HIV/HCV Coinfection: A New Era of Treatment

Hepatitis C is a life-threatening illness that can progress to cirrhosis, liver cancer, and end-stage liver failure. An estimated one-third of HIV positive people are coinfected with hepatitis C virus (HCV), and HCV-related liver disease is a major cause of death for people with HIV in the era of effective antiretroviral therapy (ART).

HCV has made headlines recently due to the approval of the first direct-acting antiviral (DAA) agents, which promise to revolutionize hepatitis C treatment. Researchers at the 2011 Conference on Retroviruses and Opportunistic Infections (CROI) and the Infectious Disease Society of America (IDSA) annual meeting presented the first data from studies of these drugs in HIV/HCV coinfected people.

Hepatitis C Basics

Hepatitis C is a disease of the liver that typically becomes chronic and causes slow disease progression. HCV primarily attacks and replicates inside hepatocytes, or liver cells. The virus was first identified in 1989; prior to that, hepatitis C was known as “non-A/non-B” hepatitis.

The National Health and Nutrition Examination Survey (NHANES) of U.S. households found that approximately four million people—or 1.6% of the general population—are living with hepatitis C. However, estimates that include higher prevalence populations not included in NHANES—such as prisoners, homeless people, and individuals in long-term care facilities—suggest that the true number may be five to seven million.

An estimated 10,000 deaths per year are attributed to hepatitis C and its complications, and HCV-related liver failure is the leading reason for liver transplants in the U.S. A study presented at the American Association for the Study of Liver Diseases (AASLD) annual meeting this November found that deaths due to hepatitis C in the U.S. now exceed those due to HIV.

Hepatitis C Disease Progression

The liver carries out many crucial bodily functions, including metabolizing sugars, lipids, and proteins; storing vitamins and other nutrients; detoxifying metabolic waste products and toxins, including drugs and alcohol; and synthesizing blood proteins, clotting factors, and immune factors. Therefore, damage to the liver can lead to a variety of symptoms and associated conditions.

Most people with acute HCV infection exhibit no symptoms. A small proportion may experience fatigue, fever, nausea, loss of appetite, abdominal pain, muscle or joint aches, and malaise, but these may be mistaken for the flu or other illness.
A minority develop jaundice and scleral icterus (yellowing of the skin and eyes) due to elevated bilirubin. Laboratory tests may reveal high levels of the liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

An estimated 20% to 40% of individuals with acute HCV infection spontaneously clear the virus without treatment, but the rest develop chronic hepatitis C lasting more than six months. The likelihood of chronic infection is higher for people with HIV.

Approximately two-thirds of people with chronic hepatitis C experience some degree of disease progression, developing necroinflammation (hepatocyte inflammation and death), liver fibrosis (buildup of fibrous scar tissue), or liver steatosis (fat accumulation). Chronic hepatitis C symptoms, if they occur, are similar to those of acute infection. Many people also report “brain fog,” or impaired concentration and memory.

About 10% to 25% of people with chronic hepatitis C progress to severe liver disease, including cirrhosis (replacement of normal liver cells with nonfunctional scar tissue), hepatocellular carcinoma (a form of primary liver cancer), decompensation (inability of the liver to carry out its critical functions), and end-stage liver disease. Progression to severe disease typically takes ten to 40 years, and many people have no symptoms until they reach advanced stages.

In people with advanced cirrhosis, scar tissue blocks the flow of blood through the liver, which can cause portal hypertension (high blood pressure in the portal vein), bleeding varices (varicose veins) in the esophagus or stomach, ascites (abdominal fluid accumulation), and edema (swelling) in the feet and legs.

Impaired synthesis of coagulation factors can lead to poor blood clotting and easy bleeding or bruising. When the liver is no longer able to efficiently filter the blood, buildup of toxins such as bile salts and ammonia can lead to pruritis (itching) and hepatic encephalopathy (brain impairment).

The only long-term treatment for end-stage disease is liver transplantation, but there are too few donated organs to meet the demand.

Although it is difficult to predict which individuals will experience disease progression, several factors have been linked to worse outcomes, including male sex, older age, heavy alcohol consumption, obesity, insulin resistance or diabetes, and HIV/HCV coinfection.

Hepatitis C Testing and Monitoring

HCV screening generally has not been done as part of routine health care for people without traditional risk factors, and a large proportion of infected individuals are thought to be unaware of their status. Some experts recommend that all “baby boomers” (those born during 1945–1965) be screened due to the higher prevalence of chronic hepatitis C in this age cohort.

Antibody assays (e.g., ELISA, RIBA) are used to test for HCV exposure. HCV antibodies do not confer long-lasting immunity, and people can become infected again after clearing the virus spontaneously or with treatment. There is currently no effective preventive HCV vaccine.

Viral load tests (e.g., PCR, bDNA, TMA) can determine the presence and quantity of HCV RNA (genetic material) in the blood, which indicates active viral replication. RNA tests can detect HCV in people who have not yet produced enough antibodies—or whose immune system is too impaired to produce antibodies—and they are used to monitor treatment effectiveness.

Most studies show that, unlike HIV, HCV viral load is not closely correlated with disease progression; however, high levels do increase the risk of transmission and decrease the likelihood of treatment response.

Genotype tests are used to identify HCV genotypes (1 through 6) and subtypes (e.g., 1a and 1b). HCV genotypes are differentially distributed around the world. Genotype 1, which is most common in the U.S., is considered the most difficult to treat. Genotypes 2 and 3, found throughout the world, respond better to interferon-based therapy. Genotype 4 is most often seen in the Middle East and North Africa, genotype 5 in South Africa, and genotype 6 in Asia.

Liver function tests measure biomarkers associated with liver health. ALT and AST are enzymes released when liver cells are damaged; elevated levels are a sign of liver inflammation, but are not a reliable indicator of fibrosis. Other laboratory tests used to determine overall liver health include alkaline phosphatase, bilirubin, gamma-glutamyl transpeptidase (GGT), platelet count, and prothrombin time (a measure of blood clotting ability).

The “gold standard” for assessing liver damage is biopsy, in which a small sample of liver tissue is withdrawn using a needle and examined under a microscope. Various classifications are used, including the Metavir system that stages liver necroinflammation (stage A0 to A4) and fibrosis (stage F0 to F4).

Clinicians also use several noninvasive methods to assess liver damage. Transient elastometry, or FibroScan, uses sound waves to measure liver “stiffness,” expressed as kilopascals (kPa); greater stiffness suggests more advanced fibrosis. Various biomarker indices including APRI (AST-to-platelet ratio) and FIB-4 (ALT, AST, platelet count, and patient age) are calculated to estimate liver disease progression. ALT alone is not a good indicator because people with persistently normal levels can still develop advanced fibrosis.

Noninvasive methods are not as reliable as liver biopsy for detecting and staging fibrosis. While they do a reasonably good job of distinguishing
between mild and advanced fibrosis, they are less able to determine intermediate stages. They also have not been validated as extensively for HIV/HCV coinfected patients. However, they are safer, less painful, and less expensive than biopsies, especially for repeat testing.

Other classification systems are used to describe functional liver damage. The Child-Pugh or Child-Turcotte-Pugh score incorporates laboratory markers and symptoms, including ascites and hepatic encephalopathy. The Model for End-Stage Liver Disease (MELD) score—incorporating bilirubin, serum creatinine, and prothrombin time—is used to predict survival and prioritize allocation of donor livers for transplant.

**HCV Transmission**

HCV spreads most efficiently through direct blood-to-blood contact, for example sharing syringes for drug injection, accidental needle-sticks among health-care workers, unsafe reuse of medical equipment, or tattooing with non-sterile equipment.

Injection drug users (IDUs) have a high prevalence of hepatitis C, reaching 90% in some groups. Increased awareness, needle exchange programs, and other harm reduction efforts have reduced rates of HCV transmission among IDUs over the past several years. A CDC study of 5,000 IDUs in four cities, for example, found that the proportion infected with HCV fell from 65% in 1994 to 35% ten years later.

People who use non-injected drugs are also at elevated risk for hepatitis C. HCV may be transmitted via personal items that come into contact with blood, such as toothbrushes, razors, or manicure tools; although difficult to quantify, most studies suggest that the actual risk is low.

Household transmission appears to be rare, and HCV is not spread through airborne transmission (e.g., coughing or sneezing), the fecal-oral route (contaminated food or water), or casual contact (e.g., hugging or sharing drinking glasses). A significant proportion of people with hepatitis C have no identifiable risk factors.

Compared with HIV, sexual transmission of HCV is relatively uncommon. Most studies show little or no HCV in semen and female genital secretions, though levels may be higher in HIV positive people.

Studies of steady heterosexual couples have consistently found transmission rates in the range of 0% to 3%. This has led public health authorities to advise that HCV sexual transmission is not a major concern and couples do not need to take safer sex precautions.

But over the past decade it has become clear that sexual transmission is more common than previously believed, especially among HCV positive people and men who have sex with men (see sidebar, page 34). In the Women’s Interagency HIV Study, for example, a number of women who became infected with HCV did not inject drugs themselves but had sex partners who did; the risk of HCV acquisition was about twice as high for HIV positive compared with HIV negative women. Even among HIV negative people, unrecognized sexual transmission may help explain the large number of cases with no reported traditional risk factors.

Mother-to-child HCV transmission during pregnancy, birth, or breast-feeding is also uncommon. But here too, the risk rises for HIV positive mothers. While the rate of mother-to-child HCV transmission is estimated at about 5% overall, studies suggest the risk may be three times higher for HIV/HCV coinfected women. A 2007 meta-analysis of ten studies found that having HIV increased the odds of perinatal HCV transmission by about 90%.

**HIV/HCV Coinfection**

It is generally estimated that one-quarter to one-third of people with HIV also have chronic HCV infection; in the U.S., this represents approximately 300,000 individuals. The proportion of people with hepatitis C who are also HIV positive is considerably lower, perhaps 10%. HCV is more readily transmitted via injection drug use while HIV is more often transmitted via sexual activity, so coinfection rates vary across risk groups.

In the early years of the epidemic, people with HIV usually died from AIDS-related causes, and less attention was devoted to chronic non-AIDS conditions such as viral hepatitis. Since the advent of effective antiretroviral treatment, however, many HIV positive people survive long enough for HCV to take its toll.

HIV/HCV coinfected people are more likely to progress to serious liver disease and tend to do so more rapidly. Over the past decade and a half, liver disease related to chronic hepatitis B and C has become a leading cause of morbidity and mortality among people with HIV in high-income countries; as ART becomes
more widely available, a similar trend is becoming apparent in resource-limited countries as well.

The latest U.S. Public Health Service and IDSA guidelines recommend that all HIV positive people be tested for hepatitis B and C, and vaccinated against hepatitis A and B if not already immune.

Yet at an HIV/HCV coinfection forum last year in San Francisco, several HIV positive gay men reported difficulty getting an HCV test if they did not have a history of injection drug use. Many people with HIV, their providers, and public health officials remain unaware of the growing epidemic of sexually transmitted hepatitis C in this population.

**How Does HIV Affect HCV?**

HIV positive people are less likely than HIV negative individuals to spontaneously clear acute HCV infection, and therefore more frequently develop chronic disease. In addition, coinfectected individuals have higher HCV viral load on average, are more likely to experience liver disease progression, and generally do not respond as well to interferon-based therapy.

These adverse outcomes may be attributable to weaker immune response against HCV. Several studies have seen an association between low current or nadir (lowest-ever) CD4 T-cell count and HCV persistence, fibrosis progression, and poor treatment response. An Austrian analysis, for example, found that people with a nadir below 200 cells/mm³ had twice the fibrosis progression rate of those who never fell below 500 cells/mm³.

Researchers at Massachusetts General Hospital found that people who were HIV non-progressors or who started antiretroviral treatment before their CD4 count fell below 300 cells/mm³ were more likely to spontaneously control HCV. However, individuals who had a low nadir but experienced immune reconstitution on ART did not recover HCV-specific CD4 cell responses.

In 2002, Abdul Mohsen and colleagues in the U.K. reported that HIV/HCV coinfectected people developed cirrhosis on average 22 years after HCV infection, compared with 32 years for people with HCV alone. A meta-analysis from the same era found that coinfection conferred a two-fold higher risk of cirrhosis and a six-fold greater likelihood of end-stage liver disease.

More recent studies, however, have produced mixed results. Some find less difference in liver disease progression when coinfectected people are on effective HIV treatment and have higher CD4 cell counts, but others continue to see worse progression despite ART and well-preserved immune function.

In a retrospective analysis of liver biopsies obtained between 1998 and 2008 from 180 HIV/HCV coinfectected patients with well-preserved immune function and 407 HCV monoinfected people, Mamtta Jain and colleagues found that both groups had a similar distribution of mild (39% vs. 34%), moderate (41% vs. 49%), and severe (18% vs. 16%) fibrosis.

But a recent French study found that coinfectected people were twice as likely as HCV monoinfected individuals to have advanced fibrosis or cirrhosis (39% vs. 18%), even though most were on ART and their mean CD4 count was nearly 500 cells/mm³.

Richard Sterling and colleagues from Virginia Commonwealth University examined paired liver biopsies from 56 HIV/HCV coinfectected patients and matched participants with HCV alone. As described at the 2010 European Association for the Study of the Liver (EASL) meeting, samples from coinfectected patients showed more necrosis and inflammation.

Although the frequency of fibrosis progression was statistically similar, coinfectected individuals were twice as likely to progress by two stages. Since no clinical or laboratory parameters predicted progression, the researchers recommended that all coinfectected patients consider repeat biopsies.

**HCV After HIV**

Some evidence suggests that liver disease progression may be particularly aggressive in people who are already HIV positive when they acquire HCV. Study findings have been inconsistent, however, and potential biological mechanism are not well understood.

Daniel Fierer and colleagues at Mount Sinai have been following a cohort of long-term HIV positive gay and bisexual men in New York City who contracted acute hepatitis C, presumably via sexual transmission. Unlike the IDU participants in most HIV/HCV coinfection studies over the years—who usually acquire HCV first—this group all had HIV prior to HCV.

At CROI 2007, Fierer presented a case series of four men with biopsies showing moderate (stage F2) portal fibrosis, even though they had been infected with HCV for only a short time. The following year he revealed that the group’s mean fibrosis progression rate was an astonishingly high 4.5 units per year. In 2009 he described 24 recently coinfectected men, reporting that one had advanced fibrosis, 18 had moderate fibrosis, three had mild liver disease, and only two showed no evidence of fibrosis.

Interestingly, this group lacks traditional risk factors for aggressive liver disease. The men have well-preserved immune function overall, with a median CD4 count above 500 cells/mm³; most are on ART and a majority have undetectable HIV viral load. Alcohol consumption is generally low, many report never using recreational drugs, body weight and fasting glucose are normal, and very few have coexisting hepatitis B virus (HBV)—their only notable common feature is acquiring HIV before HCV.

The Mount Sinai findings have generated some controversy, as most European researchers using the noninvasive FibroScan method
Over the past decade, clinicians have reported outbreaks of sexually transmitted acute hepatitis C among HIV positive men who have sex with men (MSM). The first cases were reported in the early 2000s in cities in the U.K. and Western Europe, followed by Australia and the United States. Daniel Fierer from Mt. Sinai has described acute HCV among MSM as “a new 21st century clinical syndrome.” It is not clear why this epidemic only started in the early 2000s, he said at a San Francisco community forum on coinfection.

Genetic sequencing has revealed clusters of cases that indicate transmission through sexual networks, both within cities and internationally. Evidence gleaned from tracing the genetic history of the virus suggests multiple introductions of HCV into MSM communities, according to Thijs van de Laar of the Amsterdam Public Health Service, some of which may have occurred as early as the 1980s.

A retrospective analysis in Amsterdam found that the prevalence of HCV infection among gay/bisexual men attending sexually transmitted infection (STI) clinics was 1% to 4% before 2000, rising to about 15% in 2007 and 20% in 2008. More recent data presented at AASLD 2011, however, suggests that the rate may be leveling off.

Brad Hare, Medical Director of the Positive Health Program at San Francisco General Hospital, and colleagues published the first U.S. report in 2006, describing nine cases of acute HCV infection among HIV positive men. At a 2009 community forum, Hare estimated that about 40% of men in the Positive Health Program are HIV/HCV coinfected, with a majority reporting only sexual risk factors.

At CROI 2007 Fierer first described a group of HIV positive MSM with acute hepatitis C in New York City who showed evidence of unusually rapid liver disease progression. In the July 22, 2011, Morbidity and Mortality Weekly Report, his team reported that between October 2005 and December 2010 they identified 74 HIV positive men—most of them on ART with well-controlled HIV disease—who had documented new HCV infection despite reporting no traditional risk factors.

Lynn Taylor from Brown University and colleagues looked at HCV incidence between 1996 and 2008 among more than 1,800 men participating in the ACTG Longitudinal Linked Randomized Trials (ALLRT) cohort, finding that 75% of new HCV infections were unrelated to injection drug use and were likely due to sexual transmission.

HIV positive people on ART are advised to receive regular liver function tests to monitor for liver toxicity. Some experts therefore suggested that people with HIV might not really be more susceptible to HCV, but rather were simply more likely to be diagnosed during the acute stage due to suspicious ALT elevations.

To test this hypothesis, Martin Fisher and colleagues in Brighton (one of the epicenters of the U.K. outbreak) screened all clients at a sexual health clinic serving gay and bisexual men during 2000–2006. They found that HIV positive MSM were 13 times more likely than HIV negative men to acquire HCV. Routine HCV screening at urban U.K. sexual health clinics starting in 2007 revealed that HCV prevalence among HIV negative MSM was 0.65%—similar to that of the English general population.

It is unclear exactly how HCV is transmitted among gay and bisexual men, as different studies implicate varying risk factors. Fierer’s group reported that MSM with acute hepatitis C were 23 times more likely to have had unprotected receptive anal intercourse with ejaculation than men without HCV; other investigators, however, have found no significant association with anal sex.

Other risk factors that have been linked to acute HCV infection include fisting, use of sex toys, multiple sex partners, sex in group settings, meeting sex partners online, concurrent STIs, and use of non-injected recreational drugs. But as Emmanuel Bottieau discovered in his cohort of acutely coinfected MSM in Belgium, “a substantial number do not report any of these practices.”

In a review article in the July 31, 2010, issue of AIDS, van de Laar and colleagues noted that the increase in HCV sexual transmission coincides with a rise in sexual risk behavior in the era of effective ART, perhaps related to serosorting (having sex only with people of the same HIV serostatus). “[M]ost MSM with HCV report a combination of various, potentially high-risk, sexual and drug practices,” they wrote. “The interaction between sex and drugs is complex, and many of these factors are highly correlated and difficult to disentangle.”

Most experts agree that HCV transmission likely occurs through exposure to blood, since semen contains little or no HCV. Yet safer sex with condoms is often the only prevention recommendation—perhaps because it is unclear what other advice to offer based on conflicting data. Some community members have adopted preventive measures such gloves for manual contact and disinfection of surfaces in sex clubs.

The role of HIV in facilitating HCV transmission also remains a mystery. “HIV probably has a critical role mediated...through behavioral and/or biological factors,” according to van de Laar’s team. It is not yet known whether low CD4 T-cell count increases the risk of acquiring HCV, they concluded, “but the fact that many MSM with acute HCV have relatively preserved CD4 cell counts suggests this may not be a critical factor.”
either have not seen unusually severe fibrosis or have observed such rapid progression that they assume test results must be erroneous.

Looking at a similar cohort of HIV positive European MSM with acute HCV infection, for example, Martin Vogel and fellow investigators with the NEAT study saw a fibrosis progression rate so high they deemed it implausible (3.8 units per year).

“Higher liver stiffness in the acute phase of HCV infection may be at least partially explained by higher inflammatory activity which has been shown to increase stiffness leading to overestimation of fibrosis,” they reported at CROI 2010.

But last year—flying largely under the radar of the HIV research community—Belgian researchers reported data that appear to support the Mount Sinai findings. In a report on rising incidence of HCV infection among HIV positive MSM in Antwerp, Emmanuel Bottieau and colleagues noted that 22 out of 37 patients (59%) who underwent liver biopsy showed moderate to severe fibrosis only seven months after diagnosis of acute hepatitis C.

Fortunately, interferon-based therapy is highly effective for treating acute hepatitis C in this population: 80% of men in Fierer’s cohort and about 60% in Vogel’s study achieved sustained virological response with 24 weeks of treatment—although this fell short of the nearly 100% success rate seen in some studies of HIV negative people with acute hepatitis C.

“The good news is that the cure rate for new HCV infections is very high with early treatment,” said Fierer, “but without regular testing of the men at risk, these largely asymptomatic infections may be missed and this opportunity lost.”

**How Does HCV Affect HIV?**

While a preponderance of research indicates that HIV promotes HCV disease progression and poor treatment response, the effects of HCV on HIV disease are less clear.

HCV does not appear to significantly influence HIV viral load or accelerate HIV disease progression. Mark Sulkowski and colleagues from Johns Hopkins, for example, found that coinfected participants in their Baltimore cohort were no more likely than HIV monoinfected people to experience disease progression, develop AIDS-defining illnesses, or die from AIDS-related causes.

Some studies have found that HIV/HCV coinfected people have higher mortality rates than those with HIV alone, but this is largely attributable to increased risk of death due to liver-related causes or cofactors such as injection drug use, not causes related to AIDS.

There is some evidence that dual HIV/HCV infection may impair immune system recovery after starting antiretroviral treatment. Back in 2000, researchers with the Swiss HIV Cohort Study reported that while HIV/HCV coinfected and HIV monoinfected participants were equally likely to achieve undetectable HIV viral load after starting ART, coinfected patients were significantly less likely to achieve CD4 cell gains of at least 50 cells/mm³ after one year of treatment.

Similarly, a study by Vincent Soriano’s team at Hospital Carlos III in Madrid, presented at CROI 2001, showed that coinfected individuals experienced an average increase of about 50 cells/mm³ after two years on ART, compared with about 100 cells/mm³ for HIV monoinfected people.

But again, more recent research looking at people using modern antiretroviral treatment has not seen such clear differences between HIV/HCV coinfected and HIV monoinfected individuals.

A 2009 analysis of participants in the U.K. Register of HIV Seroconverters, for example, found no significant differences in time to HIV suppression or rate of CD4 cell recovery between coinfected and HIV monoinfected individuals. And in the EuroSIDA cohort, coinfected participants who achieved sustained HIV suppression had annual CD4 cell gains matching those of HIV monoinfected people.

Investigators with the Co-infection Cohort Study reported that coinfected people with detectable HCV RNA—indicating active viral replication—had greater CD4 cell declines prior to starting ART and seven-fold slower recovery after ART initiation than those with HIV alone. Looking only at participants who achieved undetectable HIV viral load on ART, however, the difference did not reach statistical significance.

Furthermore, the researchers noted that spontaneous HCV clearance or sustained response to interferon-based therapy predicted better CD4 cell recovery, leading them to suggest that hepatitis C treatment might help reduce HIV disease progression as well as liver disease progression.

Some studies find that HIV/HCV coinfection can contribute to increased frequency and severity of various HIV-associated but non-AIDS-defining conditions, including neurocognitive impairment, bone loss, and cardiovascular disease.

At CROI 2010 researchers from Washington University in St. Louis reported that HIV/HCV coinfected individuals on suppressive ART performed more poorly than HIV monoinfected people on neurocognitive tests, though they saw no significant differences in neural imaging. Another team reported that coinfected patients showed significantly worse neurocognitive performance than those with HIV alone prior to starting antiretroviral treatment, but this was no longer the case six months after ART initiation.

Roger Bedimo and colleagues retrospectively analyzed osteoporosis-related wrist, hip, and vertebral fractures among 56,660 HIV positive patients enrolled in the Veterans Affairs Clinical Case Registry. During the ART era,
coinfected participants had a higher fracture rate than HIV monoinfected people (4.06 vs. 2.86 per 1,000 person-years, respectively); coinfected patients accounted for one-half of reported fractures even though they made up just one-third of the study population.

Bedimo’s team performed another case registry analysis looking at risk factors and incidence of cardiovascular events. HIV/HCV coinfected patients had higher rates of myocardial infarction (heart attack) and stroke than HIV monoinfected individuals, even though they were less likely to have abnormal blood lipids. Coinfection was associated with a 40% higher risk in the pre-ART era, falling to 20%–25% higher after the advent of ART.

People with HIV/HCV coinfection—especially those with advanced fibrosis or cirrhosis—are more susceptible to drug-related liver toxicity; conversely, successful hepatitis C treatment may enable patients to better tolerate antiretroviral therapy.

Certain nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and HIV protease inhibitors have the potential to cause various types of liver damage. But the worst culprits—including didanosine (ddI; Videx), stavudine (d4T; Zerit), and full-dose ritonavir (Norvir)—are no longer commonly used in the U.S. Widely used modern antiretroviral agents are generally not associated with significant liver problems, but periodic liver function monitoring is nevertheless recommended.

ART and Inflammation

By preserving or restoring immune function, effective antiretroviral treatment appears to partially hold in check or even reverse some of the detrimental impact of HIV on HCV disease progression and vice versa.

In 2007 Hla Hla Thein and colleagues reported findings from a meta-analysis of 17 studies showing that liver fibrosis progression was slower among HIV/HCV coinfected people on ART and those with CD4 counts above 400 cells/mm³. Coinfected ART recipients were 1.7 times more likely to develop cirrhosis than people with HCV alone, but the risk was 2.5 times greater for untreated coinfected patients.

In a study presented at the 2011 European AIDS Conference in October, Massimiliano Fabbiani’s group used the noninvasive FibroScan index to analyze liver damage in more than 1,500 coinfected people from the time they initiated ART. Longer duration of ART and more time with undetectable HIV RNA were both significantly associated with less fibrosis progression. Fabbiani suggested that ART may have a beneficial anti-inflammatory effect on the liver beyond its impact on HIV viral load and CD4 cell count.

The CCR5 antagonist maraviroc (Selzentry) may be particularly beneficial, as it blocks CCR5 receptors on stellate cells in the liver that produce collagen and other scar tissue material. Laboratory studies have shown that HIV can enter stellate cells and trigger collagen production, and blocking CCR5 ameliorates liver fibrosis in mice.

At the 2011 Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Paola Nasta from the University of Brescia reported that liver stiffness fell by 0.8 kPa among HIV/HCV coinfected patients randomly assigned to add maraviroc to their current suppressive ART, but rose by 0.1 kPa among people who stayed on their baseline regimen; the difference was greater for patients with advanced fibrosis or cirrhosis (–2.2 vs. +4.5 kPa, respectively).

If starting ART is beneficial, stopping HIV treatment can have the opposite effect. The large SMART treatment interruption trial—in which 17% of the more than 5,000 HIV positive participants also had hepatitis B or C—found that people who stopped ART not only had a greater risk of AIDS-related opportunistic illness and death, but also higher rates of major cardiovascular, kidney, and liver disease.

More recently, a Canadian Coinfection Cohort Study analysis described in the April 24, 2011, issue of AIDS, found that ART interruption was associated with a 2.5-fold increased risk of fibrosis progression, which was only partially attributable to changes in HIV viral load and CD4 cell count.

There is a growing consensus that persistent immune activation and inflammation triggered by HIV infection contributes to chronic non-AIDS conditions (including HCV-related liver disease) in an aging patient population; not surprisingly, infection with multiple viruses can worsen immune activation.

Investigators with the Women’s Interagency HIV Study, for example, showed that coinfected women with detectable HCV RNA had a significantly higher percentage of activated CD8 T-cells than HIV positive women without HCV, as well as a higher rate of AIDS-related illness or death.

Increased immune activation can lead to T-cell senescence, or “burnout,” which may help explain the more pronounced CD4 cell declines and blunted immunological recovery seen among coinfected patients in some studies.

Looking at biopsies from 14 HCV/HIV coinfected and six HCV monoinfected individuals, researchers from the University of Toronto found that while the two groups had similar numbers of HCV-specific CD4 and CD8 T-cells in their livers, the coinfected patients also had HCV-specific T-cells as well, leading to greater total production of pro-inflammatory cytokines and more fibrosis.

Findings such as these support U.S. and European antiretroviral therapy guidelines recommending that HIV/HCV and HIV/HBV coinfected people consider earlier ART initiation, well before their CD4 cell count falls into the traditional danger zone.
Hepatitis C Treatment

For the past two decades the mainstay of hepatitis C treatment has been interferon, which stimulates the body’s immune response against the virus. The advent of direct-acting antiviral agents that target the HCV lifecycle promises to transform treatment, making it resemble combination antiretroviral therapy for HIV.

Who Needs Treatment and When?

Not everyone with hepatitis C requires treatment. Several factors should be taken into account when deciding whether to treat—including coexisting medical conditions and ability to maintain good adherence—but the primary consideration is extent of liver damage.

The traditional consensus has been that treatment for chronic hepatitis C is necessary if a person is experiencing liver disease progression. As noted, 10% to 25% of people with chronic HCV mono infection and a somewhat higher proportion of those with HIV/HCV coinfection will develop severe disease, meaning the remainder will not progress to advanced liver damage.

But it is not easy to predict which individuals will experience disease progression, or even to determine when it is occurring. This presents a dilemma, since clinicians do not want to treat people who will never progress, but once progression occurs treatment becomes more difficult.

Because treatment duration is shorter and the chances of success are greater for people with acute hepatitis C (infected less than six months) and those with HCV genotypes 2 or 3, many experts advise that such patients receive treatment as a matter of course, without undergoing liver biopsy to determine fibrosis stage. The drawback of this approach is that some people will endure the side effects and expense of treatment who never would have progressed without it.

The dilemma is magnified for HIV/HCV coinfected people, who tend to progress more frequently and more rapidly than those with HCV alone, but are less likely to respond to interferon-based therapy and face additional treatment-related complications. People with advanced liver disease are another group that stands to benefit greatly from treatment but has more treatment-related challenges.

Some experts recommend that HIV positive individuals with hepatitis C receive prompt treatment regardless of current fibrosis stage due to their elevated risk of progression. Alternatively, coinfected patients who remain untreated may undergo more frequent biopsies to monitor liver disease progression.

Recent advances in hepatitis C therapy are encouraging more people to consider treatment, as the addition of DAAs can cut treatment time and increases the likelihood of a cure. Some patients, however, continue to wait for all-oral DAA regimens that will eliminate the dreaded side effects of interferon.

Interferon-Based Therapy

Until recently the standard of care for chronic hepatitis C has been once-weekly injected pegylated interferon alfa-2a (Pegasys) or alfa-2b (PegIntron) plus weight-adjusted oral ribavirin. Only Pegasys has a U.S. Food and Drug Administration (FDA) indication for HIV/HCV coinfection, but the two brands are generally regarded as functionally equivalent.

Interferon alfa is a manufactured form of a natural cytokine, or chemical messenger, that stimulates immune response against HCV. The peglated version lasts longer in the body than the older conventional interferon alfa (Roferon-A or Intron-A), allowing administration once rather than three times weekly.

Ribavirin (brand names Copegus and Rebetol) is a nucleoside analog, in the same class as several antiretroviral agents used to treat HIV. Its mechanism of action against HCV is not fully understood, but studies show ribavirin helps prevent post-treatment relapse and thereby increases the likelihood of sustained response.

The standard regimen for HCV mono infected people is 180 mcg/week pegylated interferon alfa-2a or 1.5 mcg/kg/week pegylated interferon alfa-2b plus 1,000–1,200 mg/day weight-adjusted (genotype 1) or 800 mg/day fixed-dose (genotype 2 or 3) ribavirin.

The usual duration of therapy is 48 weeks for difficult-to-treat HCV genotypes 1 and 4, or 24 weeks for genotypes 2 and 3. Because people with HIV respond more slowly, guidelines have recommended 48 weeks for coinfected patients regardless of genotype; recent research, however, indicates that 24 weeks appears adequate for HIV positive people with genotype 2 or 3 as well.

HCV viral load is measured at specific intervals to determine treatment response (see sidebar, page 38). Overall, studies find that pegylated interferon/ribavirin produces sustained virological response—generally regarded as a cure—in about 45% of previously untreated HCV monoinfected people with genotype 1 and about 70% to 80% of those with genotype 2 or 3.

The likelihood of sustained response is lower for “difficult-to-treat” patient populations, including people of African descent, individuals with advanced fibrosis or cirrhosis, and people with HIV/HCV coinfection.

However, some populations that have traditionally been considered poor treatment candidates can do well on therapy. One such group is injection drug users. Current U.S. treatment guidelines state that drug use should not be considered a contraindication to treatment and people should be evaluated on an individual basis.

Interferon/Ribavirin Side Effects

Interferon-based therapy is notorious for its difficult side effects. Concerns
about adverse events lead many people with hepatitis C to delay or refuse treatment, and interferon-free therapy is a major goal of drug development research.

Interferon treatment causes the same types of symptoms that occur when the immune system fights the flu: fever, fatigue, malaise, headache, loss of appetite, muscle and joint aches, and depression. It can also cause neutropenia (low white blood cell count), which increases the risk of bacterial infections.

Ribavirin can cause hemolytic anemia (low red blood cell count or low hemoglobin level). It also carries a risk of birth defects if used during pregnancy, so patients must use effective contraception.

Some research suggests that certain side effects may be more frequent or more severe among HIV/HCV coinfected individuals than among people with HCV alone, but this finding is not consistent. Furthermore, interferon and ribavirin can produce additive toxicities when used with antiretroviral drugs.

Blood cell deficiencies are a particular concern for coinfected people who take antiretrovirals that cause bone marrow suppression. Anemia is a common side effect of zidovudine (AZT; Retrovir), for example, necessitating caution when combining it with ribavirin. Ribavirin can also contribute to mitochondrial toxicity, raising concern about its use with didanosine or stavudine.

Fortunately, the modern antiretroviral drugs most widely used in high-income countries—including tenofovir (Viread), abacavir (Ziagen), efavirenz (Sustiva), atazanavir (Reyataz), darunavir (Prezista), and raltegravir (Isentress)—do not appear to cause clinically significant additive toxicities or interactions with interferon or ribavirin.

While side effects are without doubt a major concern for people considering interferon-based hepatitis C treatment, it is important to note that adverse events are highly variable and not everyone experiences debilitating symptoms.

“Everyone’s experience with treatment is different,” according to Brad Hare. “I’ve had patients who went on disability for a year, but others who keep right on working.”

Predictors of Response
A number of factors predict response to interferon-based therapy, including HCV genotype, HCV viral load, patient race/ethnicity, IL28B gene pattern, extent of liver fibrosis, metabolic abnormalities, prior treatment history, treatment adherence, and early response to therapy.

With regard to viral factors, HCV genotypes 1 and 4 are harder to treat than 2 or 3, and higher baseline HCV

HEPATITIS C TREATMENT RESPONSE

Treatment response is evaluated according to various criteria:

- Biochemical response: normalization of alanine aminotransferase (ALT)
- Histological response: improvement of liver health as assessed by biopsy, such as reduced fibrosis
- Virological response: decline or clearance of HCV RNA, indicating inhibition of viral replication

Virological response is assessed by measuring HCV viral load at specific time points during and after therapy:

- Rapid virological response (RVR): undetectable HCV RNA at week 4 of treatment
- Extended rapid virological response (eRVR): undetectable HCV RNA at both week 4 and a later time point during treatment (typically week 12)
- Complete early virological response (cEVR): undetectable HCV RNA at week 12 of treatment
- Partial early virological response (pEVR): at least a 2-log decrease in HCV RNA, but not undetectable, at week 12 of treatment
- End-of-treatment response (EOT): undetectable HCV RNA at the end of treatment (typically 24 or 48 weeks)
- Sustained virological response (SVR): continued undetectable HCV RNA after completion of therapy, considered to be a cure (SVR24); some researchers also assess SVR12 at 12 weeks after completion of treatment

Nonresponders who do not achieve SVR are classified further:

- Null responders: very little or no decrease in HCV RNA during treatment
- Partial responders: some decrease in HCV RNA, but not undetectable, during treatment
- Relapsers: undetectable HCV RNA at the end of therapy, but viral rebound after treatment ends

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viral load is associated with poorer treatment response.

Turning to host factors, patient sex and age appear to have a minor effect on treatment response—younger people and women tend to respond better—but race/ethnicity exerts a major influence. People of African descent do not respond as well to interferon-based therapy as other racial/ethnic groups. Asians tend to show the highest response rates, with whites and Latinos/Hispanics falling in between.

The Virahep-C study, which looked at approximately 400 previously untreated genotype 1 patients receiving pegylated interferon plus weight-adjusted ribavirin, found that the sustained response rate for white participants approached twice that of black patients (52% vs. 28%, respectively), with racial differences becoming evident as early as week 4. The IDEAL study clarified that while black patients are less likely to experience rapid response, those who do are about as likely as whites to achieve sustained response.

The reasons for racial disparities in treatment response are not yet fully understood, but recent evidence suggests that specific genetic variations can account for much of the difference. In 2009, researchers first reported that variations in the human genome near the IL28B gene strongly influence response to interferon-based therapy. This discovery helps clinicians better understand the pharmacogenomics of hepatitis C, or how to tailor therapy based on individual genetics.

This gene on chromosome 19 encodes interleukin 28 (also known as interferon lambda) and is thought to play a role in interferon-induced antiviral response. People of European descent are significantly more likely to carry favorable IL28B patterns than people of African descent.

The most frequently implicated single nucleotide polymorphism (SNP), or variation at a specific location, is rs12979860. People with two copies of the protective C variant are more likely to spontaneously clear HCV and respond better to interferon-based therapy; people with two copies of the unfavorable T variant have the worst outcomes, while those with a mixed CT pattern fall in between. Other SNPs have also been implicated in interferon response, including rs8099917 and rs12980275.

At CROI 2010, three research teams reported that the link between IL28B and interferon response also holds for HIV/HCV coinfected people, though later findings suggest the effect may not be as quite as strong as for HCV monoinfected individuals.

Norma Rallón and colleagues at Hospital Carlos III reported that 68% of treatment-naive genotype 1 or 4 coinfected patients with the CC pattern achieved sustained response to pegylated interferon/ribavirin, compared with 28% of those with CT or TT patterns (combined); the difference was not statistically significant, however, for patients with genotype 2 or 3.

Turning to health-related host factors, extent of liver damage is a strong predictor of treatment response, with more advanced fibrosis or cirrhosis associated with poorer outcomes. Obesity and metabolic abnormalities, including insulin resistance and diabetes, also predict lower likelihood of sustained treatment response.

Prior treatment history predicts response to a later round of therapy. Overall, treatment-naive people receiving interferon-based therapy for the first time have higher response rates than prior nonresponders. Among nonresponders, prior relapers have a higher likelihood of successful retreatment than prior partial responders, who in turn do better than prior null responders (see sidebar, page 38). A similar pattern holds for both HCV monoinfected and HIV/HCV coinfected people.

People who did not respond previously to suboptimal therapy (e.g., conventional interferon, pegylated interferon monotherapy, lower dose of interferon or ribavirin, or early drug discontinuation) are more likely to achieve a cure when retreated with standard-of-care therapy than people who have already received an optimal regimen.

Good adherence is an important factor in treatment success. As a rule, interferon-based therapy is most effective when people take at least 80% of the prescribed pegylated interferon dose and 80% of the recommended ribavirin dose for 80% of the complete course of therapy.

As noted, many people must reduce their drug doses or stop treatment early due to side effects. Additional medications such as erythropoietin can help patients stay on effective doses longer. Weight-adjusted dosing and possibly drug level monitoring may help ensure optimal ribavirin concentrations.

Viral kinetics, or changes in HCV RNA over the course of therapy, is another key factor. Rapid virological response (RVR) at week 4 and early virological response (EVR) at week 12 are good predictors of which patients will go on to achieve sustained response after completion of therapy. Some studies find that HCV RNA decline even during the first 24 hours is a good indicator of later response.

Early response is such a strong predictor of ultimate outcomes that treatment discontinuation is generally recommended if HCV RNA has not fallen by at least 2 logs by week 12, as further therapy is likely to be futile.

The same response predictors still come into play with combination therapy that includes pegylated interferon/ribavirin plus DAAs, but these potent targeted drugs can help overcome some factors that contribute to interferon failure. Further research is needed to determine which predictors will remain relevant when using interferon-free DAA regimens.

Interferon for HIV/HCV Coinfected People

HIV/HCV coinfected individuals tend to respond more slowly to interferon-based therapy; people with two copies of the protective C variant are more likely to spontaneously clear HCV and respond better to interferon-based therapy; people with two copies of the unfavorable T variant have the worst outcomes, while those with a mixed CT pattern fall in between. Other SNPs have also been implicated in interferon response, including rs8099917 and rs12980275.

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based therapy compared with HCV mono-infected individuals, and are more likely to relapse after the end of treatment; this is thought to reflect weaker immune response. The pivotal APRICOT trial, published in 2004, included 860 previously untreated coinfected participants with well-controlled HIV disease; most were on ART, a majority had undetectable HIV RNA, and the median CD4 count was more than 500 cells/mm³.

The international study team reported that 29% of patients with HCV genotype 1 and 62% with genotype 2 or 3 achieved SVR using pegylated interferon alfa-2A plus 800 mg/day ribavirin for 48 weeks (compared with approximately 45% and 75%, respectively, for people with HCV alone). Other studies of more difficult-to-treat coinfected populations, however, have produced less favorable outcomes, with sustained response rates as low as 14% for genotype 1 patients.

Looking at a more challenging population of coinfected people previously treated with suboptimal therapy, the Spanish PILOT study found that retreatment with pegylated interferon plus weight-adjusted ribavirin for 48 weeks produced SVR rates of 20% for patients with HCV genotype 1 or 4 and 73% for those with genotype 2 or 3. As is typical for retreatment studies, prior relapers did better than prior non-responders.

Researchers have explored longer durations, more frequent administration, and higher doses of pegylated interferon or ribavirin for coinfected patients, with mixed results. The Spanish PRESCO trial evaluated variable durations of pegylated interferon alfa-2A plus 1,000–1,200 mg/day weight-adjusted ribavirin in about 400 previously untreated coinfected participants. Among people receiving standard-duration therapy, SVR rates were 31% for genotype 1 patients treated for 48 weeks and 67% for genotype 2 or 3 patients treated for 24 weeks, comparable to APRICOT.

People who received longer therapy had higher cure rates—53% for genotype 1 patients treated for 72 weeks and 82% for genotype 2 or 3 patients treated for 48 weeks—but side effects were more frequent and many patients discontinued treatment.

A small study by Michael Polis and colleagues showed that twice-weekly pegylated interferon alfa-2A doubled the SVR rate of standard once-weekly dosing, from 18% to 40%. A multinational study by Allison Murphy and colleagues, described in the June 1, 2011, issue of AIDS, found that coinfected people were more likely to achieve rapid, early, and sustained virological response if they used pegylated interferon twice rather than once weekly, but more frequent dosing led to worse side effects.

In the PERICO study, presented at the recent AASLD meeting, Vincent Soriano’s team evaluated high-dose (2,000 mg/day) ribavirin given with prophylactic erythropoietin to prevent anemia during the first four weeks of pegylated interferon treatment. Coinfected patients randomly assigned to the high-dose ribavirin induction arm did not have a higher SVR rate.

In general, the same factors associated with response to interferon-based therapy in HCV mono-infected individuals also hold for HIV/HCV coinfected people, including HCV genotype and viral load, patient race/ethnicity and IL28B pattern, fibrosis stage, obesity and insulin resistance, prior treatment history, and adherence. Higher CD4 cell count and effective ART are also favorable factors.

RVR and EVR are good predictors of sustained response for HIV/HCV coinfected people, and most guidelines advise that coinfected patients also should stop treatment due to inadequate early response. Because HIV positive people tend to respond more slowly to interferon, however, some experts favor continuing therapy to compensate for delayed response.

The likelihood of successful treatment of HIV/HCV coinfected patients has risen in recent years, thanks to improved understanding of how best to treat this population and better control of HIV with modern ART. Though not yet approved for coinfected patients, the new DAAs promise further advances in the near future.

Benefits of Treatment

People who achieve sustained response with interferon-based therapy—both HCV mono-infected and HIV/HCV coinfected—lower their risk of fibrosis progression, hepatocellular carcinoma, end-stage liver disease, liver transplantation, and death.

Mark Sulkowski’s team looked at a composite endpoint of liver cancer, end-stage liver disease, and death among their coinfected patients at Johns Hopkins. Among people with stage F0–F1 fibrosis at baseline, the combined rates were 27 and 22 per 1,000 person-years (PY), respectively, for untreated people and non-responders, while there were no events among relapers or sustained responders. Among patients with baseline stage F2–F4 fibrosis, combined rates were 82, 57, and 22 per 1,000 PY for untreated individuals, non-responders, and relapers, respectively, and again zero for sustained responders.

Some studies have shown that successful treatment not only prevents disease progression, but can actually reverse liver damage. In an analysis of about 300 coinfected participants with well-controlled HIV, for example, José Luis Casado and colleagues found that 38% of pegylated interferon/ribavirin sustained responders experienced at least a 1-point reduction in fibrosis score and 24% had at least a 2-point decrease.

In a Spanish FibroScan study presented at ICAAC 2011, José Antonio Carton and colleagues showed that even unsuccessful treatment appeared to improve liver fibrosis in HIV/HCV coinfected people (especially relaps-
ers) in the short-term, although the effect persisted only in patients who achieved sustained response.

While this and other studies suggest that interferon-based therapy may have some benefit even in the absence of SVR, the HALT-C trial showed that long-term pegylated interferon maintenance therapy for nonresponders did not reduce the risk of cirrhosis, liver cancer, or death among HCV monoinfected patients. The SLAM-C trial likewise found that maintenance therapy did not prevent liver disease progression among coinfected people.

**Direct-Acting Antivirals**

Novel agents that directly attack HCV have ushered in a new era of hepatitis C treatment. Unlike interferon, DAAs interfere with various steps of the HCV lifecycle, similar to the way antiretroviral drugs work against HIV.

This past May the U.S. FDA approved the first two HCV DAAs, boceprevir (VICTRELIS) from Merck and telaprevir (Incivek) from Vertex Pharmaceuticals; both were approved in the European Union this summer. More than three dozen other DAA agents are currently in the development pipeline.

Most DAAs to date have been studied in combination with pegylated interferon/ribavirin, with the goal of increasing the likelihood of sustained response and shortening therapy. As described below, interferon-free regimens are also now under investigation.

**Targeting the HCV Lifecycle**

HCV is comprised of genetic material encased in a capsid shell surrounded by an outer envelope. The virus primarily infects hepatocytes; in order to replicate, it must attach itself to receptors on a host cell’s surface, enter the cell, and take over its machinery.

The HCV NS5B polymerase enzyme first copies the viral genome—a single strand of RNA—using nucleotide building blocks present in the host cell. HCV employs an RNA-dependent RNA polymerase, meaning it uses RNA as a template to produce more RNA strands; in contrast, retroviruses like HIV use RNA-dependent DNA polymerase (better known as reverse transcriptase) to produce DNA from viral RNA.

The newly created RNA strands serve as blueprints for production of the proteins and enzymes needed to construct progeny viral particles, or virions. The HCV NS3/4 protease enzyme processes these proteins so they can be assembled into new virions, which bud out from the host cell and go on to infect additional cells.

Boceprevir and telaprevir, the first two approved DAAs, are both HCV protease inhibitors. Other candidates in this class now in Phase II or III development include asunaprevir (BMS-650032), danoprevir (RG7227; ITMN-191), vaniprevir (MK-7009), BI 201335, GS 9256, GS 9451, and TMC435.

The ATLAS trial, described by Norah Terrault at AASLD 2011, was a Phase Ib dose-ranging study of danoprevir taken every eight or 12 hours plus pegylated interferon/ribavirin for 12 weeks, followed by 24 weeks of pegylated interferon/ribavirin alone. The combination produced SVR rates up to 85% for treatment-naive genotype 1 patients, rising to 96% for those with extended RVR. Danoprevir is also being tested with ritonavir to boost drug levels and reduce pill burden.

The Phase II SILEN-C1 study, also presented at AASLD 2011, showed that once-daily BI 201335 plus pegylated interferon/ribavirin for 24 weeks, again followed by pegylated interferon/ribavirin alone, produced consistently high SVR rates across difficult-to-treat patient subgroups, reaching 71% for genotype 1 patients with the unfavorable IL28B CT and TT patterns. A follow-up study, SILEN-C3, showed that rapid responders did equally well with 12 weeks of treatment.

Researchers are also testing numerous HCV polymerase inhibitor candidates. These include both nucleoside/nucleotide analogs such as mericitabine (RG7128), PSI-7977, and PSI-938, as well as non-nucleoside inhibitors such as filibuvir (PF-868554), setrobuvir (ANA598), tegobuvir (GS 9190), ABT-333, BI 207127, and VX-222.

PROTON, another Phase Ibb study presented at AASLD 2011, showed that 400 mg once-daily PSI-7977 plus pegylated interferon/ribavirin for 12 weeks, followed by pegylated interferon/ribavirin alone, demonstrated a 91% SVR12 rate for previously untreated mostly genotype 1a patients, with no viral breakthrough.

The promising daclatasvir (BMS-790052) is a NS5A replication complex inhibitor. The function of NS5A is not fully understood, but it appears to play an important role in viral replication. Other experimental agents in this class include ABT-267, GSK2336805, and PPI-461.

The Phase IIb COMMAND-1 study of previously untreated genotype 1 patients presented at AASLD 2011 found that about 75% of those treated with daclatasvir plus pegylated interferon/ribavirin had undetectable HCV RNA at week 12; just over 70% met the criteria for a shorter 24-week course of therapy, and within that group up to 100% achieved end-of-treatment response.

Several other types of hepatitis C therapies—some targeting the virus, others the host—are currently being explored. These include HCV entry blockers, cyclophilin inhibitors, helicase inhibitors, internal ribosomal entry site (IRES) inhibitors, and toll-like receptor agonists.

Cyclophilins are intracellular enzymes that play a role in protein folding and transport. One cyclophilin inhibitor now in development, alisporivir (formerly Debio 025), has demonstrated activity against HCV, HIV, and HBV in early studies. At EASL 2011 investigators with the ESSENTIAL trial reported that alisporivir boosted SVR rates when added to pegylated inter-
threatening complications. For liver disease progression and life-threatening complications, these individuals are at greatest risk. These are crucial areas of research, as with advanced cirrhosis, and people HIV/HCV coinfected people, patients to treat patient populations, including antiretroviral drugs, opiate substitution therapy such as buprenorphine, antidepressants, statins, and immnosuppressants used by transplant recipients.

Boceprevir and Telaprevir Efficacy

Boceprevir and telaprevir were approved in May 2011 for treatment-naive and treatment-experienced people with genotype 1 chronic HCV monoinfection. They are not yet indicated for HIV/HCV coinfected people, as clinical studies have not been completed. Data have not yet been presented on their safety and efficacy in patients with decompensated cirrhosis or liver transplant recipients.

Boceprevir and telaprevir are both taken three times daily with food and are used in combination with pegylated interferon and ribavirin. They are both administered using response-guided therapy (RGT), with treatment duration determined based on early viral load reductions. While this approach allows many people to achieve a cure with a shorter course of treatment, it adds considerable complexity for patients and providers.

Since the new DAAs come with their own adverse events—notably anemia with boceprevir and skin rash with telaprevir—people taking triple therapy may experience more side effects than they would with interferon/ribavirin alone. The trade-offs are the possibility of reduced treatment duration and higher likelihood of sustained response.

“Your're not necessarily going to feel better during treatment, but treatment might be shorter and it might work better,” Brad Hare summarized.

**Boceprevir**. Boceprevir treatment begins with a four-week “lead-in” period using pegylated interferon plus weight-adjusted ribavirin, before adding 800 mg boceprevir three times daily (every seven to nine hours).

Duration of triple therapy is determined based on response at weeks 8 through 24. If HCV RNA is undetectable at weeks 8 and 24, previously untreated patients can complete all treatment at week 28; prior partial responders and relapsers continue triple therapy until week 36. Regardless of prior treatment history, people whose HCV RNA is detectable at week 8 but undetectable at week 24 stay on triple therapy through week 36, then continue on pegylated interferon/ribavirin alone through week 48.

As described in the March 31, 2011, *New England Journal of Medicine*, the pivotal Phase III SPRINT-2 trial included 1,097 previously untreated genotype 1 chronic hepatitis C patients. One cohort included 159 black patients, while the other included 938 people of other racial/ethnic groups (“non-black”); about 10% had advanced fibrosis or cirrhosis.

After a four-week lead-in of pegylated interferon alfa-2b plus weight-adjusted ribavirin, participants were randomly assigned to either continue pegylated interferon/ribavirin alone or add 800 mg three-times-daily boceprevir. Boceprevir recipients were further randomized to either receive the triple combination for a fixed duration of 44 more weeks or use response-guided therapy; the shortest possible treatment duration was 28 weeks and the maximum was 48 weeks.

Sustained response rates at 24 weeks after completion of treatment were significantly higher for the boceprevir arms compared with the pegylated interferon/ribavirin control arm. In an intent-to-treat analysis, 68% of non-black patients receiving fixed-duration triple therapy and 67% using RGT achieved SVR, compared with 40% in the control group. Among black participants, the corresponding SVR rates were 53%, 42%, and 23%.

Relapse rates in both the fixed-duration and RGT boceprevir arms were...
significantly lower than in the control arm. Nearly half of non-black patients were eligible for shorter treatment, and almost all of these achieved SVR. Although black patients had a lower SVR rate and fewer were eligible for shorter treatment, they showed greater relative improvement over pegylated interferon/ribavirin alone.

Turning to treatment-experienced patients, the Phase III RESPOND-2 trial included 403 genotype 1 prior partial responders and relapers; prior null responders were excluded. Approximately 12% of participants were black and about 20% had advanced fibrosis or cirrhosis.

Again, all participants initially received pegylated interferon alfa-2b plus ribavirin for a four-week lead-in period and then were randomly assigned to continue on either pegylated interferon/ribavirin alone or triple therapy with 800 mg three-times-daily boceprevir. Here too, they either stayed on triple therapy for a fixed duration of 44 weeks or used RGT with durations ranging from 36 to 48 weeks.

Boceprevir recipients again had significantly higher SVR rates: 66% with fixed-duration therapy and 59% with RGT, compared with 21% in the pegylated interferon/ribavirin control group. Prior relapers taking boceprevir saw SVR rates up to 75%, compared with 52% for prior partial responders.

The most common treatment-related adverse events across all arms were fatigue, headache, and nausea. Anemia and dysgeusia (unusual taste sensations) were significantly more common among boceprevir recipients. More people treated with boceprevir stopped therapy, reduced drug doses, or used erythropoietin due to anemia.

Telaprevir. When using telaprevir, triple therapy is started from the beginning with no lead-in. The usual telaprevir dose is 750 mg three times daily (every seven to nine hours), administered with standard doses of pegylated interferon and weight-adjusted ribavirin.

All patients stop telaprevir at week 12, followed by response-guided continuation of pegylated interferon/ribavirin. Previously untreated people and prior relapers with undetectable HCV RNA at both week 4 and week 12 continue pegylated interferon/ribavirin alone through week 24; those with detectable viral load at week 4 or 12 continue through week 48. All prior partial and null responders receive triple therapy for the first 12 weeks then continue pegylated interferon/ribavirin alone through week 48.

As described in the June 23, 2011, New England Journal of Medicine, the pivotal Phase III ADVANCE trial included 1,088 previously untreated participants with genotype 1 chronic hepatitis C; 9% were black and 21% had advanced fibrosis or cirrhosis. Participants were randomly assigned to receive either triple therapy including 750 mg three-times-daily telaprevir plus pegylated interferon alfa-2a and 1,000–1,200 mg/day weight-adjusted ribavirin, or else pegylated interferon/ribavirin alone. Triple therapy patients received telaprevir for either eight or 12 weeks; duration of ongoing pegylated interferon/ribavirin was determined using RGT, up to 48 weeks.

SVR rates were significantly higher for participants who used telaprevir triple therapy for eight or 12 weeks (69% and 75%, respectively) compared with pegylated interferon/ribavirin alone (44%). Among black patients, 62% in the 12-week telaprevir triple therapy arm achieved SVR compared with 25% in the control arm. Nearly two-thirds were eligible for shorter treatment.

Looking at previously treated people, the Phase III REALIZE trial enrolled 663 treatment-experienced genotype 1 chronic hepatitis C patients including relapers, partial responders, and null responders; approximately 5% were black and about 25% had advanced fibrosis or cirrhosis. Again, participants were randomly assigned to receive 750 mg three-times-daily telaprevir with pegylated interferon alfa-2a and weight-adjusted ribavirin or else pegylated interferon/ribavirin alone. Everyone in this more difficult-to-treat population received telaprevir triple therapy for 12 weeks and continued pegylated interferon/ribavirin through 48 weeks; some started with a pegylated interferon/ribavirin lead-in.

Here too, SVR rates were significantly higher in the telaprevir arms compared with the pegylated interferon/ribavirin control arm. Sustained response rates did not differ, however, between the lead-in and simultaneous triple therapy arms.

Across all treatment arms, response rates were higher for prior relapers (88% in the lead-in telaprevir arm, 83% in the simultaneous telaprevir arm, and 24% in the control arm) than for prior partial responders (54%, 59%, and 15%, respectively), who in turn did better than prior null responders (33%, 29%, and 5%, respectively).

At AASLD 2011, Stanislas Pol and colleagues reported that REALIZE participants with liver cirrhosis who received telaprevir triple therapy had an SVR rate of about 50%. While this was well below the approximate 70% sustained response rate for non-cirrhotics, it was far better than the 8% rate with pegylated interferon/ribavirin alone.

Adverse events that occurred at least 10% more often in the telaprevir arms compared with the pegylated interferon/ribavirin control arms included nausea, pruritis, skin rash, and anemia; most rashes were mild-to-moderate, but about 5% were severe. Early discontinuation due to adverse events was more common among telaprevir recipients.

**DAAs and Coinfection**

While boceprevir and telaprevir are not yet indicated for people with HIV/HCV coinfection, physicians may prescribe FDA-approved drugs as
they see fit. The new DAAs improve treatment response rates for this population as well, but coinfection introduces additional challenges related to interactions with antiretroviral drugs and the potential for additive side effects.

**Boceprevir.** Mark Sulkowski reported the first data on boceprevir for HIV/HCV coinfected people in a late-breaker presentation at IDSA 2011. This Phase Ib trial included 100 previously untreated coinfected patients with HCV genotype 1; about 80% were white and 5% had cirrhosis.

All participants started with a four-week lead-in of pegylated interferon alfa-2b plus weight-adjusted ribavirin and then were randomly assigned to receive 800 mg boceprevir three times daily plus pegylated interferon/ribavirin or else pegylated interferon/ribavirin alone. Although many HCV monoinfected people achieve SVR with a shorter duration of treatment using RTG, all coinfected patients in this study received a full 48-week course.

All participants were on optimized ART with undetectable HIV RNA and a CD4 count of at least 200 cells/mm³. Based on prior drug-drug interaction studies, they were limited to regimens containing a boosted protease inhibitor plus two NRTIs (excluding didanosine, stavudine, or zidovudine).

Boceprevir is a strong inhibitor of the CYP3A4 enzyme, which metabolizes many medications in the liver. A study of interactions between boceprevir and antiretroviral drugs in healthy volunteers found that minimum concentrations of boceprevir fell by about 40% when administered with efavirenz; the investigators concluded that the clinical implications of this interaction are unclear. Ritonavir decreased boceprevir levels by about 20%, but this was not considered clinically relevant.

In an interim analysis, 59% of patients receiving boceprevir triple therapy achieved complete EVR at week 12, compared with 26% of those receiving pegylated interferon/ribavirin alone. At 24 weeks, 71% and 34%, respectively, had undetectable HCV RNA. HIV viral load did not change significantly in either group and both absolute CD4 cell count and CD4 percentage remained stable during hepatitis C treatment.

Boceprevir was generally well tolerated; study participants taking boceprevir were at least 10% more likely to experience fever, headache, vomiting, and dysgeusia, but rates of anemia were similar in both treatment groups. According to the researchers, “the safety and tolerability profile was similar to that observed in HCV monoinfected patients.”

This ongoing study will follow patients through 24 weeks post-treatment to determine SVR; a Phase III coinfection study is expected to start this year.

**Telaprevir.** Sulkowski presented the first data from a Phase II clinical trial of telaprevir plus pegylated interferon alfa-2a and ribavirin for genotype 1 coinfected patients at CROI 2011; updated results were presented in a late-breaker poster at AASLD 2011. The analysis included 60 participants, about one-third of whom were black; two patients (3%) had cirrhosis.

Study 110 had two parts. Part A enrolled antiretroviral-naive participants who had CD4 cell counts high enough that they did not yet need HIV treatment (at least 500 cells/mm³). Part B enrolled people with at least 300 cells/mm³ on a stable ART regimen containing either efavirenz (Sustiva) or boosted atazanavir (Reyataz), both with tenofovir/emtricitabine.

These antiretroviral regimens were chosen based on prior laboratory research and studies of healthy volunteers indicating that they are not likely to have clinically relevant interactions with telaprevir.

Telaprevir is both a substrate and an inhibitor of CYP3A4. A drug-drug interaction study found that telaprevir levels decreased by 30% to 50% when administered with the HIV protease inhibitors darunavir/ritonavir, fosamprenavir/ritonavir, or lopinavir/ritonavir; telaprevir also lowered concentrations of these drugs. Conversely, telaprevir levels remained relatively stable when used with atazanavir, though atazanavir levels increased.

Efavirenz reduced telaprevir levels somewhat, but raising the telaprevir dose from 750 to 1,125 mg three times daily overcomes this pharmacological interaction. A later study showed that telaprevir increased concentrations of the HIV integrase inhibitor raltegravir by about 30% (possibly due to inhibition of P-glycoprotein), but researchers did not consider this clinically relevant.

Participants in both parts of Study 110 were randomly assigned to receive either telaprevir/pegylated interferon/ribavirin triple therapy or pegylated interferon/ribavirin alone for 48 weeks.

After 12 weeks on treatment, 79% of people using telaprevir triple therapy experienced complete EVR compared with 27% of those using pegylated interferon/ribavirin alone. Among people who reached 24 weeks of treatment, 71% of telaprevir recipients and 55% of those using pegylated interferon/ribavirin alone had undetectable HCV RNA (an unusually high rate for a coinfected control group).

Although numbers were small, people taking atazanavir appeared not to respond as well to telaprevir triple therapy as those taking efavirenz or no ART (67% vs. 75% vs. 86%, respectively, at week 24); in fact, among atazanavir recipients, triple therapy had a lower SVR rate than pegylated interferon/ribavirin alone.

HIV viral load did not change significantly in any group during hepatitis C treatment. Absolute CD4 cell count declined across the board, but CD4 percentage remained stable.
Telaprevir recipients experienced more adverse events overall than those on pegylated interferon/ribavirin alone, but serious adverse events were uncommon. Side effects that occurred at least 10% more often in the telaprevir arm included pruritis, rash, headache, nausea, fever, depression, and insomnia; no serious rashes were reported. Frequency of anemia was similar in both groups (18%).

According to Jürgen Rockstroh from the University of Bonn, side effects generally were not more common among HIV/HCV coinfected participants than among HCV monoinfected people. This was “one of the bigger surprises,” he said at a June meeting of advocates in Sitges, Spain, given that concern about adverse events has been a reason for hesitation to treat coinfected patients. The notable exception was the high likelihood of elevated bilirubin among coinfected people taking atazanavir.

Ongoing analysis will show whether response is sustained after completion of treatment.

Vertex has indicated that it will soon begin enrollment of a Phase III trial of telaprevir response-guided therapy in coinfected patients. In the Phase II study, 61% of telaprevir recipients had undetectable HCV RNA at both week 4 and week 12—the RGT threshold for HCV monoinfected people—suggesting that some coinfected patients, too, might be able to clear the virus with a shorter duration of therapy.

**Interferon-Free DAA Combinations**

While the first DAAs have been tested and approved for use in combination with pegylated interferon/ribavirin, development of interferon-free regimens is proceeding apace. Several clinical trials are evaluating all-oral combinations, including protease inhibitors plus polymerase inhibitors, nucleoside/nucleotide analogs plus non-nucleoside polymerase inhibitors, and various DAAs plus ribavirin.

The INFORM-1 study was the first to combine two DAAs without pegylated interferon or ribavirin: the HCV protease inhibitor danoprevir plus the polymerase inhibitor mericitabine. As described in the October 30, 2010, issue of *The Lancet*, at the end of this small 14-day study HCV RNA decreased by a median of about 5 logs in both previously untreated participants and prior null responders.

AASLD 2011 featured a plethora of data from studies of interferon-free regimens. The ELECTRON trial showed that a dual oral combination of PSI-7977 plus ribavirin for 12 weeks produced 100% SVR in previously untreated people with HCV genotypes 2 or 3. Adding pegylated interferon for four, eight, or 12 weeks did not improve efficacy, but significantly increased adverse events.

Because the researchers were uncertain whether this stripped-down regimen would work, they enrolled relatively easy-to-treat patients who could be “rescued” with existing therapy, explained investigator Edward Gane. Pharmasset is now enrolling additional cohorts to test PSI-7977/ribavirin in genotype 1 patients and prior nonresponders.

Kazuaki Chayama from Hiroshima University in Japan presented data from a Phase II study of the NS5A inhibitor daclatasvir plus the protease inhibitor asunaprevir for 24 weeks in genotype 1b prior null responders. By eight weeks, 90% had undetectable HCV RNA and all of them went on to achieve SVR. The regimen was generally well tolerated, with diarrhea and headache being the most common side effects.

In the Phase II SOUND-C2 trial, 76% of treatment-naive genotype 1 patients achieved undetectable viral load at week 12 with the HCV protease inhibitor BI 201335 once

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**HEALTHY LIVER TIPS FOR PEOPLE WITH HEPATITIS C**

- Get vaccinated against hepatitis A and hepatitis B if not already immune.
- Avoid or cut down on alcohol consumption, which contributes to liver damage.
- Be cautious about using prescription drugs, over-the-counter medications, street drugs, and herbal remedies; inform health-care providers about all drugs and herbs used.
- Eat a healthy, well-balanced diet.
- Get regular moderate exercise.
- Get adequate sleep at night and rest during the day as needed to help manage fatigue.
- Get regular health check-ups, including monitoring of HCV viral load, liver enzymes, and blood cell counts.
- Undergo liver biopsy or noninvasive evaluation as recommended to assess fibrosis progression.
- People with advanced liver disease should be monitored regularly for liver cancer.
daily plus the polymerase inhibitor BI 20127 twice daily plus ribavirin; response fell to 57% when ribavirin was omitted.

Researchers, regulators, and advocates are hashing out how best to develop novel combination therapy: Must all DAA regimens be tested against pegylated interferon/ribavirin alone? Can DAA combinations be tested in difficult-to-treat groups such as coinfected patients without prior separate studies of each individual agent? And will drugs tested together have to be approved and prescribed together?

Findings such as those presented at AASLD have been received with excitement because many people with hepatitis C—both those considering treatment for the first time and those with unsuccessful prior attempts—are eagerly awaiting all-oral, interferon-free regimens. But their wait is not yet over.

“All-oral regimens won’t be available for prescription for probably three to five years,” estimates Brad Hare. “Some people may want to wait, but some may decide to give [boceprevir or telaprevir with interferon] a try.”

Conclusion

Treatments for both HIV and hepatitis C have improved dramatically over the past decade, and many coinfectcd people can be successfully treated for both diseases. Recent research indicates that people with well-controlled HIV disease and relatively high CD4 cell counts can do nearly as well as those with HCV alone.

Conflicting study findings are a common thread throughout hepatitis C research, underlining the wide variability across individuals and patient populations. Many factors contribute to HCV disease progression and treatment response, making it difficult to predict who will need therapy, how long they can wait, and what regimens might work best.

AASLD published updated hepatitis C treatment guidelines in the October 2011 issue of Hepatology that include information about how to use the recently approved DAAs. The revised guidelines state that the optimal therapy for genotype 1 chronic HCV infection is boceprevir or telaprevir in combination with pegylated interferon/ribavirin, making triple therapy the new standard of care.

Several lessons learned from HIV have been fruitfully applied to the development of therapies for HCV, and hepatitis C treatment is now approaching the complexity of antiretroviral therapy. This complexity is multiplied when treating people with both viruses.

Managing response-guided therapy, side effects, drug interactions, and viral resistance will require education of both patients and providers. Ideally the care of HIV/HCV coinfected people should be managed by clinicians who have experience with both diseases, or by teams that include both liver disease specialists and infectious disease experts.

Unlike HIV, HCV does not integrate itself into the host cell genome and form a persistent reservoir. This means that hepatitis C treatment for a relatively short duration can permanently clear the virus. Some experts expect that with the new therapies coming down the pipeline, almost everyone with hepatitis C will have good prospects for a cure.

Unfortunately, high prices may prevent many people from taking advantage of the new treatments. The longest courses of boceprevir and telaprevir both cost around $48,000 each, more than tripling the $30,000 tab for pegylated interferon/ribavirin alone.

A study at AASLD 2011 found that first attempting treatment with pegylated interferon/ribavirin dual therapy is more cost-effective than initial triple
therapy for people who are likely to be good responders; public payers and insurance companies will no doubt be paying close attention to such findings in the coming years.

The approval of the first direct acting anti-HCV agents is “groundbreaking,” in the words of Brad Hare, but the revolution in treatment has just begun. “We anticipate that in the next few years many more hepatitis C drugs will become available, so it’s a big change—but it’s really just the beginning of a change.”

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