Care and Treatment for

HEPATITIS C and HIV COINFECTION

EXPANDING ACCESS Through the Ryan White CARE Act

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CONTENTS

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While attending the memorial of a coinfected patient who had died from end-stage liver disease, a colleague asked me why I wasn't treating my coinfected patients for hepatitis C. Referring them to a gastroenterologist wasn't working. I was concerned about treating patients with psychiatric comorbidities and/or ongoing substance use.

My colleague encouraged me to figure out how, rather than whether, to deliver care to these patients . . . or we would continue to attend funerals of patients dying prematurely from complications of hepatitis C. Since then, my role has changed from gloom and doom—warning patients about side effects—to one of providing education and support and encouraging patients to try HCV treatment.[1]

—Lynn E. Taylor, MD
Miriam Hospital, Providence, RI

I. INTRODUCTION

Prevalence of the hepatitis C virus (HCV) may be as high as 30 percent among people living with HIV/AIDS (PLWHA) and as high as 90 percent among PLWHA who contracted HIV infection through injection drug use (IDU). End-stage liver disease associated with HCV is now a major cause of death among PLWHA.[2-4]

Today, the standard of care is for all PLWHA to be screened for HCV and for all coinfected patients to receive comprehensive care services. Evidence suggests that this is not happening—and for many reasons.

The purpose of this publication is to help Ryan White Comprehensive AIDS Resources Emergency (CARE) Act planners, administrators, and providers address those reasons, deal with barriers to care faced by those in need, and construct a response to HIV/HCV coinfection that reflects the current standard of care.

This guide comes at a time of intense pressure on the HIV care system arising from such factors as rising health care costs and growing HIV prevalence among the poor and uninsured. It reflects that providers must cope with these difficult issues. But this publication also is full of optimism, reflecting that providers of HIV/AIDS services already have much of the capacity necessary for providing some services required by coinfected people—and that the financial barriers to ensuring access to comprehensive care that includes HCV treatment may not be as significant as may first appear.

Nonetheless, navigating the road that leads to a better system of care for coinfected patients requires commitment—the same kind of commitment that providers have shown throughout 25 years of HIV/AIDS. In this publication, the U.S. Department of Health and Human Services, Health Resources and Services Administration (HRSA) urges organizations to make that commitment and provides a framework for ensuring that comprehensive services are extended to all HIV/HCV-coinfected patients.

HCV antibody status may be a marker for poorer access to care and competing problems with addiction that lead to delays in care and failure to implement the standard of care. . . . [I]f we are to improve the health status of patients with HIV/HCV coinfection, perhaps we should focus on these issues as well the presence of the two viruses.[5]

—Graham and Koziel (2003)

2. HIV/HCV COINFECTION

HIV/HCV coinfection in the United States requires that HIV/AIDS service providers, health planners, and administrators acquire an understanding of how coinfection affects the health and well-being of their clients, and then build systems of care that respond to those effects.

But comprehending the consequences of HIV/HCV coinfection is difficult without first being familiar with the natural history of HCV monoinfection.

HCV 101

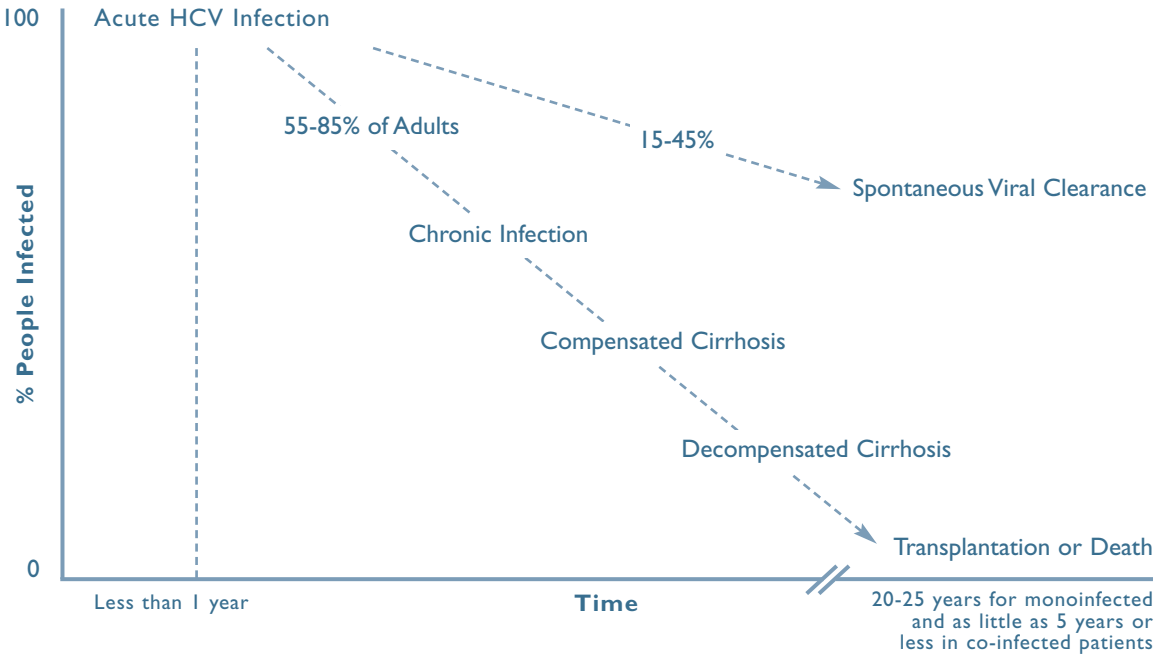
HCV is the most common blood-borne infection in the United States: At least 3.8 million people have been infected.[6]

Previously, the blood supply was a major mode of HCV transmission, but now that the blood supply is thoroughly screened for the virus, IDU with shared, unsterilized equipment accounts for 68 percent of new HCV infections.[7] HCV is also transmitted perinatally, from improperly sterilized dialysis equipment, and through unprotected sex with an infected partner. Cohort studies report that men who have sex with men (MSM) and people who have other sexually transmitted infections are at greater risk for contracting HCV from unprotected sex.[8-11]

Unlike HIV, HCV infections are not always chronic; some people clear the virus spontaneously (without treatment), usually within a few months after infection. That said, most people who are infected with HCV—55 to 85 percent—will develop chronic HCV infection.[7,12-16]

The course of HCV varies considerably, making it difficult to predict disease progression (Figures 1 and 2).

Figure 1. Sequence of Events After Acute HCV Infection



Source: Substance Abuse and Mental Health Services Administration, Unpublished data; 2005.

- Chronic HCV infection may be asymptomatic, with minimal to no liver disease, or it may present with mild to moderate liver disease (fibrosis).[17-22]
- An estimated 20 percent of people with chronic HCV infection will progress to cirrhosis over a 20- to 50-year interval.[20-22] A greater proportion of HIV/HCV-coinfected people may progress to cirrhosis (serious liver scarring), and liver disease progression is more rapid among those who are coinfected than among those with HCV alone.[23-26]
- Alcohol consumption, aging, and duration of HCV infection promote liver disease progression.
- Each year, 1 to 5 percent of people with HCV-related cirrhosis develop hepatocellular carcinoma.[27,28]
- In the United States, liver disease due to chronic HCV infection is the leading indication for liver transplantation.[29]
- Annually, at least 8,000 to 12,000 deaths are attributed to complications from chronic HCV infection.[26,30]

Figure 2. Natural History of HCV and Effects of Coinfection

Acute Infection and Early Symptoms

Of all people who contract HCV infection, just 20 percent have acute symptoms, such as fever, fatigue, loss of appetite, abdominal pain, nausea, vomiting, and jaundice. The absence of early symptoms is one of several reasons that HCV, like HIV, often goes undetected for some time after seroconversion.

Monoinfection	Coinfection
Chronic HCV Infection	
From 15 to 45 percent of monoinfected patients will clear HCV without treatment, an outcome that is known as spontaneous viral clearance. Of the remainder (55 to 85 percent), a portion will clear the virus after treatment, but most will live with HCV for the rest of their lives.	**In coinfected patients, spontaneous viral clearance and clearance with treatment occurs less frequently than among monoinfected patients.**
Fibrosis	
About 80 percent of monoinfected patients with chronic infection develop fibrosis (mild liver scarring) or experience symptoms such as depression and fatigue.	**Coinfected patients with chronic infection are more likely to develop fibrosis or symptoms than monoinfected patients.**
Cirrhosis	
From 20 to 30 percent of monoinfected patients with chronic infection develop cirrhosis (serious liver scarring) from 15 to 50 years after infection.	**Coinfected patients are more than twice as likely as monoinfected patients to develop cirrhosis, and they may develop it much more rapidly—in as little as 10 years after infection.**
Liver Cancer and Hepatic Decompensation (Loss of Liver Function)	
Every year, from 1 to 5 percent of people with cirrhosis develop liver cancer. People with cirrhosis are also at risk for hepatic decompensation.	**Coinfected patients may be at greater risk for liver cancer than are monoinfected patients. Their risk is six times greater for hepatic decompensation, and their survival after decompensation develops is significantly shorter.**

HIV/HCV Coinfection

The prevalence of HCV coinfection is higher than most people realize. In the United States, HCV prevalence among all PLWHA is estimated to be 15 to 30 percent, and it is more than three times higher—from 50 to 90 percent—among people who acquired HIV through IDU.[2-4] People who are coinfected with HCV and HIV are more likely than those with HCV alone to develop end-stage liver disease because HIV accelerates progression of HCV. Hepatitis C can be treated, even in PLWHA. End-stage liver disease is preventable in many patients: The first steps are educating patients about HCV, providing appropriate screening and diagnosis, and assessing the need for HCV treatment, all in a supportive context.

Table 1. Snapshots: HCV Prevalence Among People Who Are HIV-Positive[2,31-35]

Cohort	Sample Size	Total HCV Prevalence (%)	Prevalence in Subpopulations
Adult AIDS Clinical Trials Group (AACTG)	213	16.1	72.7% among "high-risk" group (participants with hemophilia or history of injection drug use)
AIDS Linked to the Intravenous Experience (ALIVE) Cohort Baltimore, MD	934	97.6	*
Community Programs for Clinical Research on AIDS (CPCRA)	2,705	16.6	61.9% among participants with a history of injection drug use
San Francisco Community Health Network	2,859	39.4	*
HIV Atlanta Cohort Study (HIVACS)	970	31.6	*
New York City, Cohort of HIV-Positive Current & Former Injection Drug Users	557	75.0	*

*Data not provided.

HCV is an opportunistic infection of HIV disease. In the era of highly active antiretroviral therapy (HAART), HCV coinfection has become a prominent contributor to morbidity and mortality among PLWHA.

Many experts regard HCV infection as a "different animal" in PLWHA, because liver disease progresses more rapidly in people who are HIV positive. HCV-associated liver damage appears to be more likely to develop in HIV/HCV-coinfected people than in those with HCV monoinfection. Coinfected people with <200 CD4 cells/mL are at greatest risk for end-stage liver disease.[36-38]

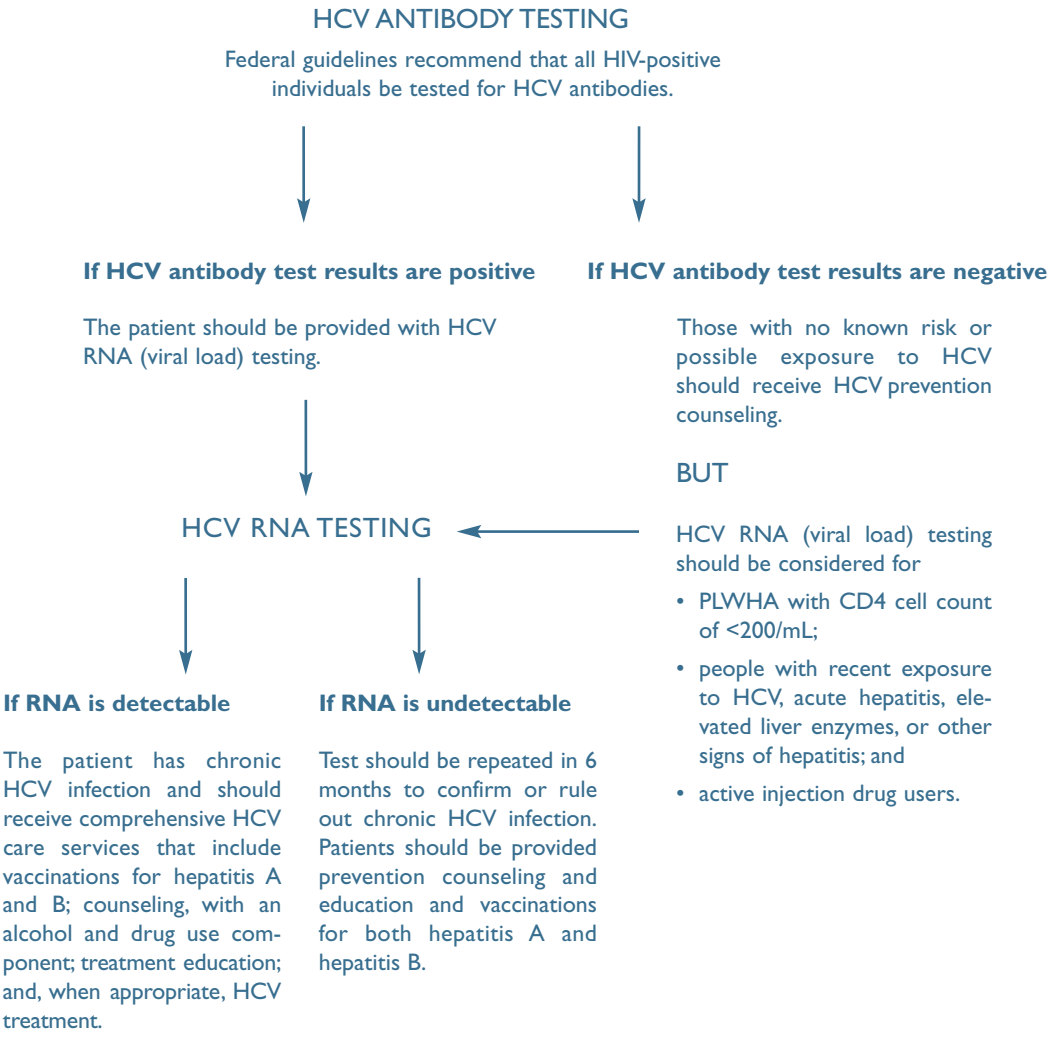
One study evaluated paired liver biopsies from 61 coinfected patients and found that liver disease progressed by two stages or more in 28 percent (17 of 61 participants) over an interval of less than 3 years.[39] A similar study in people with HCV monoinfection reported that only 11 percent (23 of 210 participants) progressed by two stages or more in a similar time period (median of 2.5 years).[40]

A meta-analysis of eight studies reported that coinfected patients were twice as likely to develop cirrhosis than patients with HCV alone. They had a sixfold greater risk for hepatic decompensation (decreased liver function due to damage for which the liver cannot compensate).[41]

HCV Diagnostic Testing

Federal guidelines recommend that all PLWHA be tested for HCV.[30,42-45] Antibody testing is not sufficient for diagnosing chronic HCV infection, however, because some people spontaneously clear the virus without treatment but remain antibody positive. A hepatitis C viral load (HCV RNA) test is necessary to confirm or rule out chronic HCV infection (Figure 3). Studies have reported spontaneous viral clearance rates from 15 to 45 percent in HIV-negative persons.[7,12-16] Although spontaneous viral clearance is less likely to occur among people who are HIV positive, some PLWHA, particularly those with higher CD4 cell counts, do spontaneously clear HCV infection.[46-51]

Figure 3. HCV Testing: Diagnostic Algorithm for HIV-Positive Patients



Prior, resolved infection can be distinguished from chronic infection by the presence of HCV antibodies and the absence of detectable HCV RNA (Table 2).

- HCV RNA is usually detectable within 2 weeks after infection.[52]
- HCV antibodies usually develop 6 weeks to 6 months after infection.[13] People who have cleared HCV are no longer infected, although antibodies usually remain in the bloodstream for years after spontaneous viral clearance.

All positive HCV antibody results should be confirmed by testing for HCV RNA, but the costs for doing so may be prohibitive in some clinical settings. Thus, to hold down costs, some providers may delay RNA testing until patients are considering treatment or require biopsy. HCV antibodies do not always develop in immunocompromised people, so when HCV infection is suspected or symptoms are present in HCV antibody–negative patients with a CD4 cell count of less than 200/mL, HCV RNA testing should be performed to confirm or rule out chronic HCV infection.[53,54]

Table 2. Diagnosing Hepatitis C

Diagnosis	Test for HCV Antibodies	HCV RNA	Alanine Aminotransferase
Resolved HCV	Positive	Undetectable; perform a second HCV RNA 6 months later to confirm resolved infection	May be normal, may fluctuate, or be elevated (for other reasons)
Acute HCV	Negative; may seroconvert to positive	Detectable; initially very high	May be as high as 7 to 10 times the upper limit of normal
Chronic HCV	Positive (may be negative if CD4 cell count is <200/mL; if HCV is suspected, test for HCV RNA)	Detectable	May be persistently normal, persistently elevated, or fluctuate

The CARE Act community is already familiar with the consequences of late diagnosis of HIV disease. Delayed diagnosis of HCV in people who are HIV/HCV coinfected also may have serious consequences. Unfortunately, clinicians are reporting that coinfected patients often are evaluated for HCV treatment after they have developed cirrhosis or end-stage liver disease and may be ineligible for HCV treatment.[55-57] Those patients still require care, however, and cirrhotic patients should be screened for varices and hepatocellular cancer.[58]

Hepatitis A and Hepatitis B Vaccination

Federal guidelines recommend vaccination against hepatitis A (HAV) and hepatitis B (HBV) for people with chronic HCV, HIV, or both.[30,42-45,59] Becoming infected with another hepatitis virus has serious consequences for people with HIV/HCV coinfection:

- HAV can cause sudden hepatic failure in people with chronic HCV.[60,61]
- Coinfection with HBV and HCV has been associated with more rapid HCV disease progression.[30,62]

Although vaccinations against HAV and HBV are an important part of care for HIV and HCV, research indicates that vaccination rates are low. A review of HAV and HBV screening and vaccination practices at nine HIV Outpatient Study sites reported wide

Acute HCV Infection

Acute HCV infections are often undiagnosed because only 20 percent of acutely infected people experience symptoms, such as fever, fatigue, loss of appetite, nausea, and vomiting.[63] Diagnosing acute HCV is important, because it offers an opportunity for improving treatment outcomes (see Treatment of Acute HCV, p. 27).

variability among sites. Of 1,071 patients, 57.2 percent (612) were screened for HAV, and 81.9 percent (877) were screened for HBV, yet only 23.3 percent of those eligible for vaccination against HAV (167 of 716) received one or more doses of HAV vaccine, and just 32.4 percent (198 of 612) of eligible patients received one or more doses of HBV vaccine. In HIV-positive people, vaccination for HAV and HBV is preferable when CD4 cell counts are higher than 200/mL because the immune response to HAV and HBV vaccination decreases at lower CD4 cell counts.[64-66]

Counseling and Support

Successful HCV care programs offer education and counseling, beginning at the initial screening for HCV antibodies.[55-57,67-70] Counseling and education must be an ongoing part of care, regardless of whether HCV treatment is initiated. In the context of HCV treatment, these valuable services support adherence to HCV treatment and remain beneficial after treatment has been completed (see box, Essential Elements of HCV Education and Support).

HCV counseling must include an alcohol abuse component, because in some cases, abstaining from alcohol may be the most important intervention for HCV. A safe amount of alcohol intake for people with chronic HCV has not been identified.[71-72] Thus, it is particularly important for providers to assess alcohol use in coinfected patients, and then offer information, resources, and support on reducing or abstaining from alcohol. Alcohol consumption, particularly more than 50 g per day (approximately four mixed drinks or glasses of wine or beer) causes and accelerates liver damage in people with HCV and increases HCV viral load, which may compromise the efficacy of HCV treatment.[23,73-75] Options to help patients reduce or eliminate alcohol intake include referral to counseling, 12-step programs, alcohol treatment programs, and pharmacotherapy with naltrexone or acamprosate.[76-78]

Alameda County Medical Center's coinfection clinic is an example of a successful program. One component is a weekly education and support group, which began in February 2002. Each 2-hour meeting includes lunch and an educational session, which is followed by an opportunity for members to share experiences and socialize. Initially, mono- and coinfected patients treated for HCV at other sites were recruited as mentors. After the first group participant initiated HCV treatment without serious side effects, a "snowball effect"

was reported: Within a few months, six participants had started HCV treatment. Although demographically diverse, the group is quite cohesive. Participants call one another between meetings, offer each other transportation to medical appointments, and continue to visit long after they have completed HCV treatment.[57-68]

For reasons ranging from the nature of HCV progression to the efficacy of available treatments, as well as the cost of treatments, most people living with HCV, regardless of HIV status, will never undergo HCV drug treatment. In fact, the U.S. Department of Veterans Affairs has identified 270,000 HCV-infected veterans since implementing HCV screening and testing, yet between 1996 and 2003, just 8 percent were ever treated.[79]

HIV/HCV Coinfection, Pregnancy, and Perinatal Transmission

People with HIV/HCV coinfection have higher serum HCV viral loads than those with HCV infection alone.[80] HCV has been detected in the semen of HIV/HCV-coinfected men[81,82] and in the genital tracts of coinfected women.[83] Thus, HIV-positive female partners of men with HCV infection should be tested for HCV and counseled about the risk of sexual and perinatal transmission of the virus.

Among coinfected women, the risk of perinatal transmission of HCV is approximately 17 percent, or four to five times greater than that among women with HCV monoinfection.[84,85] Although treatment for chronic HCV infection is contraindicated during pregnancy, coinfected mothers can reduce the risk of vertical transmission of HIV and HCV with antiretroviral therapy and cesarean delivery. A recent study reported that either elective or urgent cesarean delivery reduced the rate of perinatal transmission of HCV among coinfected women from 17.3 to 8.3 percent.[86] Because infants may carry maternal antibodies for up to 18 months, HCV viral load testing should be used to diagnose HCV infection in children under 18 months old.

Figure 4. Essential Elements of HCV Education and Support

At Screening

- What is HCV?
- HCV transmission, reinfection, and risk reduction
- Diagnosis of HCV: acute, chronic, and cleared infection
- Importance of vaccination against hepatitis A and B

After Diagnosis

- Natural history of HCV in HIV/HCV-coinfected patients
- Reduction or elimination of alcohol intake
- Drug use and risk reduction (counseling to reduce exposure to blood-borne pathogens and infections or referral to methadone, buprenorphine, counseling, support, or other drug and alcohol treatment programs)
- Risks and benefits of HCV treatment
- Use of complementary and alternative therapies
- Nutrition
- Possible implications for HIV treatment and other medical therapies

When Considering Treatment

- Timeline for new HCV therapies
- Evaluation for treatment (HCV RNA, genotype, biopsy, other tests)
- Strategies for managing side effects
- Effect of HCV treatment on absolute CD4 cell count, relationship of absolute number to CD4 cell percentage
- Making a treatment decision
- Potential interactions among antiretroviral medications, HCV treatment, and other medical therapies
- Development of a treatment plan
- Discussion of mental health, especially history of depression and stabilization as necessary
- Decision about starting prophylactic antidepressant treatment in those with a history of depression

When Undergoing Treatment

- Strategies for managing side effects
- Monitoring for drug interactions and toxicities
- Treatment efficacy at Week 12, Week 24, Week 48, and Week 72
- Self-assessment for depression and anxiety and treatment as necessary

Table 3. Establishing a Coinfection Clinic

Educate clinic staff by establishing linkages with other sites that have expertise in treating HIV/HCV coinfection. Arrange visits to learn firsthand about HCV treatment. Hold joint journal club meetings for HIV clinicians and liver specialists to review current HCV treatment information. Connect with other treatment providers to talk about their experience and models. Stay informed about HCV treatment with Internet resources (see Chapter 7).

Don't reinvent the wheel. Consult with other providers who are treating coinfected patients to see their protocols, monitoring forms, and checklists.

Arrange space for your coinfection clinic, even if it is only available once a month. Make sure that it includes space for one-on-one education and counseling sessions.

Collaborate with other specialists to seek their advice when necessary and develop or adopt interdisciplinary treatment protocols.

Prepare for situations in advance: If you are seeing patients who live in rural areas, contact staff at their local hospital emergency departments to prepare them for the possibility of patients experiencing serious adverse events.

Develop linkages with mental health providers if mental health care is not available onsite.

Consider borrowing or buying a portable ultrasound so that biopsies can be performed onsite, instead of referring patients to another site.

Encourage patients who are having an off-site biopsy by offering to have a nurse or peer escort them.

Table 3 (cont'd.) Establishing a Coinfection Clinic

Design treatment plans according to each patient's individual situation and needs.

- Comprehensive psychiatric assessment prior to initiation of treatment may not be necessary for all patients.
- If the patient engages in ongoing opioid misuse, consider prescribing buprenorphine (or facilitating access to a facility authorized to prescribe it), or provide referral to methadone maintenance or other substance abuse treatment programs.
- Some clinics do not require that patients undergo biopsy before treatment, while others require it only for patients with HCV genotype 1. Patients with genotype 1 are less likely than those with genotypes 2 or 3 to respond to HCV treatment; performing a biopsy for genotype-1 patients can identify those who need treatment versus those with mild liver damage, who can defer treatment. When biopsy presents a substantial barrier for otherwise willing patients, some centers offer treatment without one.
- Some clinicians and patients may be more comfortable with directly observed therapy (DOT) for the weekly injection of pegylated interferon. DOT also provides an opportunity to monitor clinical and neuropsychiatric side effects.

Discuss treatment plans during case conferences with mental health providers, clinic staff, and specialists.

Be creative about finding resources for your patients: Consider referring coinfected patients to a clinical trial, if appropriate. Some patients may be able to access treatment from pharmaceutical company–sponsored patient assistance programs or AIDS Drug Assistance Programs (see Access to HCV Treatment and ADAPs, p. 42). Look into free care programs at local hospitals to cover biopsies.

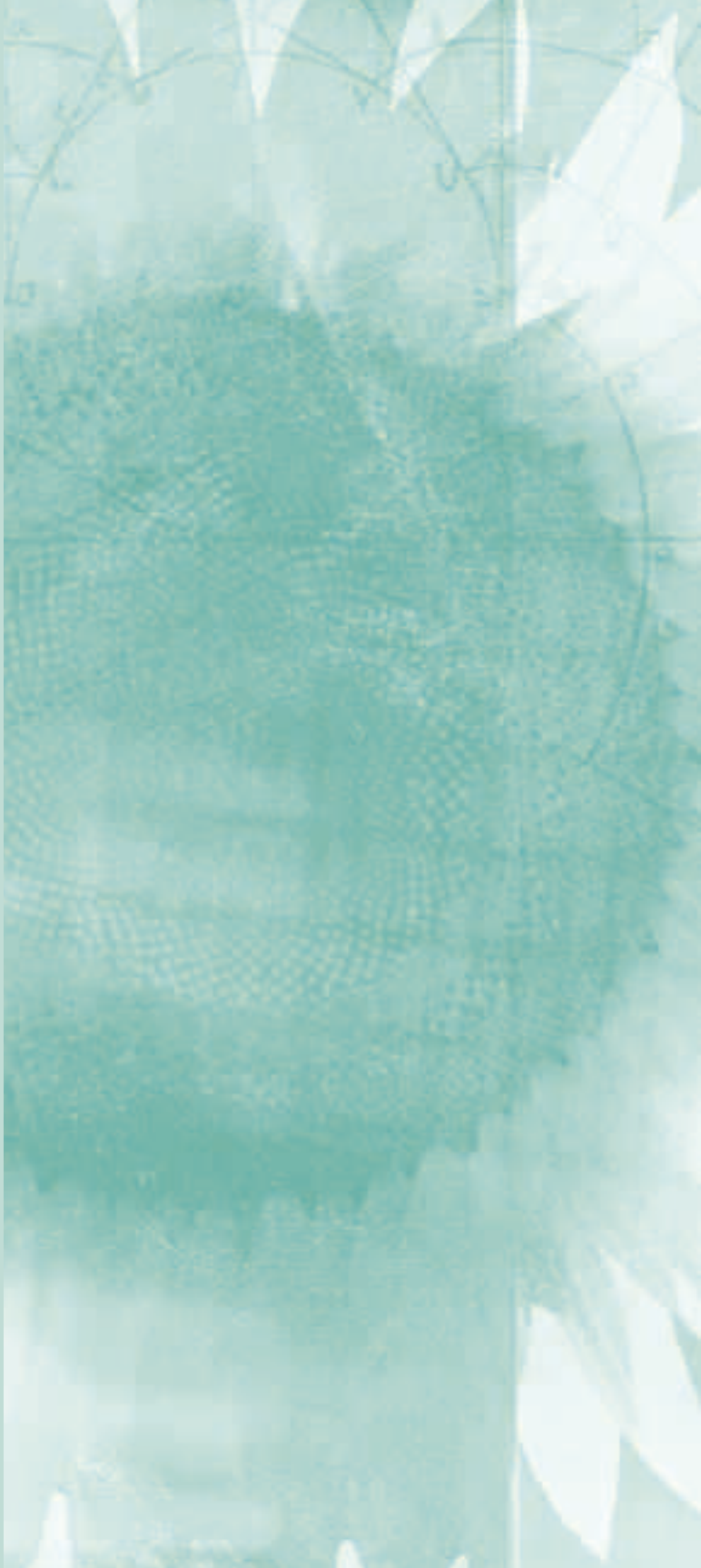
Hold support group meetings at your clinic regularly.

Support and motivate clinic staff and patients.

Don't be discouraged. Patients who do not have a virological response to treatment may benefit nonetheless. HCV treatment may slow progression of liver disease, which in turn may enable some patients to wait for better treatment.

Support groups are also a powerful motivational tool, because patients who are at earlier points in the evaluation process share in others' successes as they pass through milestones in the evaluation and treatment process. Patients begin to believe that good outcomes are attainable. Linking individual recovery to the notion of fighting back against a community epidemic produces a powerful synergy that often results in an upward spiral of self-esteem.[67]

—Litwin, Soloway, and Gourevitch (2005)



3. HCV TREATMENT

Although the medical management of HCV infection is complex, it can result in good medical outcomes. As with HIV disease, treatment for HCV infection has evolved, as has management of side effects and adverse events of treatment.

Until 1989, HCV was treated with injections of interferon. Interferon is a synthetic version of a cytokine (chemical messenger) produced by white blood cells. Response to interferon monotherapy was dismal. In 1998, treatment outcomes improved significantly when interferon was combined with ribavirin, a nucleoside analog (a class of drugs used for HIV treatment). HCV treatment improved again in 2001 with FDA approval of pegylated interferon. Attaching the polyethylene glycol (PEG) molecule to interferon (a process called pegylation) keeps the drug in the bloodstream longer and makes it more effective against HCV. Replacing standard interferon with pegylated interferon has significantly improved response to HCV treatment and requires a dosing regimen of only one injection per week (Table 4). Currently, therapy with pegylated interferon plus ribavirin is the standard treatment of HCV in HIV-positive people and the only FDA-approved treatment for coinfection.

In people with HIV/HCV coinfection, the duration of HCV treatment is usually 48 weeks, regardless of HCV genotype; some clinicians are considering 18 months of treatment for coinfected people who have HCV genotype 1. The primary endpoint of HCV therapy is *sustained virological response* (SVR), defined as no detectable HCV RNA in the bloodstream 6 months after completion of therapy. SVR is an indication of long-term remission of HCV; some experts consider it a cure.

Response to HCV Treatment: Prognostic Factors

Because of the limited efficacy and considerable side effects of HCV treatment, clinicians and their patients need to thoroughly assess and discuss risks and benefits of HCV treatment. The decision-making process should take into account individual prognostic factors.

HCV treatment is less effective for coinfected people than for those with HCV alone. In three studies (AACTG 5071, APRICOT, and RIBAVIC), however, CD4 cell count was not associated with response to treatment (Table 4). The sample size of people with CD4 cell counts of less than 200/mL in each study was small, and most study participants were taking HAART prior to and during HCV treatment.[87-93] The studies did not report an increased incidence of opportunistic infections among participants who had CD4 cell counts of less than 200/mL.[87-89]

Other factors have a significant effect on response to treatment, regardless of HIV status. The HCV genotype is a major prognostic factor. At least six different HCV genotypes have been identified. In the United States, most HCV infections are genotype 1.[94] Genotypes 1 and 4 are less sensitive to treatment than are genotypes 2 and 3.[87-89,95,96]

Although HCV viral load is not strongly associated with disease progression (unlike HIV viral load), HCV viral load is a prognostic factor for response to therapy, particularly in genotype 1 and genotype 4 infections. People with a baseline HCV RNA of more than

Table 4. Drugs Used for HCV Treatment and Management of Side Effects

Drug	Given As	Purpose
Pegylated interferon	Once-weekly injection	An antiviral and immunomodulating drug used in combination with ribavirin
Ribavirin	200 mg (tablets, capsules, or liquid) taken twice daily	A nucleoside analog that increases the efficacy of interferon
Filagrastim/pegfilagrastim*	Subcutaneous injection; dosing varies	White blood cell growth factor; used for treatment of interferon-induced neutropenia
Epoetin alfa/darbopoetin alfa*	Subcutaneous or intravenous injection; dosing varies	Red blood cell growth factor; treatment for ribavirin-induced anemia
Antidepressants (selective serotonin reuptake inhibitors)*	Pills; dosing varies	Prevent onset of or treat interferon-induced depression

* Use in patients when indicated.

Table 5. Response Rates to HCV Treatment Among Coinfected Trial Participants[87-89]

Study	SVR, Overall (%)	SVR, Genotypes 1 and 4* (%)	SVR, Genotypes 2 and 3 (%)
AACTG 5071	27	14	73
APRICOT	40	29	62
RIBAVIC	27	17	44**

**When included.*
***Includes genotype 5.*

800,000 per MIU are less likely to respond to HCV treatment than are people with lower HCV RNA levels.[87-89,95,96] HCV RNA levels are usually significantly higher in coinfected people than in people with HCV monoinfection.[97-99]

In HCV monoinfection treatment trials, response rates among African-Americans—among whom both HIV and HCV are disproportionately prevalent—have been significantly lower than response rates among non-Hispanic whites.[6,100-104] The reasons for this disparity are unclear. Data on response rates to HCV treatment among coinfected African-Americans are limited; only one pivotal HCV treatment trial in coinfected persons has been conducted solely in the United States (ACTG 5071), and race and ethnicity were not predictive of response to HCV treatment in that study.[88] HCV genotype was the most significant predictive factor for response to HCV treatment in the trial; the results could have masked the effect of race, because genotype 1 infections are more likely among African-Americans than among people of other ethnicities.[94,101,105] The predominance of HCV 1 genotype among African-Americans has been cited as a factor in decreased response rates to HCV treatment.

Data from HCV monoinfection treatment trials suggest that lifetime alcohol consumption and alcohol intake during HCV treatment are associated with poorer response rates. The treatment regimen in the studies was standard interferon monotherapy, however, and

information on adherence to HCV therapy was not included.[106-109] A more recent study using standard interferon plus ribavirin reported that alcohol intake prior to or during treatment did not influence response to HCV treatment.[110] Many clinicians withhold HCV treatment until patients have been abstinent from alcohol for 3 to 6 months, but some treat on a case-by-case basis.[56,111] Because alcohol accelerates HCV disease progression, clinicians need to work with their patients to help them reduce or eliminate alcohol consumption as part of HCV care, whether or not the patients are candidates for HCV treatment.

Liver Biopsy

Liver biopsy is the diagnostic gold standard for assessment of liver damage and its causes. However, experts are debating the requirement for a pre-treatment biopsy because of the rare but serious risks associated with biopsy (puncture of adjoining organs, hemorrhage and—very rarely—death),[112-114] the possibility of sampling error,[115,116] and patient reluctance. A liver biopsy is most useful for detecting mild to moderate liver damage,

HCV and Liver Transplantation

Liver transplantation may be the only option for coinfected patients with advanced liver disease. HCV treatment may cause hepatic decompensation in some cirrhotic patients,[117] but access to transplantation for PLWHA is limited by policies of individual transplant centers. Despite promising rates of posttransplantation survival, some centers do not perform transplants in PLWHA, and the persistent shortage of donor organs and reluctance of third-party payers to reimburse contribute to the difficulty as well, despite promising data on posttransplantation survival of HIV-positive patients, which is similar to that of HIV-negative patients.[119-121] Clinicians and their coinfected patients have another option: A trial sponsored by the National Institute of Allergy and Infectious Diseases on kidney and liver transplantation in people with HIV. For more information on study sites and eligibility, go to: http://spitfire.emmes.com/study/htr/.

because more severe liver damage, cirrhosis, can be identified with clinical, laboratory, and radiographic testing. Requiring liver biopsy as a prerequisite for HCV treatment may create a barrier for some patients.

Although researchers are working to create a less invasive replacement for liver biopsy that uses panels of blood tests and imaging techniques, nothing has been validated for use in coinfected people. Given the limited efficacy and substantial side effects of HCV treatment, some providers feel that a biopsy is necessary to identify patients who can defer treatment. Others recommend biopsy for patients with genotype 1 and a high viral load because they are less likely to respond to treatment; biopsy may not be required for patients with genotype 2 or 3 because the likelihood that they will achieve an SVR is significantly greater.[30,44,117]

Treatment Strategies

Researchers are exploring optimal strategies for treating HIV and HCV in coinfected patients. Initiating HAART prior to HCV treatment may improve response rates to HCV treatment.[122] Several factors must be considered in making treatment decisions:

- The patient must be willing and ready to treat both HIV and HCV.
- If CD4 cell count is less than 200/mL, HIV treatment should be initiated first.
- If HCV disease is mild, treatment can be delayed. If treatment is indicated according to current guidelines (Table 6) and there is patient readiness, HCV should be treated either before initiation of HAART or while the patient is on a stable antiretroviral drug regimen. Antiretroviral regimens for coinfected people should be selected carefully to reduce the risk of hepatoxicity and avoid interactions with HCV treatment. Avoid HAART regimens that contain didanosine (ddI; Videx), because of a potentially life-threatening interaction with ribavirin[123] and potentiation of the risk for hepatic decompensation in coinfected cirrhotic patients during HCV treatment.[118] If possible, zidovudine (AZT; Retrovir) should be avoided because it increases the risk of anemia from ribavirin[124]; stavudine (d4T; Zerit) may increase the risk for lipoatrophy and weight loss during HCV treatment.[96]

Table 6. HCV Treatment Recommendations for HIV/HCV Coinfected Patients

Source	Treatment Recommendation
American Association for the Study of Liver Diseases	Hepatitis C should be treated in the HIV/HCV coinfected person in whom the likelihood of serious liver disease and a treatment response are judged to outweigh the risk of morbidity from the adverse events of therapy.
Diagnosis, Management and Treatment of Hepatitis C (April 2004). Available at: www.aasld.org/eweb/docs/hepatitisc.pdf	
U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, HIV Medical Association	Because of the scarcity of published experience treating people who are coinfected with HIV/HCV, practice is dictated largely by principles established for the treatment of people who are not infected with HIV.
Treating Opportunistic Infections Among HIV-Infected Adults and Adolescents: Recommendations From CDC, the National Institutes of Health and the HIV Medicine Association/Infectious Diseases Society of America (December 2004). Available at: www.cdc.gov/mmwr/preview/mmwrhtml/rr5315a1.htm	
U.S. Department of Health and Human Services	Treatment of HCV is recommended according to standard guidelines, with preference for those with higher CD4 cell counts (>200 cells/mm^3).
Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents (2005). Available at: http://aidsinfo.nih.gov/guidelines/default_db2.asp?id=50	
Department of Veterans Affairs	All HIV patients with confirmed, chronic HCV infection should be evaluated for HCV treatment since (i) HCV treatment can lead to a sustained virological response (SVR), defined as an undetectable HCV RNA six months after discontinuing therapy; and (ii) HCV treatment may slow the progression of hepatic fibrosis and/or delay the onset of clinical consequences of decompensated cirrhosis.[45]
Management and Treatment of Hepatitis C Virus Infection in HIV Infected Adults: Recommendations From the Veterans Affairs Hepatitis C Resource Center Program and National Hepatitis C Program Office (September, 2005). Available at: http://hepatitis.va.gov/vahep?page=tp04-gd-01	
Federal Bureau of Prisons	HCV-related liver disease has now emerged as a serious concern for many persons with HIV infection. Antiviral therapy should be considered for inmates with chronic HCV and HIV coinfection, since HIV may accelerate the development of fibrosis and subsequent end-stage liver disease.
Clinical Practice Guidelines for the Prevention and Treatment of Viral Hepatitis. (February 2003). Available at: http://nicic.org/Library/016972	

Often, real-life situations are less clear-cut. Because many people present with both advanced HIV disease and advanced HCV disease, clinicians often start HAART first, so that side effects from antiretroviral agents can be identified and managed. Antiretroviral regimens for coinfected people should be selected carefully to reduce the risk for hepatotoxicity and avoid interactions with HCV treatment. Some patients who start HIV treatment with a low CD4 cell count do not achieve a CD4 count of more than 200/mL, although they have a stable or undetectable HIV RNA; those patients should be evaluated for HCV treatment on an individual basis. Although it is possible to initiate treatment for both viruses simultaneously, side effects and toxicities from medications make it difficult to do so.

Side Effects and Strategies for Managing Them

Pegylated and standard interferon and ribavirin may cause numerous side effects, including neuropsychiatric symptoms such as mood swings, anxiety, irritability, insomnia, and depression. Depression may be severe; but in HCV treatment trials, suicide or attempted suicide was reported among less than 1 percent of participants.[125,126] Hematologic toxicities (anemia, neutropenia, thrombocytopenia); fatigue; weight loss; and "flulike symptoms" also may occur.[127] Although the side effects can be daunting, strategies exist for managing them. Side effects can be alleviated by interventions such as the following:

- Prophylactic treatment for depression (i.e., before initiation of HCV therapy)
- Treatment of insomnia and anxiety as needed
- Dose reductions or use of growth factors to manage anemia and neutropenia
- Administration of the weekly shot of pegylated interferon on Friday night to mitigate side effects during the work week
- Tylenol for aches and fever
- Small, light meals; antiemetics or dronabinol (Marinol) for nausea and loss of appetite
- Adequate hydration.

The Week 12 Early-Stopping Rule

Although treatment discontinuations occur for other reasons—usually side effects and adverse events—many clinicians and their coinfected patients may decide to stop treatment at Week 12 if the patient does not have an *early virological response* (EVR), defined as achieving a 2-log drop in HCV RNA or undetectable HCV RNA after 12 weeks of treatment. As with HCV monoinfection, the likelihood of SVR in the absence of EVR is extremely low. Clinical trials of HCV treatment in HIV/HCV-coinfected patients have reported that 94 to 100 percent of participants who did not have EVR also did not achieve SVR.[96,128,129] Some clinicians and patients may prefer to continue HCV treatment in the absence of an EVR because some patients may have a delayed response to treatment. The Week 12 "early-stopping rule," however, spares nonresponders from the side effects and expense of HCV treatment.

Treating HCV: Long-Term Benefits

In HCV monoinfection, follow-up studies of people who experience SVR have found that more than 85 percent maintain undetectable HCV RNA levels for up to 10 years after completion of HCV treatment[130-132]; retrospective studies have reported a reduction in liver-related deaths, especially among people who have SVR.[133,134] Data on long-term outcomes of coinfected patients are limited; one study reported that no HCV-related clinical complications occurred among sustained virological responders after a mean posttreatment follow-up period of 58 months.[135]

Treatment of HCV offers significant benefits to people with coinfection, even in the absence of SVR. HCV treatment may improve the condition of the liver, even in virologic nonresponders.[88,136] Moreover—and crucially—HCV treatment may increase tolerability of antiretroviral therapy for HIV/AIDS.[137]

Treatment of Acute HCV

Treating HCV during acute infection has a major impact on treatment outcome. The biggest barrier to treatment of acute HCV is that it is rarely diagnosed; therefore, screening for acute HCV, when suspected, is crucial. In HCV monoinfection, HCV treatment during acute or early infection has been associated with high rates of SVR—80 to 98 percent—in nonrandomized, uncontrolled trials.[15,138] Treating acute HCV may be a promising approach in HIV/HCV-coinfected patients as well; an open-label, uncontrolled study reported that 16 of 27 HIV-positive men (59 percent) treated during acute or early HCV infection achieved SVR after 24 weeks of treatment with pegylated interferon and weight-based ribavirin.[139] The optimal regimen, duration, and time to initiate treatment are not clear, and problems with toxicity and limited efficacy have been reported.[140-143]

HCV therapy has been successful even when the patients have not abstained from continued drug or alcohol use or are on daily methadone. . . . [I]t is recommended that treatment of active injection drug use be considered on a case-by-case basis, and that active injection drug use in and of itself not be used to exclude such patients from antiviral therapy.[30]

—National Institutes of Health Consensus Statement on Management of Hepatitis C (2002)

4. EXPANDING ACCESS TO TREATMENT

Clinical and systemic barriers to treating HCV coinfection are substantial. For example, patients often have psychiatric or medical comorbidities, struggle with addiction to drugs and alcohol and have chaotic lives. These issues must be overcome, because all PLWHA should receive HCV education and screening, HAV and HBV vaccination, and counseling on alcohol use and HCV transmission. All providers should offer these services, regardless of whether HCV treatment is offered onsite.

Some clinics will decide to offer onsite HCV treatment and care on the basis of the following factors:

- Local priorities
- Demographics and needs of patient population
- Access to consultation or collaboration with a gastroenterologist or hepatologist
- Lack of an acceptable referral option that offers culturally competent care and treatment.

Models have been developed for addressing HCV in PLWHA, including referral and co-management, co-locating services, and integrated care. Some clinics may not have the capacity to treat coinfected patients for HCV and thus refer patients to a gastroenterologist or hepatologist.

Although referral may be the most economically feasible and realistic option for some sites and providers, this approach has drawbacks and has been shown to be minimally effective in securing continuity of care over time. Disappointing follow-up rates among coinfected patients referred to liver specialists have been reported; for example, Clanon and colleagues reported that less than 10 percent of their coinfected patients kept their appointments.[68] Low follow-up rates can be improved by identifying liver specialists who are experienced with or are willing to treat coinfected patients, by establishing and maintaining a relationship between HIV and liver specialists, and by developing a

communication mechanism among providers. Support groups can help bolster referral follow-up rates, both by word of mouth and by group members' accompanying each other to appointments.[57,144]

Co-location of liver specialty care in an HIV clinic may be a viable option, because many patients with HIV prefer "one-stop shopping" at a familiar and comfortable place. Co-location also enhances communication and collaboration among providers. Care can be co-located by providing a liver specialist at an HIV clinic one or two afternoons per month.When referral and co-location are not feasible, clinicians may need to provide their coinfected patients with educational resources (see Chapter 7).

Integrating Care: Starting a Coinfection Clinic

Care and treatment for HCV coinfection have been successfully integrated into several different venues, including CARE Act–funded clinics, VA programs, and methadone clinics. Many use a multiple-visit model to counsel, educate, screen, vaccinate, diagnose, and assess patients for HCV treatment (Figure 5). People who have opened coinfection clinics agree that the key element is a dedicated, full-time nurse or physician assistant who is able to schedule appointments, educate patients, facilitate support groups, provide one-on-one counseling, work on reimbursement for medications, manage side effects of treatment, and secure case management and transportation services for patients.[1,67,68,70,144-147] Most coinfection clinics have a dedicated nurse or doctor who is available by pager on a 24-hour basis; they report that patients do not abuse this service.

The Coinfection Clinic at Alameda County Medical Center, Oakland, CA

In Oakland, CA, Kathleen Clanon and her colleagues established a coinfection clinic in 2001 because so few of their coinfected patients were being treated for HCV by gastroenterologists; less than 10 percent were keeping appointments. The clinic has a monthly coinfection session and weekly support group meetings. Liver biopsies are performed at the HIV clinic by a gastroenterologist who uses a borrowed portable

Figure 5. Multiple-Visit Model for Providing HCV Care and Assessing Treatment Options

ultrasound machine. Patients recover from the biopsy in the HIV clinic, where they are already accustomed to receiving care. The key elements of the program are as follows:

- Sufficient funding to hire a dedicated nurse to provide monitoring and support for patients receiving treatment
- A cooperative relationship with a gastroenterologist, who has become part of the treatment team
- A patient support group.

So far, 35 patients at Alameda County Medical Center have been treated or are currently being treated. "It's a slow movement and needs to be built up," says Michael Harank,

Preparing for the Future: New Treatments for Hepatitis C

Clinicians and coinfected patients who are reluctant to treat HCV, given the limitations and toxicities of the current treatment, can anticipate therapeutic advances in HCV treatment in the coming years. Despite a promising pipeline of new HCV therapies, pegylated interferon is likely to remain the backbone of HCV therapy for some time, because most new drugs will need to be used in combination with interferon to avoid the development of resistance—an approach paralleling combination therapy for HIV. Coinfected people may need to wait even longer for new drugs, because HCV treatment trials in coinfected people often lag behind trials in people with HCV monoinfection, despite growing pressure from advocates.

Many different types of drugs are in development. Although a trial of an HCV protease inhibitor, BILN-2061, was discontinued, proof-of-concept for this class of drugs was established and two HCV protease inhibitors are in clinical trials.[148] Agents in development include helicase and polymerase inhibitors, drugs targeting the internal ribosomal entry site, and small interfering RNA.[148]

who coordinates care and facilitates the education and support group.[57] The SVR rate among Clanon's patients is astoundingly high: 53 percent. That rate can be attributed to a combination of factors: favorable HCV genotype, adherence to treatment, prompt management of side effects, consistent support from peers and staff, and eligibility criteria that include abstinence from drugs and alcohol prior to initiating HCV treatment and a CD4 cell count of more than 350/mL.

Clinic staff recommend the following approach to treatment:

- Maintain the full dose of pegylated interferon and ribavirin. Use growth factors instead of dose reduction, and consider pretreatment with erythropoietin.
- Assess for depression before initiating treatment, and reassess on a monthly basis. Pretreat for depression with selective serotonin reuptake inhibitors if the patient has a history of depression or a moderately high depression score prior to treatment. Switch medication if necessary.
- Advise patients to drink at least 3 liters of water per day; doing so seems to reduce pain, fatigue, and headaches. Almost all patients who drink sufficient quantities of water report no need for additional pain medication.[68]
- Encourage patients to utilize other services that can help them stay in care and manage quality of life.[57,68,147]

Miriam Hospital's Immunology Center, Providence, RI

In contrast to many other coinfection treatment providers, Lynn Taylor and her colleagues at the Miriam Hospital do not exclude coinfected drug and alcohol users from HCV treatment. Patients at Taylor's coinfection clinic often have advanced liver disease and unfavorable HCV genotypes, so the main goals of treatment often are to delay HCV progression and improve liver histology, not necessarily to achieve SVR.

The coinfection clinic opened in 2001 as part of Miriam Hospital's Immunology Center, which provides CARE Act–funded clinical care to more than 1,000 PLWHA, 43 percent

of whom are coinfected. Care and treatment for HIV and HCV are multidisciplinary. Treatment plans are made on an individualized basis. Coordinated psychiatric care, addiction treatment, and home-based case management are provided through collaboration with a community-based mental health agency, and the clinic has a collaborating hepatologist.[56]

The coinfection clinic takes place on 2 half-day sessions each month. At their first visit, patients receive comprehensive, individualized education. A support group meets once per week for breakfast, and the clinic offers monthly group educational sessions, the opportunity for individual sessions, and educational materials in English and Spanish. Patients often speak with one another on the telephone when they are unable to come to sessions. An interventional radiologist performs liver biopsies, which are not required for treatment. Weekly injections of pegylated interferon are given at the clinic, and patients are given a week's supply of ribavirin at that time. Directly observed administration of pegylated interferon allows for assessment and management of side effects. The adherence rate for weekly clinic visits has been 99 percent. So far, none of Taylor's 17 patients has discontinued treatment because of ongoing drug use or relapse. Five patients are currently receiving therapy, and seven have completed 48 weeks of HCV treatment. So far, one patient completing 48 weeks of treatment has achieved SVR.[1,56]

"This can be done with just two people," Taylor says.[1]

"I was reluctant at first but realized that we can do a better job because of what we already know about adherence and supporting people. HIV providers are already accustomed to working in advance of peer reviewed data and using treatment with low efficacy and lots of toxicities. This doesn't have to be cutting-edge; you, too, can have a coinfection clinic."[147]

—Kathleen Clanon, MD
Alameda County Medical Center
Oakland, CA

5. BARRIERS AND KEY ISSUES

HCV Treatment: Estimating the Cost

Providers planning to offer care and treatment to coinfected patients must adequately plan to meet client needs. Part of this planning means estimating the cost of care and establishing mechanisms for paying for it. HIV service providers are operating in a world with growing health care costs and growing HIV prevalence among the poor and uninsured. Many HIV/HCV-coinfected patients are also poor and underserved, and most rely on public support to meet care and treatment needs. Thus, providers must ask, Will we be overwhelmed by the high costs of providing HCV care and treatment to coinfected patients?

By any standard, HIV diagnostics and treatment are expensive, as are the interventions for management of side effects, and providers must plan accordingly. Most Medicaid programs include medications for HCV treatment in their formularies, and 17 State AIDS Drug Assistance Programs (ADAPs) cover pegylated interferon and ribavirin (see Access to HCV Treatment and ADAPs, p. 42).

- The cost of a 30-day supply of ribavirin (based on a dose of 800 mg/day) ranges from $500 to $1,100, depending on the manufacturer.*
- The cost of four once-weekly injections of pegylated interferon also varies by product and ranges from $1,300 to $1,500 per month.

But as discussed in the preceding pages, most people living with HCV do not receive treatment. It is hoped that improvements in access to high-quality, culturally competent care services will increase the number of people who do receive HCV treatment. But given the low utilization today of treatment—which is, by far, the most expensive element of care for coinfected patients—the cost of providing comprehensive HCV services will be less than prevalence data might suggest.

* All costs described in this section are based on prices listed at drugstore.com (accessed May 22, 2005).

Working With Patients Who Have Multiple Needs

Underserved coinfected patients may face many barriers to care, but many of those barriers can be successfully addressed. For example, case management can link coinfected patients with services that help mitigate the effects of poverty and lack of health insurance. Users of illicit substances can be offered buprenorphine, methadone, or referral to other drug treatment services. Patients with uncontrolled psychiatric disorders can be offered the opportunity to work with a psychiatrist or a psychologist as part of preparing for HCV treatment.

Concerns About Relapse to Active Drug Use and Reinfection

Clinicians and their patients have valid concerns about HCV treatment in active or recovering illicit substance users. The side effects of interferon are similar to those of opiate withdrawal, and patients have relapsed or reported cravings during HCV treatment.[55,67,111,149] Clinicians have an opportunity to intervene and support such patients by providing referrals to counseling, support groups, 12-step programs, and drug treatment or by initiating therapy with methadone or buprenorphine rather than discontinuing treatment. Some clinicians increase methadone dosage during HCV treatment to ameliorate cravings and side effects of HCV treatment.[67,150] One study reported that occasional drug use during HCV treatment did not have a significant effect on response to HCV treatment[111]; another continued HCV treatment for people who had relapsed to active drug use. No significant difference in response rates to HCV treatment was found among drug-free patients, those who relapsed before reinitiating methadone maintenance, and those who relapsed and did not reinitiate methadone maintenance during HCV treatment.[149]

The use of pain medication to manage the side effects of HCV treatment may be a problem for patients who want to remain drug free. One clinician has developed an innovative strategy: Patients sign a contract stipulating that they will get help in discontinuing pain medication if needed.[70]

Although reinfection with HCV after treatment has been a concern among clinicians who are considering treating injection drug users, few cases of HCV reinfection have been reported.[151] Concern about reinfection with HCV and other blood-borne pathogens can be addressed by providing counseling to reduce exposure to blood borne pathogens, making referrals to drug treatment and other harm-reduction modalities appropriate to the patient.

Depression and HCV Treatment

Depression is a common comorbidity of HIV and HCV, and it is common among drug users.[152-157] Treating depression among PLWHA has improved adherence to antiretroviral therapy[158] and is a key management strategy for interferon-induced depression.

Schaefer and colleagues reported that patients with a psychiatric history were successfully treated for HCV when a pretreatment psychiatric evaluation and ongoing multidisciplinary care were offered with HCV treatment.[110] Some clinicians and patients prefer to start antidepressants prior to HCV treatment, whereas others favor antidepressant use only if it becomes necessary. Because treatment discontinuations often occur due to psychiatric adverse events, it is sensible to avert such events when possible by incorporating mental health care into HCV treatment planning.

Treatment Eligibility and Uptake

According to *Practice Guidelines: Diagnosis, Management and Treatment of Hepatitis C,* from the American Association for the Study of Liver Diseases (AASLD), the "characteristics of persons for whom therapy is currently contraindicated" are as follows:

- Major, uncontrolled depressive illness
- Renal, heart, or lung transplantation recipient
- Autoimmune hepatitis or other condition known to be exacerbated by interferon and ribavirin
- Untreated hyperthyroidism
- Pregnancy or inability or unwillingness to comply with adequate contraception
- Severe concurrent disease, such as severe hypertension, heart failure, significant coronary artery disease, poorly controlled diabetes, or obstructive pulmonary disease
- Age younger than 3 years old
- Known hypersensitivity to drugs used to treat HCV.[44p1155]

Providers should note that alcohol and drug use are not on this list. Many providers establish their own eligibility criteria, which may or may not reflect treatment guidelines. Some do not treat active drug or alcohol users, whereas others have used adherence to medical appointments as an alternative criterion for active users.[56,74,111]

Fleming and colleagues assessed HCV treatment eligibility in a cohort of 274 HIV/HCV-coinfected patients at an inner-city coinfection clinic. Only 33 (12 percent) were eligible for treatment. Reasons for treatment ineligibility included the following issues:

- Nonadherence to clinic visits*
- Active psychiatric disease*
- Ongoing injection drug or alcohol use*
- Advanced HIV disease*
- Decompensated liver disease
- Comorbid conditions (refractory anemia, renal or cardiac disease).

Only 21 of the 33 eligible patients initiated HCV treatment; 9 of the 21 patients prematurely discontinued their treatment due to acute psychiatric illness (*n*=4), medical complication (*n*=4), or loss to follow-up (*n*=1). Four patients were on HCV treatment when the paper was written. Ultimately, of the eight patients who have completed treatment, only two achieved SVR.[55]

In a study of treatment uptake among HCV mono- and coinfected veterans, Bini and colleagues found that only 69 percent of coinfected patients who were eligible for HCV treatment agreed to initiate treatment. The main reasons for treatment refusal were worries about potential side effects of current therapy and desire to postpone treatment until better options are available.[159]

Rauch and colleagues assessed eligibility for HCV treatment among 107 coinfected patients in the Swiss HIV Cohort Study, using the following exclusion criteria:

- CD4 cell count of less than 250/mm^3
- Anemia (hemoglobin level less than 11 g/dL)
- Cytopenia (neutrophil levels of less than $1.5 \cdot 10^9$ cells/L or a platelet count of less than $70 \cdot 10^9$ cells/L)
- Liver diseases other than hepatitis C
- Decompensated liver disease

* Does not reflect AASLD treatment guidelines.

- Significant comorbidities (e.g., psychiatric disorders, seizures, cardiopulmonary disease, immunologically mediated diseases)
- Uncontrolled addiction (illicit drug abuse or alcohol consumption of more than 40 g/day)
- Pregnancy
- Poor adherence to prescribed drugs (according to the physician).

Of the 107 patients, a total of 82 (77 percent) were ineligible for HCV treatment; most (73 percent) had more than one ineligibility criterion, and 33 percent had more than three. Of the 25 eligible candidates, 16 refused treatment because of fear of side effects and concern about the duration of HCV therapy, and 4 with HCV genotype 1 declined treatment because they had mild fibrosis. Only nine patients started HCV treatment.[160]

Treating Anemia and Neutropenia With Growth Factors

Two commonly reported hematologic toxicities of HCV treatment—anemia and neutropenia—can be managed with growth factors or by dose reductions in ribavirin (for anemia) or pegylated interferon (for neutropenia). Dose reduction may compromise efficacy of therapy, however, and anemia may become treatment limiting, particularly for HIV-positive patients. Growth factors are extremely expensive; a month's supply of treatment for anemia or neutropenia costs about $8,000. Some State ADAPs cover growth factors, and they may be accessible through patient assistance programs (see Chapter 7).

Despite the price of HCV treatment and growth factors, treating HCV with pegylated interferon and ribavirin may be cost-effective in HIV/HCV coinfection. Two recent models from Wong and colleagues assessed the economic value of HCV treatment in HIV/HCV coinfection; the researchers based their calculations on the costs of treatment in Spain and the United States.[161,162] HCV treatment was determined to be cost-effective in people with a Metavir biopsy score of F2, indicating moderate liver disease, and a CD4 cell count of more than 200/mL. The cost-effectiveness of treatment increased for coinfected patients with a CD4 cell count of more than 350/mL because their risk for developing serious liver disease increased with longer life expectancy. The authors of the studies assumed that HCV treatment would be discontinued at Week 12 in the event of virological nonresponse. In the U.S. study, the cost of growth factors was included in the analysis; nonetheless, treatment was still considered cost-effective.

Access to HCV Treatment and ADAPs

Currently, 20 State ADAPs provide access to interferon; 17 States also cover pegylated interferon and ribavirin. Many ADAPs provide access to at least some of the drugs needed to manage side effects of HCV treatment along with vaccinations for HAV and HBV. Table 7 provides a list of which drugs are available in each State as of March 2006.

According to a survey from the National Association of State and Territorial AIDS Directors (NASTAD), only 216 ADAP participants were being treated for HCV during July 2004. The following reasons were cited for low treatment uptake:

- Side effects of the medication (*n*=6)
- Patients and providers not aware that HCV treatment had recently been added to the formulary (*n*=4)
- Providers not treating HCV or not trained in treating HCV (*n*=2)
- Provider requiring liver biopsy created a barrier to treatment (*n*=1)
- Client eligible for patient assistance programs (*n*=1)
- Preferred drugs not included on the formulary (*n*=1; California's ADAP does not cover pegylated interferon).[163]

To offer HCV treatment in the context of limited resources, some ADAPs have developed cost-containment measures for their HCV programs. For example, Maryland's ADAP has medical eligibility criteria stating that the patient's HCV infection must, "in the judgment of the clinician . . . be expected to be eradicated. . . . Treatment for histological benefit alone is not eligible." The physician must "treat to cure," not to maintain the patient's current condition. Maryland's ADAP also requires a liver biopsy for genotype 1. So far, HCV treatment uptake has been limited: Only $35,000 of the $2,000,000 dedicated to HCV treatment was used in 2005.[164] The Washington State ADAP has implemented a monthly copayment of $10.00 to $25.00, based on income, for all formulary drugs; the copayment is collected at the pharmacy.

State ADAP programs report that financial impact of adding HCV treatment to their formularies has been minimal. As of September 2001, ADAP programs in New York, California, Massachusetts, and New Jersey reported that they were spending less than 1 percent on HCV treatment.[165]

Table 7. State ADAP Coverage of HCV Treatment, Therapies for Side Effect Management, and HAB/HBV Vaccines (as of March 2006)[166,167]

State and Information	PEG-IFN	RBV	SSRIs	EPO	G-CSF	HAV & HBV Vaccine	Other Contact Information & Wait Lists for ADAP (as of 3/06)
Alabama (334) 206-5364				X			Waiting list
Alaska (907) 561-0453						X	Waiting list
Arizona (602) 364-3610	X	X	X	X	X	X	
Arkansas (501) 661-2118							Waiting list
California (916) 449-5900		X	X	X	X	X	Covers standard IFN and consensus IFN*
Colorado (303) 372-1713							
Connecticut (800) 233-2503	X	X	X	X	X	X	
Delaware (302) 739-3032	X	X	X	X	X	X	Covers standard IFN
District of Columbia (202) 724-4900	X	X	X	X			Covers standard IFN
Florida (850) 245-4335				X	X	X	
Georgia (404) 657-3129				X			
Hawaii (808) 732-0026			X	X	X		Waiting list
Idaho (208) 334-6657							Waiting list
Illinois (800) 825-3518							Covers standard IFN
Indiana (317) 233-7450			X				Waiting list
Iowa (515) 242-5838							Waiting list
Kansas (785) 296-8701							
Kentucky (800) 420-7431						X	Waiting list
Louisiana (504) 568-7474							
Maine (207) 287-5551							

Table 7 (cont'd). State ADAP Coverage of HCV Treatment, Therapies for Side Effect Management, and HAB/HBV Vaccines (as of March 2006)[166,167]

State and Information	PEG-IFN	RBV	SSRIs	EPO	G-CSF	HAV & HBV Vaccine	Other Contact Information & Wait Lists for ADAP (as of 3/06)
Maryland (800) 205-6308	X	X	X	X	X		Covers standard IFN
Massachusetts (800) 228-2714	X	X	X	X	X	X	Covers all FDA-approved drugs
Michigan (888) 826-6565	X	X	X	X	X	X	Covers standard IFN
Minnesota: Twin Cities metro area: (651) 582-1980 Other areas: (800) 657-3761			X				
Mississippi (601) 960-7723	X	X	X				
Missouri (573) 751-6439			X			X	
Montana (406) 444-4744			X	X	X		Waiting list
Nebraska (402) 559-4673			X				Waiting list
Nevada (775) 684-5952					X		
New Hampshire (603) 271-4502 or (800) 852-9945 x4502			X	X	X		
New Jersey (609) 984-6125	X	X	X	X	X	X	Covers all FDA-approved drugs
New Mexico (609) 984-6125				X		X	
New York (800) 542-2437	X	X	X	X	X	X	Covers HCV diagnostic tests
North Carolina (919) 715-3111							Waiting list
North Dakota (800) 472-2180			X	X	X	X	
Ohio (800) 777-4775			X			X	
Oklahoma (405) 271-4636							

Table 7 (cont'd). State ADAP Coverage of HCV Treatment, Therapies for Side Effect Management, and HAB/HBV Vaccines (as of March 2006)[166,167]

State and Information	PEG-IFN	RBV	SSRIs	EPO	G-CSF	HAV & HBV Vaccine	Other Contact Information & Wait Lists for ADAP (as of 3/06)
Oregon (800) 805-2313				X	X		
Pennsylvania (800) 922-9384	X	X					
Puerto Rico (787) 763-4575	X	X	X	X	X		Covers standard IFN
Rhode Island (401) 277-2320 x107	X	X	X				Covers standard IFN
South Carolina (800) 856-9954			X				
South Dakota (800) 592-1861					X		
Tennessee (615) 741-7500	X	X	X	X	X		Covers HCV genotype
Texas (800) 255-1090							Covers standard IFN
Utah (801) 538-6397							
Vermont (802) 863-7253			X		X	X	
Virginia (804) 864-8019	X	X		X		X	
Washington (800) 272-2437	X	X	X				Covers standard IFN, HCV genotype, and RNA tests
West Virginia (304) 558-2950							Waiting list
Wisconsin (800) 991-5532	X	X				X	Covers standard IFN
Wyoming (307) 777-5800			X			X	

ADAP, AIDS Drug Assistance Program; EPO, epoetin-alfa (erythropoietin alfa); G-CSF, granulocyte-colony stimulating factor (filagrastim); HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; PEG-IFN, pegylated interferon; RBV, ribavirin; SSRIs, selective serotonin reuptake inhibitors.

Note: Formularies are subject to change.

* Consensus interferon (interferon alfacon-1) is a synthetic interferon that combines elements of several naturally produced interferons. It is used to treat people who have not responded to previous HCV treatment.

[I]nitiating HCV treatment is almost never an emergency; there's no reason for clinics to exceed what they feel they can safely handle at any given time. A clinic thinking about beginning an HCV treatment program should assess its resources, start slowly, and build capacity as [staff] gain experience.[145]

—Michael Rigsby, MD
Director, VA HIV and Hepatitis C
Program Office

6. CONCLUSION

In the United States, HCV coinfection is a major contributor to morbidity and mortality among PLWHA. Many coinfected people are from traditionally underserved, uninsured, and hard-to-reach communities. HIV/HCV coinfection is linked with psychiatric disorders, drug and alcohol dependence, poverty, homelessness, incarceration, and race.[168,169,170] Those barriers are amplified by limited access to HCV diagnostic testing and treatment and restrictive eligibility criteria for treatment. The side effects and limited efficacy of drug therapy in people with HIV/HCV coinfection create additional obstacles for coinfected patients and their clinicians. Despite these challenges, HCV can be successfully treated in PLWHA.

CARE Act providers have already developed innovative models for delivering HCV care and treatment.[56,68,171] The CARE Act community has a wealth of experience in providing culturally competent care and treatment to underserved individuals and diverse communities. Providers have demonstrated the capacity to respond to changes in care and treatment paradigms, patient demographics and, most significantly, decreasing resources in the face of increasing need. Thus, the CARE Act community is ideally suited to tackle HCV/HIV coinfection.

Addressing coinfection seems daunting, but that is not the reality. Not all coinfected patients require HCV treatment, and not every clinic will—or should—provide comprehensive treatment services for coinfected patients. All HIV treatment providers, however, should develop a supportive structure for coinfected patients, whether or not they plan to deliver HCV drug treatment onsite. Specifically, providers should provide screening, education, and support—services that can be coordinated and delivered by clinic staff, case managers, and peers.[56,57,67,68] Those services create the foundation for referrals when onsite care is not feasible.

Referring patients to off-site providers may seem like the best option for many HIV/AIDS services providers. Many liver specialists, however, are not comfortable treating HIV-positive people and do not have experience treating patients with multiple psychosocial needs. Fortunately, experienced HIV care providers have many tools at

their disposal with which to increase their capacity to deliver HCV care and treatment, including collaboration with culturally competent liver specialists, miniresidency programs, journal clubs, consultation, and co-locating care.

In the coming years, we are likely to see significant progress in HCV treatment, echoing the advent of HAART in HIV disease. Several therapies have entered clinical trials, and early data are promising. Novel, potent oral agents may significantly shorten the course of treatment and increase SVR rates. Yet, coinfected patients will not benefit from upcoming improvements in HCV treatment unless care and treatment are delivered in a supportive, multidisciplinary context. Coinfected patients require education and integrated medical, mental health, and addiction treatment services.

As CARE Act providers have learned during more than 15 years of experience with HIV disease, a strong infrastructure is crucial for successful delivery of care and treatment, particularly for people with multiple diagnoses. Models for delivering HCV care must be developed now—to meet current needs, anticipate therapeutic improvements, and accommodate corresponding increases in HCV treatment uptake among people with HIV/HCV coinfection. The CARE Act community has successfully reached underserved PLWHA and increased the length and quality of their lives, and it has the skill and expertise to do the same for coinfected persons.

7. RESOURCES

PATIENT ASSISTANCE PROGRAM INFORMATION

GENERAL

Helping Patients.org (Pharmaceutical Research and Manufacturers of America [PhRMA]-sponsored Web site)
www.helpingpatients.org/intro.php

Partnership for Prescription Assistance (PhRMA-sponsored Web site)
(888) 4PPA-NOW (888-477-2669).
www.pparx.org/intro.php

Needy Meds.com (State and local programs; downloadable patient assistance program applications)
www.needymeds.com/programs/applications.shtml

HEPATITIS C TREATMENT

Roche (pegylated interferon alfa-2a [Pegasys] and Copegus [ribavirin])
For reimbursement information: 877-PEGASYS
www.pegasys.com/resources/pegassist.asp

Schering (pegylated interferon alfa-2b [PEG-Intron] and Rebetol [ribavirin])
The National Association of State and Territorial AIDS Directors and Schering-Plough have initiated the Commitment to Community Program. When HCV treatment is not included in a State ADAP formulary, the Commitment to Community Program will provide 1,500 slots for ADAP participants. This program is administrated via Schering's Commitment to Care Program: (800) 521-7157.
http://pegintron.com/pegintron/commitment.html

Valeant (interferon alfacon-1[Procrit])
www.infergen.com/wt/page/reimbursement
www.infergenaspine.com
1-888 move fwd (1-888 668-3393)

GROWTH FACTORS

Ortho-Biotech (epoetin alfa [Procrit])
(800) 553-3851; fax (800) 987-5572
www.procrit.com/immunology/help/program.html

Amgen (filagrastim [Neupogen] and pegfilagrastim [Neulasta])
Reimbursement Connection (800) 272-9376
www.reimbursementconnection.com/neulasta/other_programs/other_programs_services.jsp#safetynet_program
www.neulasta.com/professional/reimbursement/rc.jsp

RESOURCES FOR PROVIDERS

AIDS Education and Training Center Mountain Plains
HIV/Hepatitis C Center of Excellence
www.aids-ed.org/aidsetc?page=ab-01-11

American Association for the Study of Liver Diseases
Strader DB, Wright T, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases. Practice guideline: diagnosis, management, and treatment of hepatitis C. *Hepatology.* 2004;39:1147-71.

Australasian Society for HIV Medicine (ASHM)
Dore G, Sasadeusz J, eds. *Coinfection—HIV and Viral Hepatitis: A Guide for Clinical Management.* Rev. ed. Darlinghurst, NSW, Australia: ASHM; 2005.
www.ashm.org.au/index.php?PageCode=1305&SD=10&DExpand=1

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Treating opportunistic infections among HIV-infected adults and adolescents. *MMWR.* 2004;53(RR15);1-112.
www.cdc.gov/mmwr/preview/mmwrhtml/rr5315a1.htm

Centers for Disease Control and Prevention
Viral Hepatitis C (Web site)
www.cdc.gov/ncidod/diseases/hepatitis/c/index.htm

Federal Bureau of Prisons
Clinical Practice Guidelines for the Prevention and Treatment of Viral Hepatitis
http://nicic.org/Library/016972

Hepatitis Resource Network
Information on Management Algorithms, Educational Resources, and Clinical Trials
(Web site)
www.h-r-n.org/

National Institutes of Health
Consensus Statement on Management of Hepatitis C: 2002
http://consensus.nih.gov/cons/116/091202116cdc_statement.htm

U.S. Department of Health and Human Services
Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents. 2005. http://aidsinfo.nih.gov/guidelines/default_db2.asp?id=50

U.S. Department of Veterans Affairs
VA National Hepatitis C Program
http://hepatitis.va.gov/vahep?page=home-00-00

- *Management of Psychiatric and Substance Use Disorders in Patients With Hepatitis C: A Reference for Hepatitis C Care Providers*
  http://hepatitis.va.gov/vahep?page=tp03-gd-01
- *Treatment of Patients With Cirrhosis and Portal Hypertension,* October 2003, v.1
  http://hepatitis.va.gov/vahep?page=tp08-01-rr
- *Treatment Recommendations for Patients With Chronic Hepatitis C*
  http://hepatitis.va.gov/vahep?page=tp03-01-04-01
- Clinician Tools: http://hepatitis.va.gov/vahep?page=tm-ct-00

RESOURCES FOR PATIENTS

AIDS Community Research Initiative of America
Viral Hepatitis and HIV (Web site)
www.acria.org/treatment/treatment_edu_viral_hep.html

Hepatitis C Support Project
HCV Advocate (Web site)
www.hcvadvocate.org

HIV and Hepatitis.com
www.hivandhepatitis.com

National AIDS Treatment Advocacy Project
www.natap.org

Treatment Action Group
Swan T, Raymond D. *Hepatitis C Virus and HIV/HCV Coinfection: A Critical Review of Research and Treatment.* New York: Treatment Action Group; 2004.
www.aidsinfonyc.org/tag/coinf/hcv2004

U.S. Department of Veterans Affairs
VA National Hepatitis C Program
Patient and Community Education (Web site)
http://hepatitis.va.gov/vahep?page=tm-ce-00

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