progress, such as liver disease, in those patients co-infected with HCV. For example, an earlier pre-HAART study performed by the same group as Anderson and colleagues[9] failed to detect any effect of HCV on HIV disease progression.[61] Moreover, many of the studies that reported no evidence of HCV's effect on HIV were conducted in the early to mid 1990s, most likely before HAART was available,[59,60] though some patients did receive HAART in another study.[62] Indeed, a recent study comparing the effect of HCV infection on HIV disease progression before and after the introduction of HAART reported no association between co-infection and disease progression before HAART. But this study did find that co-infected patients progressed faster than HIV-positive, HCV-negative patients in the HAART era.[63] One point that must be emphasized is that the makeup of pre- and post-HAART populations is not identical, and thus there may be other factors influencing these observations. For example, the shifting demographics of the HIV epidemic may have led to differing study populations, making comparisons more difficult.

At this time, no direct interactions between HIV and HCV have been identified that would explain the potential effect of each virus on the other. In terms of HIV's effect on HCV, some authors speculate that an impaired or altered immune response could help explain the negative effect HIV has on HCV disease progression.[4] Several studies have reported that the level of immunosuppression may influence HCV viral load[52,55] and liver fibrosis rate.[35] Of note, the effect of HIV on HCV is consistent with another scenario describing HCV-positive patients who were immunocompromised because of a condition called hypogammaglobulinemia. In these patients, HCV-related liver disease was severe and progressed rapidly.[64]

Though the influence of HCV on HIV disease progression is still somewhat murky, several studies have provided evidence that co-infection with HCV could at least complicate the management HIV disease. One hypothesis is that HCV blunts the immune system's T-cell response to antiretroviral medications,[58] but others have shown no evidence of this phenomenon.[9,62] Notably, because of altered liver function caused by HCV infection, successful use of antiretroviral medications may be limited because hepatotoxicity is such an obvious concern.[6,35] However, it is unclear whether chronic HCV infection affects the tolerability of and response to antiretroviral medications. Clinicians who are reluctant to prescribe HIV medications should reconsider because patients can be successfully managed with careful selection of antiretrovirals and regular monitoring of liver enzyme levels. In one study, hepatotoxicity was more prevalent in co-infected patients compared with patients positive for HIV only, though the majority of these co-infected patients tolerated the medications and no irreversible outcomes were observed among those patients experiencing severe toxicity.[65] These findings led the authors to conclude that antiretroviral therapy should not be withheld in co-infected patients because of concerns of hepatotoxicity, even in the presence of mild-to-moderate hepatic ALT elevations—as long as the patients are carefully monitored.

CONCLUSION

The greatest challenge to treating HIV/HCV co-infected patients is that there are few published studies on how best to treat such patients. Specifically, in the US there are no formal treatment guidelines available for treating co-infected patients. This lack of guidance is further complicated because co-infected individuals are frequently excluded from clinical trials that examine potential treatments. In addition, those populations with the highest prevalence of co-infection are also often excluded (eg, drug/alcohol users and incarcerated individuals). Part of the challenge exists because of the current patient care infrastructure, as many patients do not have access to healthcare (see page 17 for a complete discussion on policy issues affecting individuals with HIV and HCV). Liver disease is obviously a leading cause of morbidity and mortality in co-infected individuals—and the leading cause of death among HIV-infected individuals in the US—but physicians that specialize in infectious disease, including many HIV specialists, are not always familiar with hepatic disease. Moreover, hepatologists and gastroenterologists may not be familiar with treating HIV. This situation leaves the patient without a consistent healthcare provider who can simultaneously monitor, assess, and treat both illnesses. Programs that focus on HCV screening and prevention are impeded by a lack of funding, and injection drug users (a group most at risk for contracting HCV) are confronted with enormous hurdles when and if they attempt to receive care. Obviously, both diseases are responsible for significant mortality and morbidity in the US and worldwide. Though great strides have been made in treatment of HIV and HCV as separate diseases, much is still required to effectively treat those patients facing co-infection with both diseases.

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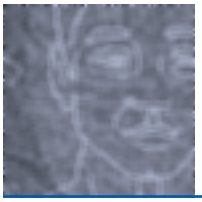

Current challenges in hepatitis C

By Tracy Swan

Hepatitis C is a global health problem. Worldwide, approximately 170 million people have been infected with the hepatitis C virus (HCV). In the US, at least 4 million people have been infected with hepatitis C, and an estimated 250,000 are HIV/HCV co-infected. Despite a growing appreciation of the severity of the hepatitis C epidemic, gaps in hepatitis C research and policy span the continuum from prevention to liver transplantation.

Prevention: Policy and research needs

Initiatives to raise awareness of hepatitis C; prevent new infections; offer potentially life-saving hepatitis A and B vaccinations; and diagnose, monitor, and treat people with hepatitis C have been hampered by inadequate funding. Surveillance of acute hepatitis C infections is conducted nationally, but because only 20% of acutely infected persons are symptomatic, most new infections go undiagnosed. In terms of chronic hepatitis C disease, surveillance is conducted only through a pilot program in which physicians report to sentinel sites. Comprehensive data collected from a national surveillance system is needed to advocate for sufficient funding to prevent, diagnose, and treat hepatitis C.

Effective disease prevention combines information about transmission with access to prevention tools and services. People must know how HCV is transmitted and how to reduce their risk of infection. Even though the majority of new hepatitis C infections in the US are acquired through injection drug use (IDU), hepatitis C is also more prevalent among men who have sex with men (MSM), partners of HIV/HCV co-infected persons, sex workers, people who have had multiple sex partners, and non-injection drug users than among the general population. However, the routes of transmission in such cases and the risks of specific sexual acts have not been adequately clarified.

Given that the major route of HCV transmission is via IDU, hepatitis C will continue to spread until injection equipment is widely available through pharmacy sale and syringe exchange programs. We must end the ban on federal funding of syringe exchange programs. These programs are a valuable resource to communities of injection drug users and typically function as an entry point into a range of services and healthcare.

Access to care and treatment

Both hepatitis C and HIV are disproportionately prevalent among African-Americans, people living in poverty, and incarcerated persons—groups who have had little or no access to healthcare. The number of uninsured people in the US has grown to more than 43 million, while inadequate federal funding has left states scrambling to contain the costs of AIDS Drug Assistance Programs (ADAPs) and Medicaid by limiting eligibility. The current scenario is grim for co-infected ADAP beneficiaries seeking hepatitis C treatment because most states cannot afford to add costly hepatitis C treatments to ADAP formularies. It is not clear how the new Medicare prescription drug benefit will affect access to hepatitis C treatment when introduced in 2006.

In the US, more than 2 million people are incarcerated. Hepatitis C is endemic in correctional facilities; estimates of hepatitis C prevalence among inmates range from 255,000 to more than 500,000. To complicate matters, hepatitis C treatment policies differ in each state. Duration of residency

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requirements are often used by correctional facilities as a method for withholding hepatitis C treatment from prisoners, regardless of the urgency of their need. Making treatment accessible to prisoners entails more than just providing the drugs. Peer support and education about hepatitis C, side effects of therapy, and access to mental health care must be provided as well.

Addressing needs of current and former drug users

Despite an HCV prevalence rate of 50% to 90%, injection drug users face enormous barriers to care and treatment. Until 2002, active injection drug use was a contraindication for treating hepatitis C. Many clinicians still withhold treatment from injection drug users instead of making a case-by-case decision with each patient, as recommended by the National Institutes of Health *Consensus Statement on Management of Hepatitis C: 2002*.

If we are to treat hepatitis C successfully, the medical and mental health care needs of current and former drug users must be prioritized. Many clinicians do not receive any training on working with patients with drug and/or alcohol dependency. Providers who have received additional education report feeling more confident about their capacity to care for people who are dependent on drugs and/or alcohol.

Harm reduction must be integrated into medical care. Clinicians must provide active drug users with options to reduce the risk of becoming re-infected with hepatitis C, acquiring HIV, and being exposed to other blood-borne pathogens. Options to mitigate consequences of drug use include demonstration of safer injection techniques, prescription of syringes, referral upon request to drug treatment or methadone maintenance programs, and prescription of buprenorphine (a treatment for opiate and cocaine addiction).

Treatment guidelines and provider education

In the US, there are separate treatment guidelines for HIV and hepatitis C. These resources have not been integrated into guidelines specifically for treatment of hepatitis C in persons co-infected with HIV. In turn, there are no guidelines for selecting and monitoring HIV treatment in persons with hepatitis C co-infection, despite their increased risk for antiretroviral-induced hepatotoxicity and metabolic abnormalities. Care and treatment guidelines for HIV/HCV co-infection would be an essential resource for both clinicians and patients.

In the absence of treatment guidelines, the need for provider and patient education is even greater. Primary care providers are not always sufficiently knowledgeable about hepatitis C. Also, HIV/HCV co-infected people do not always receive care from a specialist in liver disease. Some people are left to coordinate their own care between different providers. Peer programming and support groups are an enormous resource for people who are considering treatment or treating hepatitis C, especially because our healthcare system is hobbled by managed care and poorly equipped to provide the multidisciplinary care and support required for a disease as complex as hepatitis C.

Managing side effects of hepatitis C treatment

Hepatitis C treatment may induce many side effects, most commonly fatigue, flu-like symptoms, neuropsychiatric symptoms, and hematologic abnormalities (anemia, neutropenia, and thrombocytopenia). In rare instances, interferon can result in severe depression, suicidal ideation, or suicide. Side effects may be more severe for HIV/HCV co-infected persons, who also may experience interactions between HCV and HIV treatments. A sustained virologic response to hepatitis C treatment is more likely among people who are able to adhere to at least 80% of their full doses of ribavirin and

pegylated interferon for at least 80% of the entire duration of therapy. Adherence must be supported by informing patients about all possible side effects of therapy and strategies for their management. Although depression is a common side effect of interferon, we have much to learn about the causal mechanism(s) and management of interferon-induced depression. Pre-emptive treatment of depression is often used clinically, but has not been evaluated in a randomized clinical trial.

Research gaps: Optimizing hepatitis C treatment

Large hepatitis C treatment trials have historically under-enrolled African-Americans and excluded active drug users and those with psychiatric disorders. As these trials do not reflect the demographics of the hepatitis C epidemic, the safety and efficacy data from these trials may not be applicable to members of high-prevalence populations. Hepatitis C therapy has also not been adequately studied in children and the elderly.

More research is needed to improve hepatitis C treatment outcomes for people with HCV genotype 1 and a high viral load, African-Americans, non-responders to previous HCV treatment, and people who are co-infected with HIV. Because hepatitis C treatment is less effective for HIV-positive people, several strategies to increase sustained virologic response rates merit investigation:

- Extending the duration of treatment in co-infected persons with genotype 1 and a high (hepatitis C) viral load from 48 weeks to 72 weeks, while determining which patients are most likely to benefit from this intervention.
- Using weight-based dosing of ribavirin to increase sustained virologic response rates instead of the standard 800 mg/day (because of concerns about anemia). This approach should be accompanied by vigilant monitoring for anemia and swift treatment if it develops.
- Establishing the optimal duration of hepatitis C treatment for co-infected people with genotypes 2 and 3 in a randomized controlled trial by comparing treatment outcomes after 24 and 48 weeks of treatment. High relapse rates were reported in co-infected people with genotype 3 in on trial, but may have been a result of sub-optimal dosing of pegylated interferon, rib avirin, or both.
- Developing strategies to optimize hepatitis C treatment for those with the most urgent need: people with CD4 T cell counts less than 200 cell/mm^3 and those with advanced liver disease.

Also, the long-term durability and clinical benefit of a sustained virologic response to pegylated interferon-based therapy should be evaluated in cohorts of people receiving HCV treatment, including those co-infected with HIV. Histologic and clinical benefits of HCV treatment for relapsers and non-responders should also be characterized. This is of particular importance to co-infected people, who may be taking hepatotoxic drugs. An improvement in liver histology may increase the capacity to tolerate antiretroviral agents, prophylactic drugs, medications used to treat other co-morbid conditions, and complications of antiretroviral therapy.

Expediting research of novel HCV therapies in HIV-positive people

Co-infected people are in dire need of more effective and tolerable treatments for hepatitis C. Several new anti-HCV drugs are in early-phase development (see article on page 21 in this issue of RI*TA!*). Traditionally, safety and efficacy studies of hepatitis C treatment in co-infected people have been initiated years after mono-infection treatment trials. Given the urgent need in this population, this delay is not acceptable. Sponsors of new HCV therapies should allow co-infected people to participate as soon as a safe and effective dose has been determined.

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Pharmacokinetic evaluation of antiretroviral agents in co-infected people

Pharmacokinetic evaluation of antiretroviral drugs in co-infected people is not required, despite the increased risk for hepatotoxicity in this population. Hence, we know little about the drug levels of antiretrovirals in this population. This is crucial information because the liver metabolizes most antiretroviral drugs. People may be experiencing increased liver toxicity, drug interactions, or other side effects because they are receiving too high a dose of a given drug.

Expanding access to and availability of liver transplantation

Hepatitis C is the leading indication for liver transplantation in the US. In 2003, 16,925 people were waitlisted for a liver transplantation. Only 5,327 were transplanted and 2,371 died while waiting. If there was a sufficient supply of organs, the mortality rate among those awaiting transplantation could be drastically decreased.

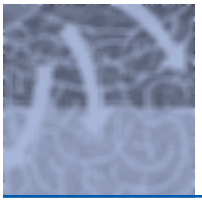
Transplant candidates have been evaluated with the Model for End-Stage Liver Disease (MELD) system since February 2002. MELD prioritizes people with the most urgent need for transplantation within a 3-month period. MELD is intended to decrease waitlist deaths, but the chronic shortage of donor organs may mean that only candidates with high MELD scores—who may be less likely to survive transplantation—will receive a transplant. Obviously, the donor pool must be increased to meet the need. One possible solution is to consider an opt-out system, in which organ donation is presumed unless otherwise stipulated by the individual.

As highly active antiretroviral therapy has dramatically increased the HIV-related survival of co-infected people, the incidence of hepatitis C-related end-stage liver disease is increasing, and with it, the need for liver transplants. Co-infected people face barriers to liver transplantation beyond the organ shortage. The United Network for Organ Sharing does not regard HIV infection as a contraindication, but the decision of whether or not to perform transplantation in HIV-positive candidates rests with individual centers. Not all are willing to perform transplants in people with HIV. Despite a handful of HAART-era reports on post-transplantation outcomes roughly equivalent to HIV-negative transplant recipients, insurers have withheld reimbursement for transplantation in HIV-positive candidates. They claim that expanding the indication for transplantation to HIV-positive people changes an established procedure into an experimental, and therefore non-reimbursable, procedure.

The National Institutes of Health is funding a multi-center study on the safety and efficacy of kidney and liver transplantation in HIV-positive people. This research, and observational data on transplantation in HIV-positive people, will clarify risks of transplantation and identify clinical strategies to improve quality of life and extend survival of co-infected transplant recipients. Hopefully, this will dispel the reluctance to provide reimbursement for a life-saving procedure.

The need for hepatitis C education, prevention, and broadened access to care and treatment is vast, as is the need for coordinated publicly and privately funded research. Hepatitis C advocacy must chart its own course, but it can draw from the experiences and successes of HIV activism.

Tracy Swan is the Coinfection Project Director with Treatment Action Group (TAG) in New York. She recently co-authored the TAG report "Hepatitis C Virus (HCV) and HIV/HCV Coinfection: A Critical Review of Research and Treatment" with Daniel Raymond. This publication is available online at ***aidsinfonyc.org/tag/coinf/hcv2004****.*



The hepatitis C drug development pipeline

By Daniel Raymond

Current hepatitis C treatment has many drawbacks, including significant side effects, high cost, and the need for injections of pegylated interferon. While the major clinical trials of pegylated interferon and ribavirin show about a 50% success rate in clearing the virus—deemed a sustained virologic response (SVR)—in real-life clinical settings, SVR rates are frequently lower. Moreover, treatment outcomes are poorer for African-Americans and for people with genotype 1, high viral loads, and/or HIV co-infection. Because of toxicities, including psychiatric side effects, treatment is often contraindicated for many people with hepatitis C. As a result, many people avoid or delay hepatitis C treatment, and only a relatively small proportion of people with hepatitis C—perhaps 10%—have been treated to date, with many failing to achieve an SVR. Thus, there is an urgent need for new, more effective, and better-tolerated treatments.

The hepatitis C virus (HCV) offers a number of potential targets for drug development. HCV undergoes a relatively simple replication cycle: cell entry; translation and cleavage of viral proteins; replication of viral RNA; and assembly and release of new viruses. Each of these stages in the replication cycle are, in theory, susceptible to inhibition by new drugs, though some aspects of replication—particularly cell entry and assembly and release—are still not well understood. In addition, novel treatments could stimulate more effective immune responses targeting HCV and facilitating viral clearance. Finally, in lieu of eradicating HCV, new drugs could benefit people who do not respond to current therapy by slowing or ameliorating liver damage.

Most current approaches to HCV drug development focus on one of 2 strategies: targeting the hepatitis C virus itself, or improving on current modes of treatment. Pegylated interferon and ribavirin therapy has both antiviral and immunomodulatory effects, but neither drug was developed specifically as an anti-HCV therapy (unlike, for instance, HIV protease inhibitors, which directly target the HIV protease enzyme). Primary viral targets for HCV include 2 enzymes: the NS3 serine protease and the NS5B RNA-dependent RNA polymerase (RdRp; "NS" refers to "non-structural protein"). Drugs targeting these enzymes are still in relatively early stages of development. Strategies aimed at improving current treatment include the addition of a third (non-HCV-specific) drug to pegylated interferon and ribavirin to boost their effectiveness, or alternative forms of interferon and ribavirin intended to show greater efficacy and/or less toxicity. Many of the drugs focused on these approaches are in later stages of development, and clinical trials of these agents often focus on non-responders to current interferon-based therapy.

HCV protease and polymerase inhibitors offer the most promise for radically transforming the nature and success of hepatitis C treatment. However, as with HIV, these agents will inevitably face the challenge of drug resistance, and they will only be successful when used in combination. Ideally, a combination of HCV protease and polymerase inhibitors could eventually replace interferon and ribavirin, improving SVR rates while reducing side effects and shortening the duration of treatment. In turn, such a paradigm shift would likely result in a dramatic increase in the number of people with hepati-

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tis C seeking treatment and expand the pool of HCV-treating physicians beyond a relatively small number of liver specialists.

However, these developments are still several years off and would not occur until the next decade. In the meantime, projected rises in HCV-related deaths by 2010 lend increasing urgency to the search for new drugs. The following review describes agents currently in clinical trials, focusing on the drugs that show the most promise or those furthest along in development.

HCV PROTEASE INHIBITORS

HCV protease inhibitors have generated the most attention in the hepatitis C community, in part because of the success of HIV protease inhibitors. As with HIV, inhibition of the HCV protease interrupts the viral replication cycle by blocking cleavage of HCV proteins. Early trial results from Boehringer Ingelheim's protease inhibitor BILN 2061, presented in late 2002, heightened enthusiasm for this class of agents. Over a 2-day dosing period, people with hepatitis C experienced dramatic reductions in their HCV viral load. People with genotype 1 (the least responsive to standard treatment) showed a 2- to 3-log drop in HCV RNA. People with genotype 2 or 3 showed a lesser decline in HCV viral load, as BILN 2061 was specifically designed to target the genotype 1 HCV protease. Unfortunately, further development of BILN 2061 was halted after the discovery of cardiac toxicity in monkeys treated at high doses, though Boehringer Ingelheim is pursuing the development of follow-up protease inhibitors. It remains unclear whether the cardiac toxicity (not seen in humans treated for 2 days) was specific to BILN 2061 or is a potential side effect of all HCV protease inhibitors.

The HCV protease enzyme is a challenging target because the binding site is extremely shallow. Indeed, many companies that initially pursued development of HCV protease inhibitors have subsequently abandoned their programs or shifted focus to other targets. However, new agents are entering clinical development, including Vertex Pharmaceuticals' VX-950, which has completed initial Phase 1a testing in healthy volunteers and moved into a placebo-controlled Phase 1b trial in 60 healthy volunteers and people with hepatitis C, who will be treated for up to 14 days. Schering-Plough has also begun clinical testing of its HCV protease inhibitor, and InterMune is expected to begin human trials of its lead candidate in 2005.

HCV POLYMERASE INHIBITORS

A number of companies are developing HCV polymerase inhibitors, which prevent replication of HCV RNA through one of 2 ways: blocking the elongation of new viral RNA strands (nucleoside analogs) or inhibiting the HCV polymerase enzyme itself (non-nucleoside inhibitors). Ribavirin itself is a nucleoside analog, though its precise mechanism of action remains unclear, and ribavirin used as monotherapy has no durable antiviral efficacy.

Idenix is developing a nucleoside analog, dubbed NM-283. At its highest dose (800 mg once daily), people with HCV genotype 1 experienced about a 1-log drop in viral load during 15 days of treatment in a Phase 1 study; lower doses were less effective. Initial results of a Phase 2a, 28-day study of NM-283 in combination with pegylated interferon showed an average drop of 2.7 logs in HCV RNA levels. Nausea and vomiting were the most common side effects in people treated with NM-283; these side effects appeared early after starting the drug and were generally transient. In 2005, Idenix will conduct a 6-month Phase 2b trial of NM-283 and pegylated interferon, compared to pegylated interferon and ribavirin or NM-283 alone, in 165 people with HCV genotype 1 who did not respond to prior treatment.

Several other companies, including Japan Tobacco, ViroPharma, Roche, and Rigel, have also conducted clinical trials of HCV nucleoside analogs, though none has reached Phase 3 testing. Other companies, notably Abbott, also have HCV polymerase inhibitor programs and are expected to bring additional drug candidates into human trials in 2005 and 2006. As of yet, no non-nucleoside HCV RdRp inhibitors have moved into Phase 1 studies.

NON-SPECIFIC ANTIVIRALS AND IMMUNE MODULATORS

Phase 3 studies

InterMune's Infergen (consensus interferon) is an alternate form of interferon approved as monotherapy for hepatitis C treatment in the 1990s, but seldom used. Side effects are similar to those of the pegylated interferons, but some clinicians report that their patients find Infergen much harder to tolerate. In addition, InterMune has not developed a pegylated version of Infergen, which needs to be taken 3 times a week by injection. InterMune is conducting 2 large Phase 3 studies of high-dose Infergen in combination with ribavirin in non-responders to standard treatment (patients who typically will not respond to retreatment with pegylated interferon and ribavirin). Preliminary results of uncontrolled studies show that over a third of prior non-responders may achieve an SVR using Infergen and ribavirin; as with pegylated interferons, African-Americans do not respond as well to Infergen. The first Phase 3 study, the DIRECT trial, will study the efficacy of this regimen (evaluating 2 different doses of Infergen).

Valeant's Viramidine is a prodrug of ribavirin that targets the liver. The prodrug formulation should reduce the major drawback of ribavirin, hemolytic anemia, resulting from ribavirin's uptake into red blood cells. Indeed, initial data indicate that Viramidine is equally effective as ribavirin when used in combination with pegylated interferon, but with a substantially lower incidence of anemia: 27% in people taking ribavirin, compared with 0% to 11% at various doses of Viramidine. Valeant is conducting further testing of Viramidine in comparison with ribavirin in 2 Phase 3 studies, both with pegylated interferon, and each study will enroll approximately 1,000 people. Valeant expects to market Viramidine in 2007.

SciClone's Zadaxin (Thymosin alfa-1; thymalfasin) is a synthetic peptide, derived from human thymus gland extracts, that modulates immune responses. Zadaxin requires twice-weekly injections. In the US, SciClone has launched 2 Phase 3 studies of pegylated interferon, given with or without Zadaxin, in patients who did not respond to prior treatment. Results from these studies are expected in 2006. A European study, conducted by SciClone's partner Sigma Tau, is evaluating 550 non-responders who will receive pegylated interferon and ribavirin, with or without Zadaxin.

Phase 2 studies

Maxim's Ceplene (histamine dihydrochloride) is an immune modulator that prevents oxidative stress, thereby protecting immune cells and possibly liver tissue. Ceplene is given by injection. Maxim has conducted a Phase 2 study in more than 300 patients who did not respond to prior treatment; they will be given pegylated interferon and ribavirin, with or without Ceplene. Maxim has indicated that it will focus further clinical development efforts on an oral version of Ceplene, which completed Phase 1a testing in 2004.

InterMune's Actimmune (interferon gamma-1b) is a synthetic version of gamma interferon, a human protein with antiviral and immune-modulating effects that overlap with those of alpha interferon (the basis for the pegylated interferons). Actimmune is administered by injection 3 times per week and has side effects similar to those of

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pegylated interferon. InterMune is conducting a Phase 2 study of Actimmune with Infergen (consensus interferon) in non-responders to standard treatment.

Human Genome Sciences' Albuferon is a form of synthetic alpha interferon fused to albumin, giving the drug a longer half-life and potentially enabling a dose schedule of every 2 to 4 weeks. Side effects are comparable to those of pegylated interferon. In late 2004, Human Genome Sciences launched a 48-week Phase 2 study in patients who did not respond to prior treatment, comparing different doses of Albuferon given with ribavirin.

Vertex Pharmaceuticals' Merimepodib is an IMPDH (inosine-5'-monophosphate dehydrogenase) inhibitor, thought to boost the antiviral activity of ribavirin. Vertex recently launched the METRO study, a Phase 2b trial examining the efficacy of pegylated interferon and ribavirin, with or without Merimepodib, in patients who did not respond to prior treatment.

ADDITIONAL INVESTIGATIONAL AGENTS

- Imino sugar derivatives: These compounds may work by targeting the formation and proper folding of HCV envelope proteins, or through inhibiting ion channel formation and possibly preventing the release of new virus from infected cells. Migenix's Celgosivir (MX-3253) is currently under evaluation as monotherapy in a 12-week, 60-person Phase 2 study. United Therapeutics' UT-231B failed to demonstrate efficacy in non-responders in a Phase 2 study, but the company is planning another trial in partial responders to standard treatment (people whose viral load declined but who did not achieve an SVR) to assess whether UT-231B can prevent virologic relapse.

- Anadys' ANA975 is an oral prodrug of Isatoribine (ANA245), a nucleoside analog that functions as a toll-like receptor agonist, increasing the production of alpha interferon and stimulating immune responses. Based on promising results showing that high doses of Isatoribine produced on average a 0.76-log drop in HCV RNA over a 7-day dosing period, Anadys plans to begin Phase 1 testing of ANA975. Side effects will likely resemble those of pegylated interferon. Coley Pharmaceuticals also has a toll-like receptor agonist, Actilon, currently in Phase 1-2 testing in people with hepatitis C.

- Isis Pharmaceuticals' ISIS 14803 is an antisense oligonucleotide, a short synthetic strand of RNA designed to bind to HCV RNA and block replication. The drug requires injection. In 2003, the company launched a Phase 2 study of ISIS 14803 in combination with pegylated interferon and ribavirin in patients who did not respond to prior treatment. Unfortunately, the company recently announced that it was dropping further development of this compound.

- Idun Pharmaceuticals' IDN-6556 is a liver-targeting caspase inhibitor that prevents apoptosis (cell death). IDN-6556 is being evaluated in a 3-month, placebo-controlled Phase 2 trial in people with hepatitis C to determine its potential to decrease liver damage.

- Innogenetics and Intercell have conducted Phase 2 studies of therapeutic vaccines for hepatitis C. Innogenetics has reported that its therapeutic vaccine, designed to stimulate immune responses to one of HCV's envelope proteins, showed improvements in liver histology (reducing inflammation and/or fibrosis) in over a third of treated subjects with hepatitis C, despite having no effect on viral load. Intercell has reported that its vaccine, based on 5 HCV epitopes, successfully stimulated or strengthened anti-HCV immune responses, though without substantial effects on viral load. Further studies of these vaccines are planned.

CONCLUSIONS

The encouraging range of activity in HCV drug development bodes well for future treatment options, though dramatic short-term improvements in treatment safety and efficacy are unlikely. While several agents offer some hope for people who cannot tolerate or did not respond to current treatments, interferon will remain a mainstay of HCV treatment for the foreseeable future, and the most promising drugs—HCV protease and polymerase inhibitors—are still several years away from approval. Advocates following the HCV pipeline should press for clinical trial designs relevant to "real-world" people with HCV—particularly those who respond poorly to current therapy, including people co-infected with HIV.

Table. HCV therapeutics in development

Company	Drug	Class	Status
Vertex	VX-950	protease inhibitor	Phase 1b
Schering-Plough	(unnamed)	protease inhibitor	Phase 1
Idenix	NM-283	polymerase inhibitor	Phase 2b
Japan Tobacco	JTK-003	polymerase inhibitor	Phase 2
ViroPharma	HCV-086	polymerase inhibitor	Phase 1
ViroPharma/Wyeth	HCV-796	polymerase inhibitor	Phase 1
InterMune	Infergen	alpha interferon	approved; Phase 3 with ribavirin
Valeant	Viramidine	ribavirin prodrug	Phase 3
SciClone	Zadaxin	immune modulator	Phase 3
Maxim	Ceplene	immune modulator	Phase 2b
Maxim	HD-O	Ceplene prodrug	Phase 1
InterMune	Actimmune	gamma interferon	Phase 2 with Infergen
Human Genome Sciences	Albuferon	alpha interferon	Phase 2
Vertex	Merimepodib	IMPDH inhibitor	Phase 2b
Migenix	Celgosivir	imino sugar derivative	Phase 2
United Therapeutics	UT-231B	imino sugar derivative	Phase 2
Anadys	ANA975	toll-like receptor agonist	Phase 1
Coley	Actilon	toll-like receptor agonist	Phase 1-2
Idun	IDN-6556	apoptosis inhibitor	Phase 2
Innogenetics	INNO 101	therapeutic vaccine	Phase 2
Intercell	IC41	therapeutic vaccine	Phase 2

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Clinical perspective: Battling hepatitis C in our HIV-infected patients

By Daniel Alvarez, MD

Almost 5 and a half years ago I began a new stage in my career when I started working exclusively with people living with HIV/AIDS. I was amazed at how, with great science and the humanitarian efforts of people who care, we were able to give hope to many patients that before were considered to have a fatal illness. Unfortunately, I realized rather quickly that many patients were dying from liver-related complications, despite having controlled HIV disease. The literature clearly corroborated what I was seeing in our clinic, and I became very interested in understanding the effects of hepatitis C virus (HCV) in people with HIV.

I started to talk to my patients and colleagues about the situation. To my surprise, many patients had no idea they were carrying HCV. Medical providers were not routinely testing for HCV or sometimes not even discussing this diagnosis with patients when they *were* infected. In addition, most of the HIV-positive patients who knew they were also positive for HCV were unaware of the potentially fatal aspect of this infection, and some of them realized they had a serious disease only after experiencing symptoms of decompensated liver disease. Looking back, there were many reasons why we were not aggressive in pursuing the diagnosis and treatment of HCV or discussing it with patients. One of the main issues was the providers' belief that an expensive, difficult to tolerate, and relatively ineffective treatment for HCV probably should not be offered to HIV-positive patients. I agreed that there was not enough data supporting treatment HCV in co-infected patients. However, I was uncomfortable with this pessimistic and paternalistic approach. I was unable to sit back and do nothing for these patients.

My first challenge was to let patients know that they were infected with HCV. There were many types of emotional reactions, in particular disappointment: "After all this, I have another virus." I understood their fears. They had worked so hard to manage their HIV and now they had to deal with another illness, one that was potentially more deadly. Other patients were more optimistic: "We've tackled one virus; we can tackle this other one too." Some of them did not understand the nature of HCV disease or were perhaps just more resilient: "you take care of that 'doc;' I'll do whatever you think is best." Regardless the reaction, I felt that for most people it was better that they knew about their hepatitis C infection. I wanted them to know everything so they could make informed decisions. Nonetheless, it is also true that some research shows that just knowing you have HCV can decrease a person's quality of life and may be associated with fatigue.[1]

The next challenge was to find out how much damage the liver had already sustained by assessing the degree of fibrosis. Often it was a relief to find out. I assured many patients with no or minimal fibrosis that we could wait to treat their HCV; they were not in any immediate danger.[2] For other people, finding out that their livers were being irreversibly scarred helped them stop using alcohol.

Unfortunately, it wasn't that easy for many patients. Not every story was a success. One of my patients with depression and anxiety became very upset after learning of his liver biopsy results. I couldn't treat him, and he had advanced liver fibrosis. Even so, in general, my patients have been very thankful to know where they stand, and it has always been their choice to find out.

It took us 3 years to start our HIV/HCV co-infection clinic. But even before that, we started treating HCV. We were somewhat prepared: we had knowledge, will, and courage, but maybe not enough resources. Treatment was tough, difficult to tolerate, time consuming, and resource intense—with a relatively small chance of virologic response. Also, we were familiar with some data suggesting a histologic benefit could be obtained even in patients with transient or non-virologic response to HCV treatment. So we became selective, careful but very proactive, about choosing whom to treat. Our aim was to offer treatment mainly to patients with stage 2 to stage 4 fibrosis. And, we did not expect to clear the virus more than 40% of the time. Instead, our main goal was to delay or reverse fibrosis in these patients. Nevertheless, we had several virologic successes where patients cleared the virus. Every time it happened, I considered it a blessing, an extra "bonus."

Treating our patients has been very challenging and complex. We were fortunate to have a pharmacist, a nutritionist, case managers, and a mental health specialist on-site. *All of them* are necessary to treat HCV in co-infected patients. Above all, we have wanted to provide all of our patients with all the available choices and to keep them abreast of their liver disease. In my opinion, most circumstances require us to know a patient's liver histology before starting or delaying a potentially toxic and very expensive treatment. Liver histology is the "CD4 T cell count of hepatitis C" and it has been shown to improve with treatment. Of course, therapy goals should be individualized to each patient. The way we treat HCV will undoubtedly change in the next several years. New drugs that are easier to tolerate and more effective will change the way we approach this disease.

Unfortunately, there will not be enough time for some of our patients. Their livers cannot wait another 3 to 4 years. I realized that several of my patients' livers were succumbing to HCV, and those patients died soon after. Liver transplantation is the only option, and I refer such patients to transplant centers. So far, no one in our practice has received a liver transplant. Three of my patients on the waiting list have died or will die soon. Maybe the criteria for liver transplantation ought to be different in co-infected subjects? After long discussions with surgical and hepatological colleagues at my university, we have decided to start transplanting livers in HIV-positive patients with HCV. We will encounter new challenges but we are ready to face them. I guess we will never stop trying. We should not rest until we do a better job saving people's lives—the lives of people whom we've taken care of for years and who have become special to us.

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My personal experience in being HCV/HIV co-infected & how I cured hepatitis C

By Jules Levin

I have had HIV for 20 years and was infected with the hepatitis C virus (HCV) at least 20 years ago. So I was co-infected. The reason I say "was" is that I am no longer co-infected; that is, I don't have HCV anymore. I successfully finished my second course of treatment for HCV about 2 years ago I eradicated HCV, or "cured" it. This essay is about me and my experience in addressing my HCV. RI*TA!* asked me to write this article about my experience to help others in dealing with HCV. I agree that others can learn from my experience, so I hope this helps.

I strongly suspected that I had HIV 20 years ago because I had been injecting drugs for years. So I tested for HIV and was positive. But I did not realize that I might have HCV. In 1995, with the advent of protease inhibitors, which I believed would lead us to control of HIV, I started the National AIDS Treatment Advocacy Project (NATAP) whose sole mission was to educate people about HIV treatment and help people to improve treatment decision-making. I knew HIV could be beaten, and the answer was simply to make good treatment decisions. About 9 years ago, I figured out that I could also have HCV, not because my doctors told me but because I realized this on my own. I was tested and as suspected, I had HCV. Of course, I had a liver biopsy immediately, as the liver biopsy is the most reliable way to diagnose the stage of liver disease. Liver enzyme tests (ALT, AST) are not reliable barometers of the stage of liver disease. It is usually crucial to know your stage of liver disease in deciding when to begin HCV treatment. Unfortunately, I was told I had an advanced stage of liver disease—cirrhosis. There is no way to know how long I had HCV, but I believe I had it for at least 12 years and perhaps 15 years. Having HIV probably accelerated the progression of my HCV disease.

I went into action against HCV just like I did with HIV. I very quickly started therapy with standard interferon plus ribavirin. At the time, pegylated (peg-) interferon was not available yet, so I self-injected the interferon 3 times per week. I was genotype 2, so I expected a great response to therapy. Unfortunately, I had absolutely no response. I anticipated attempting re-treatment with peginterferon plus ribavirin, but I had to wait for its availability. I couldn't wait very long because my ALTs were increasing to over 200, and I had an uncomfortable feeling around my liver. I suspected I needed to be treated rather quickly. Once you have cirrhosis, the risk of progression to a serious stage called "decompensated cirrhosis" is up to 4% per year. To gain access to peginterferon, I traveled over 1000 miles from my hometown in New York City to enter a study. I was the second study participant and took once weekly injections of peginterferon plus 800 mg ribavirin daily. At first, I had to travel every week from New York to the study site for drug pick-up and bloodwork. After about 1 month, the visits were less often, every 2-3 weeks. And after several months, I could begin to increasingly space out my visits. My first viral load test was after 6 weeks on therapy and it was undetectable. When 2 weeks passed, I tested my liver enzymes and they had declined appreciably, so I knew I was responding well. Seeing such a good early response is an important signal that you have a good chance to achieve a "sustained virologic response" (SVR). Studies show that 99%

of patients who achieve an SVR are "cured." Every piece of research data confirms that HCV is "curable," which means simply that HCV can be eradicated. Studies have followed several thousand patients with SVR for about 4 years and about 100 patients with SVR for as long as 10 years. No sign of virus has been found in the blood or the liver of either group.

It's been 2 years since I completed my second course of HCV therapy with peginterferon plus ribavirin, and I have not felt better in more than 20 years—I feel great. Just as studies have found in patients who achieve and sustain an SVR, I have much improved energy and mental skills. I didn't realize how much HCV was affecting me until after therapy when I saw the improvement. I started to feel more energy and noticed improved mental skills shortly after finishing therapy, but since then I have continued to experience incremental improvements over the past 2 years. I feel very lucky.

The best decision I made was to start therapy and to stick with it. Of course therapy is difficult to tolerate as you may be aware of, but for me it wasn't as bad as I thought it would be. It affects everyone differently. For some patients, the side effects are not so bad and for others they might be worse. But for me it was well worth it.

The only way for me to evaluate the condition of my liver now post-treatment is to do another liver biopsy, but I am not planning to perform a biopsy. An improvement in the condition of one's liver is to be expected along with an SVR. So I expect that my liver disease—my cirrhosis—is reversing and improving. The latest studies show that cirrhosis IS reversible. Of course, the best approach is not to delay therapy until you have cirrhosis. Response rates to therapy are best when therapy is started at earlier stages of disease. You have to be very careful if you have HIV and HCV because HIV can accelerate HCV disease progression by 2 times. So, if you have a liver biopsy performed and even if you only have stage 1 or 2 (stage 3 is bridging cirrhosis and stage 4 is cirrhosis, depending on the system and test used), I suggest starting therapy.

For a decision about treatment, there are a few things I recommend considering. There is no way to figure out if you will respond well to therapy unless you try it. You can always stop therapy. After 12 weeks of therapy, you can evaluate your chances for a "cure." The early viral response (EVR) formula tells us that if after 12 weeks there is a 2-log decline in viral load or an undetectable viral load, the chances of achieving an SVR or cure are good, 60% to 70%. If this status is not achieved by 12 weeks, the chance for success with therapy is very low and you can consider stopping therapy. Good adherence is crucial to achieving an SVR. Studies show that greater than 80% adherence significantly improves response rates. Because therapy is only for 12 months, there is no excuse (in my opinion) to miss any doses. One additional point regarding my therapy: although the standard duration of therapy for co-infected individuals is 12 months, I continued therapy for an extra 6 months for a total of 18 months. The reason I did this is because results from several studies suggest that if you see an EVR and if your viral load is undetectable by week 24, you are more likely to achieve an SVR if you prolong therapy an extra 6 months. So I did this. I suggest you consider this if your circumstances are similar.

An important point to also consider is that interferon has certain properties that allow it to slow down liver disease progression even if the viral load is not reduced. This is important because in about 4 years, new drugs being developed now will start to

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become available. It's crucial to prevent progression to cirrhosis while waiting for these new drugs, so be careful about delaying initiation of therapy. Undue delay in starting therapy may put you in a bad situation. HCV disease might progress. As well, if you think by waiting you can avoid taking interferon, think again. Even if we have a new drug or 2 in several years, peginterferon will most likely have to included as part of the regimen.

In conclusion, I am very fortunate to have had success with HCV therapy and eradicated HCV. This has given me a whole new life. Of course, I have used the improved energy I have by increasing the amount of work that I do. If you don't know what I do, NATAP provides up-to-date HIV and hepatitis treatment information and education through our website at ***natap.org***, our HIV and HCV newsletters and *HCV Handbook*, and our community forums that we hold in cities throughout the US. Please access our website or call us toll free at 888.26.NATAP for information and newsletters.

Jules Levin is the Founder and Director of NATAP.