Center for Substance Abuse Treatment
Division of Pharmacologic Therapies

Hepatitis in Opioid Addiction Treatment

Medical Management of Hepatitis Infection and Pharmacologic Therapy for Substance Abuse

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Substance Abuse and Mental Health Services Administration
Center for Substance Abuse Treatment
www.samhsa.gov

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1 Choke Cherry Road

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Abbreviations appearing in the text… AASLD- American Association for the Study of Liver Disease; AATOD- American Association for the Treatment of Opioid Dependence; ACTG-AIDS Clinical Trials Group; AIDS- acquired immunodeficiency syndrome; ALT- alanine amino transferase; ASAM- American Society of Addiction Medicine; AST- Aspartate aminotransferase; ATC- Addiction Treatment Center; CAGE Questionnaire-Cut down, Annoyed, Guilty, Eye opener; CD4- helper lymphocytes; CD8- killer lymphocytes; CDC-Centers for Disease Control and Prevention; DHHS- Department of Health and Human Services; DNA- Deoxyribonucleic Acid; EASL- European Association for the Study of Liver Disease; ESLD - end-stage liver disease; FDA-Food and Drug Administration; HAV- hepatitis A virus; HBe Ag- Hepatitis B nucleocapsid core antigen; HBs Ag- Hepatitis B envelope antigen; HBV- hepatitis B virus; HCC-hepatocellular carcinoma; HCV- hepatitis C virus; HDV-Hepatitis D Virus; HIV = human immunodeficiency virus; IDU- injection drug use; NCCAM-National Center for Complementary and Alternative Medicine; NHANES III- National Health and Nutrition Examination Survey; NIAAA-National Institute on Alcohol Abuse and Alcoholism; NIH-National Institutes of Health; NIDA- National Institute on Drug Abuse; NOMs- National Performance Outcome Measures; OLT- orthotopic liver transplantation; ONDCP- Office of the National Drug Control Policy; OTP- Opioid Treatment Program; PCR- polymerase chain reactions; RNA-ribonucleic Acid; SAMHSA- Substance Abuse and Mental Health Services Administration; SML- serum methadone level; SVR- sustained virologic response; TEDS- Treatment Episode Data Sets; TIP-Treatment Improvement Protocol.

Reviewers

The following persons served as independent reviewers of this document, offering critical commentary and revision suggestions:

Joanna Buffington, MD, MPH
Medical Epidemiologist
Prevention Branch
Division of Viral Hepatitis, Mail Stop G-37
Centers for Disease Control and Prevention
Atlanta, GA

Kenneth Hoffman, MD, MPH
Division of Pharmacologic Therapies
Center for Substance Abuse Treatment
Substance Abuse and Mental Health Services Administration, DHHS
Rockville, MD

Alain H. Litwin, MD
Division of Substance Abuse
Albert Einstein College of Medicine
Montefiore Medical Center
Bronx, NY

Leonard Seeff, MD
National Institute on Diabetes, Digestive, and Kidney Diseases
National Institutes of Health, DHHS
Bethesda, MD

Diana L. Sylvestre, MD
Assistant Clinical Professor of Medicine
University of California, San Francisco
Director; Organization to Achieve Solutions In Substance Abuse (O.A.S.I.S.)
Oakland, CA

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Executive Summary

Many cases of hepatitis, or liver inflammation, have been associated with substance abuse in the form of chronic alcohol consumption and alcoholism. However, the majority of new and existing cases of hepatitis virus infections are related to injection drug use. In 2002, the National Household Survey on Drug Abuse, conducted by the Substance Abuse and Mental Health Services Administration (SAMHSA), reported that an annual average of 338,000 persons aged 12 or older used needles to inject cocaine, heroin or stimulants during the previous year. An estimated 16% of individuals were reported to share needles to inject drugs.

Substance abuse is a complex disorder composed of multiple physiologic, social and behavioral factors, and treatment programs need to address all aspects of substance abuse to provide optimal treatment. Most addiction treatment specialists, therefore, advocate what can be called "wholistic treatment" that includes behavioral, biological (pharmacological) and social rehabilitative components as part of a comprehensive approach to foster recovery from drug addiction. Behavioral interventions have been extensively researched and are critical to the successful treatment of all drug addictions.

The Food and Drug Administration (FDA) has approved several pharmacological treatments for opioid addiction. Among these, methadone is the most widely used and is designed to relieve opioid withdrawal symptoms and reduce the craving for illicit or prescription opiates. The Treatment Improvement Protocol (TIP) 43, entitled "Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs," provides a detailed description of medication-assisted treatment for opioid addiction (SAMHSA 2005). In addition, buprenorphine treatment is available for the treatment of

opioid addiction in primary care settings, when prescribed or dispensed by qualified physicians. Opioid treatment programs (OTPs) that dispense methadone may also offer buprenorphine treatment. The medical management of opioid addiction in primary care settings is described in TIP 40: "Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction" (SAMHSA 2004). TIP 40 and TIP 43 are also useful resources for managing patients with substance use disorders involving the use of multiple drugs, including alcohol.

Injection drug use may lead to hepatitis virus infection because the virus can be transmitted directly to the blood from use of injection equipment contaminated with the hepatitis virus or indirectly through sexual contact with an infected individual. In the latter case, drug use may contribute to hepatitis transmission by lowering a person's inhibitions against risk-taking behaviors; that is, under the influence of drugs an individual may be more likely to engage in unprotected sexual activity with an infected partner.

Individuals who inject drugs are at-risk for infection from different forms of the hepatitis virus. The three most common types are termed *hepatitis A, B*, or *C*. Those with hepatitis B virus infection also face additional risk should they become co-infected with hepatitis D virus. Protection from the transmission of hepatitis virus is best achieved by vaccination. Hepatitis C virus infection is the most common chronic blood-borne infection in the United States. Currently, vaccines are available for two forms of hepatitis viruses, hepatitis A and hepatitis B. Individuals who are receiving pharmacologic therapy for opioid addiction or beginning it are also at–risk for hepatitis infection. For those with a history of injection drug use or who currently inject drugs, the medical management of

hepatitis infections consists of screening, testing, counseling and providing care and treatment. Components of the medical management of hepatitis infection for these individuals include:

- Periodic testing for hepatitis A infection, hepatitis B infection, hepatitis D and hepatitis C infection;
- Education and counseling regarding at-risk behavior and hepatitis transmission, acute and chronic hepatitis infection, liver disease, and care and treatment for liver disease;
- Vaccination against hepatitis A infection and hepatitis B infection , if vaccination eligible; and
- Integrative primary care as part of the comprehensive treatment approach to recovery from opioid addiction.

Patient populations seeking recovery from opioid addiction or who are currently receiving pharmacotherapy for opioid addiction have a high prevalence of liver disease, particularly liver disease resulting from hepatitis virus infection. Pharmacotherapy for opioid addiction can be provided concurrently with the evaluation, care, or treatment of liver disease resulting from hepatitis virus infection; providing comprehensive treatment is not contraindicated. Providing opioid-addiction treatment stabilizes patients, improves patient compliance with care and treatment regimens, and promotes positive patient outcomes. Implementation of effective hepatitis prevention programs, care programs, and treatment regimens in concert with the pharmacological therapy of opioid addiction can reduce the public health burdens of hepatitis and injection drug use.

Hepatitis in Opioid Addiction Treatment:
Medical Management of Hepatitis Infection and Pharmacologic Therapy for Substance Abuse

Injection Drug Use, Substance Abuse Treatment and Hepatitis

Injection drug use (IDU) leading to opioid dependence is a problem of significant public health importance (Brown 2004). Infectious diseases associated with IDU include Human Immunodeficiency Virus (HIV) infections and viral hepatitis infections. Social costs are vast and include crime, poverty, and devastating impacts on individuals and families. Recent research has clearly shown that addiction to drugs of abuse is a brain disease, and if left untreated, may result in a chronic debilitating medical disease with comorbidities (NIH 1997; Qureshi et al. 2000). Thus, individuals addicted to opiates may exhibit complex problems and require substantial care and services for the medical management of substance abuse (see Table 1).

Liver disease in persons who use illicit drugs and/or alcohol is a problem of immense proportions. Substance-induced liver disease may be compounded by infectious hepatitis, such as the hepatitis B virus (HBV) or hepatitis C virus (HCV). Both of these are major viral infections that result in liver disease and which are difficult to treat. HCV infection is the most common chronic blood-borne infection in the United States. The prevalence of HCV is epidemic among current drug users and former injection-drug users (Sylvestre et al. 2004). The Centers for Disease Control and Prevention (CDC) have

estimated that 60% of all new cases of HCV infection are related to IDU (2004). IDU practices include the use of heroin, cocaine, methamphetamine and prescription opioids.

It has been estimated that there are at least 800,000 untreated injection-heroin users in the United States (ONDCP 2002). Compared to the general population, people addicted to opioids experience a reduced quality of life in both physical and mental functioning (Puigdollers et al. 2004). The multiple comorbidities associated with substance abuse and addiction also contribute to the lower quality of life experienced and documented by opiate users (Millson et al. 2004). Life priorities of injection drug users include concerns about HIV infection and treatment for it, as well as social and financial issues such as housing, money, and protection from violence (Mizuno et al. 2003).

Table 1 –Comorbidities Associated with Substance Abuse and Addiction

- **Medical**- hepatitis C virus infection, hepatitis B virus infection, tuberculosis and other pulmonary disease, immune deficiency, human immunodeficiency virus infection, sexually transmitted diseases, sexual disorders, dental and periodontal disease, nutrient deficiency, cardiovascular disease, sleep disorders, chronic pain syndromes
- **Psychiatric**- Axis I spectrum disorders such as depression, anxiety, post-traumatic stress disorder, personality disorder, bipolar disorder, attention deficit /hyper reactivity disorder, schizophrenia, cognitive dysfunction; Axis II personality and developmental disorders
- **Social**- poverty, homelessness, family dysfunction, corrections/prison, violence, sexual abuse, drug-using peer-groups, easy drug access, lack of occupation and skills
- **Other Addictions and Abuse-** alcohol, nicotine, stimulants, cocaine, hallucinogens, marijuana, prescription-drug, internet, gambling

Methadone treatment for opioid addiction has more than 35 years of success in helping addicted individuals abstain from illicit drug use and achieve recovery. In addition to methadone treatment, Opioid Treatment Programs (commonly referred to as

OTPs or methadone programs) can provide a comprehensive therapeutic milieu comprised of primary medical care, psychosocial counseling, vocational rehabilitation, Human Immunodeficiency Virus (HIV) testing and counseling, viral hepatitis education and testing, and other vital medical and social services. OTPs are required, as a condition to obtain or maintain certification by the Substance Abuse and Mental Health Services Administration (SAMHSA) to satisfy rigorous accreditation standards of SAMHSA-approved accreditation bodies (Federal Register 2001).

Many patients dependent on opiates are polydrug users and may meet criteria for several substance use disorders. For example, patients dependent on heroin also have high rates of comorbid alcohol and/or cocaine abuse (Conway et al. 2003). For these individuals, the combination of pharmacotherapy, behavioral intervention, and network therapy--which utilizes family members and/or friends to support compliance with addiction treatment (Galanter et al. 2004)--may be most useful to reduce risk-taking behavior. Addressing alcohol use is an important issue for individuals addicted to opioids since alcohol stimulates the release of dopamine in the brain and this alcohol-dopamine activation, inducing drug craving, can be blocked by opiate receptor antagonists (Gonzales and Weiss 1998). Thus, opioid addicted individuals may use or view alcohol as part of their "stepping down" process away from opioid dependence, although alcohol use may lead to further addiction. Alcohol consumption exacerbates co-occurring liver disease, and all patients with viral hepatitis infection should be counseled to refrain from alcohol consumption (Kulig and Beresford 2005). Among patients infected with HCV, hepatitis C viral loads have been shown to be elevated in those who consume alcohol. Elevated hepatitis C viral loads and alcohol use are also associated with a decreased

therapeutic response rate to treatment regimens. Alcohol consumption is a factor that reduces the survival rate of patients with hepatocellular carcinoma (HCC) (liver cancer) resulting from hepatitis B virus (HBV) infection (Wong et al. 2005).

In addition, patients acutely or chronically infected with HBV have an increased risk of liver failure when they also become infected with hepatitis D virus (HDV). For individuals with co-occurring liver disease, an additional (and preventable) risk may be encountered when they become infected with Hepatitis A virus (HAV), an infection that normally resolves in situations in which the liver was otherwise relatively healthy.

Hepatitis Infection in Opioid Addiction: Elements Needed for Recovery

Pharmacological therapy for opioid addiction and medical care for liver disease should be provided to patients, as indicated, to promote positive medical outcomes. In combination with pharmacological therapies, patient education about liver disease and prevention of infectious diseases, plus enrollment in primary medical care are important in the medical management of acute and chronic stages of viral infections in the liver (Edlin et al. 2005). Counseling of young injection drug users about prevention of infectious disease is critical since roughly half of injectors under the age of 23 may be free of human immunodeficiency virus (HIV) and viral hepatitis infections (Backmund et al. 2005). However, young injection drug users are frequently not vaccinated to prevent viral hepatitis infection (Kuo et al. 2004), even though vaccination may be the best course of action. Counseling individuals who have hepatitis infection about a healthy lifestyle promotes treatment readiness for those individuals with progressive liver disease (Zweben 2001). Providing integrated primary care and pharmacologic treatment for

opioid dependence can facilitate both recovery from opioid addiction and medical treatment of co-occurring conditions, such as viral hepatitis infections (Fiellin et al. 2003).

Current clinical practice guidelines recommend care and treatment for patients infected with viral hepatitis who might benefit from treatment and virus eradication. However, barriers seriously limit hepatitis care and treatment for injection drug users (Edlin et al. 2005; NIH 2002; Schaefer et al. 2004). One significant barrier is the lack of definitive data on efficacy of hepatitis C treatment for injection drug users. In a review of the research clinical trials literature published between 1987 and 2003 that focused on the treatment of chronic hepatitis C virus (HCV) infection, Schaefer et al. found only seven clinical trials involving patients with drug addiction (2004). None of the published clinical trials used pegylated interferon, the medication currently considered the standard of care for HCV treatment.

A current clinical trial open to patient recruitment (NCT00087594 at www.ClinicalTrials.gov) is supported by the Hoffmann-La Roche Pharmaceutical Company and is designed to test the safety, feasibility and tolerability of pegylated interferon for individuals with a history of injection drug use (IDU) who are currently enrolled in a methadone treatment program. Inclusion criteria are strict and require at least 6 months of continuous attendance in methadone treatment prior to the study and abstinence from illicit drug use during and after the study. This clinical trial will provide needed information on a select group of patients. More prospective, controlled, clinical trials of standard-of-care treatments for HCV infection in patients who are injection drug users are needed to establish and apply new clinical guidelines.

There are numerous reasons for the lack of data on the medical management of co-occurring hepatitis infection and drug addiction. These include the generalized stigma and prejudice associated with substance-dependent persons, their disenfranchisement from the medical community, their complex medical management issues, healthcare providers' lack of current treatment knowledge about patients who are injection drug users, and a lack of infrastructure to deliver effective care to them (Edlin et al. 2001; Dore and Thomas 2005). Recent studies have shown that substance abusers a have a low eligibility for therapy because of the strict treatment entry criteria employed (Rauch et al. 2005). Consequently, treatment for chronic liver disease has been delayed or withheld for current or former substance-dependent persons, as well as for those in recovery who are receiving pharmacologic therapies for addiction. Individuals not receiving care and treatment for hepatitis infection, as well as those not responsive to hepatitis treatment, are at risk of progressing to end-stage liver disease or decompensated cirrhosis, leaving orthotopic liver transplantation (OLT) as the only life-saving alternative. Indeed, hepatitis C-related cirrhosis is the leading etiology of OLT (in 30-46% of cases), followed by alcohol-related disorders (in 23-25% of cases) (Botero 2004; Mandayam et al. 2004).

Patient/ Provider Relationship

Care and treatment of hepatitis infection and other comorbidities associated with injection drug use are complex, and numerous barriers prevent high quality care and positive outcomes. When treatment programs attempt to engage patients who are injection drug users in health care and medical treatment, patients' responses tend to form a continuum of behaviors. On one extreme are individuals who are not engaged in care and have not been tested for hepatitis infection or other comorbidities. Some disengaged

individuals may have been tested for infectious diseases, but are unaware or not cognizant of their health status. Others with known hepatitis infection may not have been referred to a specialist for care and treatment or did not follow though on the referral, effectively declining care and treatment. Others may be infrequent users of the health care system and may use it only for emergency matters. At the other end of the continuum, are patients in various degrees of engagement in care and treatment, as well as various stages of readiness to seek care for hepatitis infection and other comorbidities. At the same time, there are barriers to care and treatment for injection drug users that contribute to the individual's engagement level with the health care system and readiness to address two or more illnesses.

In the population of injection drug users and those who are at risk for viral hepatitis, there are higher prevalence rates of psychiatric diagnoses such as major depression, anxiety disorder and bipolar disorder, and some patients use drugs or pharmaceuticals in an attempt to self-medicate an underlying psychological illness. Such untreated co-occurring disorders may increase risk-taking behaviors. This complex scenario is further complicated by negative experiences of injection drug users with the health care system in general and with individual health care providers more specifically (Davis and Rodrigue 2001; Golub et al. 2004; Stein et al. 2003). A trusting relationship with a member of the health care team who can help patients anticipate, plan for, and endure the difficulties that arise in the medical management of addiction and its associated comorbidities is fundamental for drug users as they seek care. A patient-provider relationship that will support a dialogue in which both parties are able to communicate openly about their expectations and frustrations is critical. However, the

health care system may not support such a dialogue. (Shine 1996). Drug users often believe that the health care they receive is judgmental and condescending, unresponsive to their needs, and often delivered without respect. As a result, drug users fail to follow through with medical advice, take prescribed medication, or keep appointments.

The extensive experience gained from treating injection drug users for medical conditions, especially HIV infection, has led to the development of effective principles for engaging drug users in health care relationships. Successful programs have a respectful approach to drug users, understand the medical and behavioral sequelae of addiction, refrain from moralistic judgments and utilize a multidisciplinary team approach (Batki and Sorensen 1999; O'Connor et al. 1994; Robertson 1998). These strategies embody a client-centered approach in which a care provider works with a client to identify changes that the client is motivated to make to enhance health and well-being (Brands et al. 2003). Even if global behavior change (such as ceasing all drug use) is not possible or likely in the short run, many other measures can nevertheless reduce the medical consequences of high-risk behavior (Des Jarlais et al. 1993). In this setting, health care providers can work with the patient to develop a treatment regimen that is able to fit the lifestyle of the patient (for example, once-daily therapy) rather than attempting to restructure the patient's lifestyle.

In addition, misunderstandings about the nature of addiction as a chronic, potentially recurring disease influence the nature of the relationship between the patient and the provider. Reports of "relapse" or "recidivism" during care and treatment sometimes have conveyed misleading impressions. Much of recidivism may actually be relatively benign with brief "lapses" of sobriety or abstinence sometimes called "slips."

Distinctions between lapses and relapses have been discussed in a number of texts on addiction medicine (Finney et al. 1999; Graham et al. 2002). Within the context of an ongoing addiction treatment program, neither lapses nor relapses need to be permanent impediments to recovery. However, rarely does the treatment field define measures in addiction recovery that are more likely to result in long-term abstinence and better outcomes (Weinrieb et al. 2000).

Strong patient-provider relationships are essential, because treatment regimens for HBV and/or HCV infection are difficult and stressful for patients. Drug users who test seropositive for hepatitis infection should be presented with a comprehensive health program that constitutes high quality hepatitis care and substance abuse treatment. Hepatitis care should include screening and counseling for at-risk behavior, HCV infection testing and genotyping, HBV infection testing, HIV infection testing, prevention counseling and education, vaccination against hepatitis A virus (HAV) and HBV infections (if eligible), and evaluation for comorbidities (Edlin et al. 2005). This evaluation should include determining the need for substance abuse services, psychiatric care, and social support. It should also include an effort to engage the patient in primary care, as well as a liver evaluation and an assessment for treatment of HBV infection and/or HCV infection, using the current treatment guidelines. Initial treatment trials of acute HCV infection have shown that programs that employ a multidisciplinary team and address psychological co-occurring disorders result in excellent treatment outcomes (Sustained Viral Responses [SVR] of 75% at 12 weeks of interferon treatment) compared to programs that do not address treatment barriers (Bargiacchi et al. 2005; Broers et al. 2005).

Studies have shown that substance use disorders and early IDU are associated with childhood traumatic events (Molnar et al. 2001; Ompad et al. 2005). It is also possible to intervene early to encourage individuals who abuse non-injection drugs to enter treatment to prevent them from progressing to injection drug use. Recent studies have identified risk factors that appear to lead individuals to make the transition to injection drug use. These risk factors include the following: 1) Individuals who engage in emerging drug practices, such as early onset inhalant drug use, tend to have a higher likelihood of progressing to IDU; 2) Certain factors appear to influence whether those who inhale drugs progress to IDU or not. For example, those who inhale drugs who also have an intact family structure appear less likely to progress to IDU. Also, homeless individuals and those who have sex partners who are IDUs are more likely to progress to IDU. 3) Certain patient-related factors also appear to predict entry into substance abuse treatment (Lankenau and Clatts 2004; Maxwell et al. 2004; Storr et al. 2005).

The importance of preventing individuals from progressing to IDU can be vividly seen from data comparing the HCV infection incidence between injection and non-injection drug users (Fuller et al. 2004). This longitudinal surveillance study in New York City showed an annual incidence rate of HCV infection in young non-injectors of 0.4/100 person years compared to 35.9/100 person years for injection drug users. Thus, delaying or preventing the transition to IDU may have a significant health benefit by reducing the risk of comorbid conditions associated with IDU and addiction.

Comprehensive Substance Abuse Treatment Planning and Pharmacologic Therapy

Substance abuse is a complex physiologic, social and behavioral disorder that often coexists with psychiatric illness as well as medical comorbidities. For this reason,

screening substance users for comorbid psychiatric illness should be considered an integral part of any medical intervention and comprehensive substance abuse treatment program (Sylvestre et al. 2004). Although it may be difficult to ascertain which comorbidity--substance abuse, mental illness or infectious disease--should be addressed first, an initial focus on the medical treatment of substance use disorders or misuse is often necessary to create sufficient stability before other treatments may begin. Stability is further increased when both mental health services and substance abuse treatment are combined, subsequently enhancing the medical outcomes of treatment for comorbidities. *Substance Abuse Treatment for Persons with Co-Occurring Disorders*, TIP 42, (SAMHSA, 2005a) provides up-to-date information about co-occurring substance use and mental disorders as well as recommended best practices in the treatment of these disorders.

Understanding that substance abuse is a complex multifactor disorder, it is appropriate to develop, through case management, a comprehensive substance abuse treatment plan that comprises behavioral, social rehabilitative components, and biological (pharmacological) treatments, (Table 2).

Table 2. Pharmacotherapy and Behavioral Therapy Comprising a Comprehensive Substance Abuse Treatment Plan

o *Pharmacotherapy*

Opioid Dependence

Methadone--Federally regulated through Opioid Treatment Programs; opioid receptor agonist for pharmacological therapy

Buprenorphine--office based opioid treatment or Opioid Treatment Programs; Federally regulated, partial opioid receptor agonist for pharmacological therapy

Naltrexone--office-based and substance abuse treatment programs; used when opioid abstinence is possible without significant relapse risk; opioid receptor antagonist for relapse prevention

Alcohol Dependence

Naltrexone--an "anti-craving" agent, opioid receptor antagonist; reduced reward effect with daily use; new forms are long acting

Acamprosate--an "anti-craving" agent that normalizes glutamatergic neurotransmission; slow acting, attenuates relapse

Disulfiram--a "vicarious" aversive medication supporting complete abstinence to alcohol that blocks complete oxidation of alcohol with accumulation of acetaldehyde and resultant unpleasant "allergic" physical symptoms when alcohol is absorbed (e.g., flushing, headache, and vomiting)

Nicotine Dependence

Nicotine replacement therapy; many over the counter, such as patches, gum and inhalers used to replace the daily physical requirement for nicotine and may be used for nicotine withdrawal or maintenance

Buproprion--an antidepressant also found to be an "anti-craving" agent that reduces the psychological craving for tobacco

o *Behavioral Therapy*

- Brief interventions--for 1 to 3 visits (low intensity); for early drug use and substance abuse; available in many different outpatient settings
- Motivational enhancement interviewing and therapy
- "12-step" facilitation
- "stage of change" model interventions
- Long term multi-modal and multi-dimensional comprehensive therapies and interventions--to restructure belief and cognitive systems, enhance coping strategies, change friendships and environment, and change behavior

Individual interpersonal one-on-one therapy such as cognitive behavioral therapy and insight-oriented psychotherapy

Group therapy--such as family or faith-based, Therapeutic Communities

"12-step" programs and "clean and sober" recovery living environments in which peer groups interested in sobriety mutually help one another stay sober

Pharmacologic Therapy

Pharmacological treatments, both agonists and antagonists, have been developed and FDA approved for specific drug addictions. Currently, addiction treatment medications are available for nicotine, alcohol, and opiates. Although none are available for stimulants, like cocaine and methamphetamine, many potential medications are now being developed for these addictions, and medication-based therapies are expected to be available over the next few years. Several marketed medications have shown efficacy to reduce cocaine use in initial clinical trials (Vocci and Ling 2005). They include disulfiram, baclofen, modafinil, naltrexone, ondansetron, tiagabine, and topiramate. To date, no medications tested in clinical trials have shown efficacy to reduce methamphetamine use.

National Performance Outcome Measures (NOMS)

An effective treatment strategy for drug abuse and dependence is to match a comprehensive treatment plan to the individual's particular substance abuse problems and needs. Desired treatment outcomes are: a) reduce dependence on drugs of abuse, b) reduce morbidity and mortality of infectious diseases associated with drugs of abuse, and c) maximize the patients' abilities to access services and achieve social integration. SAMHSA has recently developed ten domains (see Table 3) comprising the National Performance Outcome Measures (NOMs) to be utilized in determining the effectiveness of mental health and substance abuse services (SAMHSA, 2005b). The domains identify meaningful, real life outcomes for individuals who strive to attain and sustain recovery from addiction as well as psychiatric illness. They focus on living, working and fully participating in the community. The domains include abstinence from drug use and

alcohol abuse and decreased symptoms of psychiatric illness. Improved functioning also may include such recovery achievements such as getting or keeping a job, staying in school, obtaining housing, re-establishing and/or maintaining social connectedness, and reducing involvement in the criminal justice system. Treatment outcome measures include client perception of care, cost effectiveness of the substance abuse treatment plan and use of evidence-based practices.

Table 3 – National Performance Outcome Measures for Substance Abuse and Mental Health Services

Domain	Outcome	Measure
Abstinence	Abstinence from Drug/Alcohol Use	*Substance abuse treatment*--reduction in frequency of use [reduction in use during treatment; recidivism after treatment]
		Substance abuse prevention—no use in prior 30 days; perceived risk of drug use; age at first use; perception of disapproval of drug use
Employment/ Education	Increased/Retained Employment; Return to/ Stay in school	*Substance abuse treatment*—increase in school attendance or employed during treatment
		Substance abuse prevention--school suspensions or expulsions; workplace drug use; and perception of workplace policy
Housing	Increased stability in Housing	*Substance abuse treatment*--increase in housing stability during treatment
		Mental health treatment--change in living situation including homelessness
Crime and Criminal Justice	Decreased criminal justice involvement	*Substance abuse treatment*--reduction in arrests during treatment
		Substance abuse prevention--drug related crime/arrests including driving under influence; alcohol or drug related care crashes and injuries
Access/ Capacity	Increase access to services (Service Capacity)	*Substance abuse treatment*--number treated versus number in need
		Substance abuse prevention--Mental health treatment--number of persons served
Retention	Increased retention in treatment; decreased utilization of inpatient beds	*Substance abuse treatment*--number treated; length of time in treatment
		Mental health treatment--decreased re-admission into psychiatric hospitals
Social Connectivity	Increased social support	Measure under development
Perception of Care	Client self report	*Mental health treatment*--client report of positive outcome

Cost Effectiveness	(Cost Effectiveness) Average cost	*Substance abuse treatment*--number of states providing services within approved cost *Substance abuse prevention*--increases services within cost bands Mental health treatment—number of persons receiving evidence-based practices
Use of Evidence-Based Practices	Use of evidence-based practices	*Substance abuse prevention*--total number of programs and strategies *Mental health treatment*—number of persons receiving evidence-based practices in a state
Elements are from SAMHSA 2005b		

A substantial body of knowledge exists documenting the effectiveness of pharmacological therapies, as part of a comprehensive substance abuse treatment plan, in reducing heroin use and providing an opportunity for improvement in health and social functioning for individuals addicted to opioids (see Figure 1; Gowing et al. 2004; Johnson and McCaugh 2000; NIDA 2000a). Two recent TIPs from SAMHSA, TIP 40 and TIP 43, provide the best practices guidelines for the use of either methadone or buprenorphine as part of a comprehensive treatment plan for opioid addiction (SAMHSA 2004; SAMHSA 2005).

Addiction treatment services which follow the recommended best medical practices are more likely to manage the care and treatment of hepatitis successfully and to prevent progressive liver disease. The key medications used in the management of opiate dependence are metabolized through the liver, and therapeutic blood levels can be affected by liver disease. Two pharmacologic therapies, methadone and buprenorphine, illustrate the interaction between appropriate pharmacotherapy and the possible impact of liver disease.

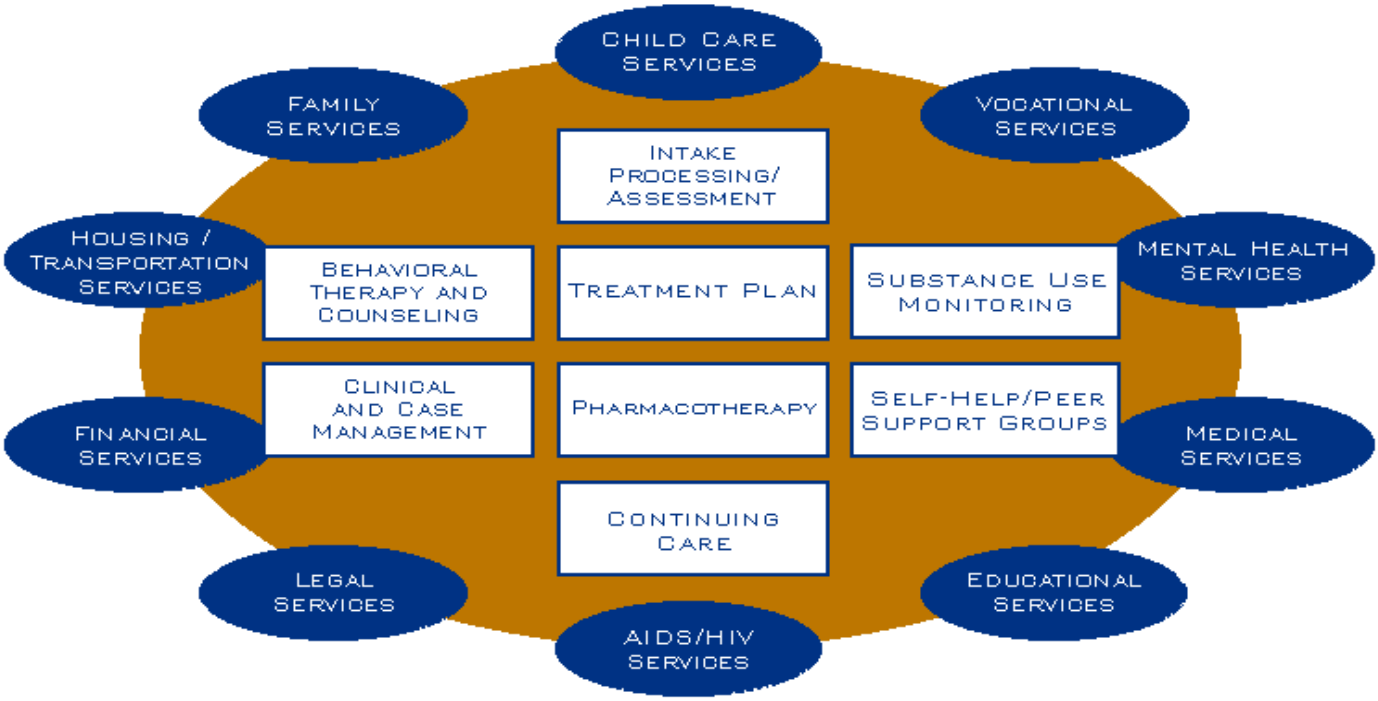

Figure 1: Diagram of the elements of a comprehensive substance abuse treatment plan (from NIDA 2000a).

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Methadone- Methadone, a full opiate agonist, is the mainstay of pharmacotherapy treatment for opioid addiction and helps dependent individuals abstain from illicit drug use and achieve recovery. Methadone is a synthetic μ-opioid ("μ" is also referred to as "mu") receptor agonist with pharmacological properties qualitatively similar to morphine. Methadone doses are up to 80 percent orally bioavailable. Methadone's rate of clearance from the body individually varies by a factor of almost 100, with a consequential risk of drug accumulation and respiratory depression. The elimination half-life averages 24 to 28 hours, but may range from as low as 4 hours to a high of 91 hours. Administered daily as an oral dose, methadone should be present in the blood at levels sufficient to maintain an asymptomatic state during a 24-hour period, without episodes of opioid overmedication

or withdrawal (Payte and Zweben 1998). The serum methadone level (SML) and its elimination half-life may be influenced by individual factors such as poor absorption, variable metabolism and protein binding, changes in urinary pH, concomitant medications, diet, physical condition, patient age or pregnancy, and vitamins or herbal products, such as St. John's wort. Considerable flexibility in dosing is required to stabilize patients and an adequate physiologic methadone level is critical for therapeutic success (Eap et al. 2002).

Methadone has a favorable safety profile when used as indicated (SAMHSA 2005). Research studies have not demonstrated liver toxicity, particularly in patients with underlying liver disease. Serious adverse reactions or cumulative organ damage has not been reported when daily methadone is used in appropriate dosages. Mortality rates of patients in methadone treatment from all causes are typically one-third those of untreated opioid addicts (SAMHSA 2004a). However, fatal overdoses with methadone have been reported as well as deaths of clients in methadone treatment (Clarck et al. 1995; Maxwell et al. 2005; Shah et al. 2005). A recent study of patient in methadone treatment in Texas (Maxwell et al. 2005) revealed 20% of deaths due to liver disease, 18% of deaths due to cardiovascular disease, and 14% due to drug overdose or trauma. In the latter case, it was a younger cohort of patients who died from drug overdose or trauma while older patients died from chronic diseases. In New Mexico, (Shah et al. 2005), 50.3% of deaths from 1998-2002 were from methadone in combination with illicit drugs, while 23.8% were from methadone in combination with prescription drugs (possible pain management patients), and 3.5% due to methadone in combination with alcohol. These data show the importance of other addictive drugs in combination with methadone in unintentional

methadone-related deaths. In treatment, methadone-associated deaths can occur during the induction phase when a patient's level of tolerance to opioids is not correctly assessed or when a patient continues to use other central nervous system depressant drugs in combination with methadone.

Buprenorphine- Primary care physicians may expand patients' access to substance abuse treatment while mitigating the stigma associated with drug use and treatment through the use of buprenorphine. Buprenorphine, a partial agonist of the mu-opiate receptor (Ling and Smith 2002), differs significantly from full agonists (Table 2). At higher doses, buprenorphine reaches a plateau in its agonist properties. This limitation on agonist effects results in an improved safety profile compared with a full agonist such as methadone. Specifically, buprenorphine has a favorable 'ceiling effect' on respiratory depression (Walsh at al. 1994). However, the abuse of other substances which may cause respiratory depression (e.g., benzodiazepines) remains a contraindication with buprenorphine, as with methadone. In addition to improved safety, flexible dosing (e.g., thrice weekly) is feasible since buprenorphine has a high binding affinity for the opiate receptor and slowly dissociates. However, buprenorphine has a higher binding affinity for the mu-opiate receptor than heroin and can precipitate opiate withdrawal when buprenorphine is taken by an opiate dependent patient (Schuh et al. 1996). It is for this reason that buprenorphine inductions must occur in patients already in mild to moderate opiate withdrawal.

A report from France has noted an elevation in liver function tests (especially alanine amino transferase) after the use of intravenous buprenorphine. This report was limited by the small sample size, retrospective analysis, and short time in which

buprenorphine was given (Petry et al. 2002). However, the use of buprenorphine in individuals with known liver disease is of concern and many clinicians have avoided buprenorphine in this patient population. Since 2001, no additional reports of hepatotoxic effects with buprenorphine have been reported in the literature despite the expansion in the number of patients receiving buprenorphine. In 2002, the FDA approved two sublingual buprenorphine products for use in the United States as a treatment for opioid addiction, and in Europe large scale use of buprenorphine continues.

Buprenorphine has been a component of the substance abuse treatment plan for individuals infected with HCV. To date, 36 individuals who are HCV antibody positive and HIV positive have been treated with buprenorphine through a mobile outreach intervention in New Haven, Connecticut No elevations in liver function tests have occurred as a result of the introduction of buprenorphine into this co-infected population (Kresina et al. 2005). Alhough monitoring is required when any medication is added to the other medications that a patient may be taking, the presence of HIV/HCV co-infection or use of antiretroviral therapy is not a contraindication to the use of buprenorphine.

Pharmacotherapy for Alcohol Addiction- Patients with co-occurring IDU, alcoholism, and liver disease may need treated aimed at ending alcohol use. Pharmacotherapy for alcohol addiction includes acamprosate, naltrexone, or disulfiram (Fiellin et al. 2004). Acamprosate and naltrexone have different mechanisms of action and modify different behavioral aspects of addiction. Acamprosate, a long acting compound, prolongs periods of abstinence by normalizing glutamate neurotransmission that is dysregulated during chronic alcohol consumption and withdrawal. Naltrexone is designed to be a fast acting opioid receptor antagonist with a long half-life that was found

to reduce heavy drinking by decreasing the rewarding effects of ethanol. Safety and efficacy of treatment using both drugs for alcohol addiction has been shown in double blind studies (Littleton and Zieglgansberger 2003). A long acting, injectable naltrexone for alcohol dependence is now being tested so that the naltrexone can be taken on a monthly basis (Garbutt et al. 2005). Disulfiram is designed to help motivate patients to remain abstinent from alcohol through "vicarious aversive therapy" in which the patient is informed of the adverse consequences of drinking when taking disulfiram. The drug works by blocking the oxidation of alcohol at the acetaldehyde stage in its metabolism which increases the levels of acetaldehyde. Should alcohol be ingested or absorbed into the body, the patient experiences a series of unpleasant allergic-like symptoms (e.g., flushing, headache, and vomiting).

Current Hepatitis Treatment Guidelines

Hepatitis B Infection.

Numerous medical management guidelines addressing chronic hepatitis B infection are available and are focused on achieving two important patient outcomes: 1) reversing decompensated cirrhosis, so that the patient is no longer a candidate for liver transplantation; and 2) reducing progression of liver disease, so that hepatocellular carcinoma (liver cancer) does not develop (AASLD 2003; Fung and Lok 2005; Kanwal et al. 2005). In 2005, the FDA approved two pharmacologic therapies for the treatment of chronic HBV infection, Pegasys (peginterferon alfa-2a) and entecavir. These therapies join interferon alfa-2b, lamivudine, and adefovir dipivoxil as approved initial therapies for the treatment of chronic HBV infection. All treatment algorithms, using currently approved therapies, have advantages and disadvantages. Issues for consideration in the

development of a treatment regimen include efficacy, safety, incidence of development of viral resistance to therapies, method of administration, and cost effectiveness. A recent analysis of the cost effectiveness of treatment options for the treatment of chronic HBV infection in patients with elevated liver enzymes and minimal to no liver disease indicates that the use of interferon as a first line therapy is cost effective (Kanwal et al. 2005). A hybrid salvage strategy reserving adefovir for lamivudine-associated viral resistance was also determined to be cost effective across health care settings.

Hepatitis C Infection

The medical management of hepatitis C has been addressed by consensus statements or clinical practice guideline development groups in the United States (AASLD 2004; NIH 2002), Canada (Sherman et al. 1997), France (Galmiche 1998), and Europe (EASL 1999). The latest update of treatment guidelines from the National Institutes of Health do not specify the need for a drug-abstinence period but indicate that patients should participate in addiction treatment as an important adjunct to hepatitis C therapy. The updated consensus statement is supported by a systematic evidence review prepared for the Agency for Healthcare Research and Quality (Gebo et al. 2002). It indicates that treatment of chronic HCV infection has been successful even when the patients have not abstained from continued drug or alcohol use. The consensus statement notes that the medical management of HCV-infected injection drug users is enhanced by linking these patients to drug-treatment programs. Treatment for drug and alcohol abuse should be made available to all patients who want and need it.

Health care providers should encourage HCV infected IDUs to enter opioid addiction treatment whether or not they are receiving treatment for HCV infection.

Methadone treatment has been shown to reduce risky behaviors that can spread HCV infection, and it is not a contraindication to treatment for HCV infection. Treatment for HCV infection has been successful when patients are on daily methadone. Efforts should be made to promote collaboration between experts in the treatment of viral hepatitis infections and healthcare providers specializing in substance abuse treatment. However, few data are available on treatment of viral hepatitis infections for patients who inject drugs and who are not in drug treatment programs.

The current clinical practice guidelines of the American Association for the Study of Liver Disease (AASLD 2004) entitled "Diagnosis, Management and Treatment of Hepatitis C" expand on the consensus statement. These guidelines state "The use of methadone or buprenorphine is an effective means of reducing illicit drug use and its complications.… Therefore, methadone use does not directly effect [sic] the management of HCV infection." (p. 1164) The three hepatitis C treatment recommendations for active drug users are as follows:

"Treatment of HCV infection should not be withheld from persons who currently use illicit drugs or who are on a methadone maintenance program, provided they wish to take HCV treatment and are able and willing to maintain close monitoring and practice contraception....

"The decision of whether to treat should be made considering the anticipated risks and benefits for the individual….

"Continued support from drug abuse and psychiatric counseling services is an important adjunct to treatment of HCV infection in persons who use illicit drugs." (p. 1165)

As can be seen, hepatitis C clinical practice guidelines and treatment recommendations have advanced in the context of substance use and abuse. Currently, no established medical rationale justifies denying medical treatment to a methadone patient in need of hepatitis C treatment. Addressing the care and treatment of HCV infection extends to those who continue their addiction with or without methadone treatment. The complexity of hepatitis C care and treatment and treatment decisions in persons using illicit drugs underscores the value of multidisciplinary management and the provision of comprehensive, integrated care and treatment that addresses not only HCV infection but also drug use and social services for the patient.

Achieving Recovery from Addiction and Co-Occurring Hepatitis: Summary

Individuals receiving pharmacologic therapies often have co-occurring disorders that can complicate substance abuse treatment regimens. Addressing co-occurring disorders and co-infections through screening, testing and medical management can facilitate successful patient outcomes of substance abuse treatment. For hepatitis infections, the decision of whether to treat should be made considering the anticipated risks and benefits for the individual. Treatment for hepatitis infections should not be denied to any patient needing it, and efforts encompassing proven supportive interventions may be required for these individuals to become ready for treatment. Individuals stabilized on methadone and otherwise well engaged in an addiction treatment program have been recognized as viable candidates for treatment for HCV infection. Physicians are not required to cease treatment with the methadone and other medications in common use for addiction treatment in order to establish that these patients are ready to begin treatment for HCV infection. Addiction treatment programs promote abstinence from illicit substance use

and alcohol, but also compliance with therapeutic treatment regimens. They facilitate medical follow-up, as well as foster social, psychological, and vocational rehabilitation. OTPs offer a viable way to prepare injection drug users for pharmacotherapies for chronic liver disease and help promote medication compliance and favorable treatment outcomes. Alternatively, individuals receiving pharmacotherapy for addiction through office-based treatment services may require treatment for hepatitis infections during their substance abuse treatment. Thus, hepatitis prevention, care and treatment programs need to be available and integrated into office-based pharmacotherapy for opioid addiction.

Viral Hepatitis Infections and Injection Drug Use

Epidemiology

Chronic liver disease resulting from viral hepatitis infection is a major health problem and is the tenth most frequent cause of death in the United States. A common feature of hepatitis viruses is their potential acquisition and transmission through shared drug use practices, primarily involving injection of drugs. The disease burden and estimated incident infections of HAV, HBV and HCV are summarized in Table 4 (CDC 2004).

Hepatitis A Virus (HAV)

Although generally transmitted by the fecal-oral route, HAV infection in injection drug users can have significant medical consequences. In particular, concurrent infection with HAV in a patient already chronically infected with HBV or HCV places a patient at risk of accelerated progressive liver disease and fulminant hepatic failure (Vento et al. 1998). Individuals with HIV infection are also at increased risk for HAV infection, and a recent national study of HIV-infected individuals in primary care revealed that only 12.5% of injection drug users were vaccinated against HAV infection (Tedaldi et al. 2004).

Epidemiology, Biology, and Transmission. Hepatitis A is a most common food borne disease in the United States with an incubation period ranging from 15-50 days. In uncomplicated cases, the infection is completely resolved by 6 months after infection (Figure 2).

Table 4 – Disease Burden From Viral Hepatitis Estimated in the US in 2003

Virus	Infections		Comment
	New	Chronic	
A (HAV)	61,000*	none	No chronic disease: A third of all Americans have evidence of past HAV infection.
B (HBV)	73,000* acute	1.25 million	About 5% of Americans have evidence of past or current HBV infection.
C (HCV)	30,000* acute	2.7 million	About 3.9 million Americans have evidence of past or current HCV infection.
D (HDV)	Unreliable		Only concurrent with HBV infection.

*estimated new infections in 2003. Data are influenced by annual incidence fluctuations and variable estimates of unreported and/or undiagnosed cases.

Data are from www.cdc.gov/ncidod/diseases/hepatitis/resource/PDFs/disease_burden2004.pdf

Fecal shedding of the virus—which increases the spread of contagion--occurs 10-20 days after infection and may occur when the infected individual is asymptomatic. Fecal shedding lasts for, at most, 10 days after the onset of jaundice, a symptom of liver disease. Post infection, elevated liver enzymes are transient while serum antibodies to HAV are persistent. A serological diagnosis of acute HAV infection is made by the observation of IgM antibody to HAV, IgM anti-HAV, which is detectable through a serum test as early as 20 days after infection (see Figure 2). Concurrent with IgM anti-

HAV is the elevation of liver enzymes (ALT- alanine aminotransferase) indicative of liver injury and reduction of fecal virus shedding. A weekly determination of liver enzymes provides a surrogate marker for the time course of HAV infection.

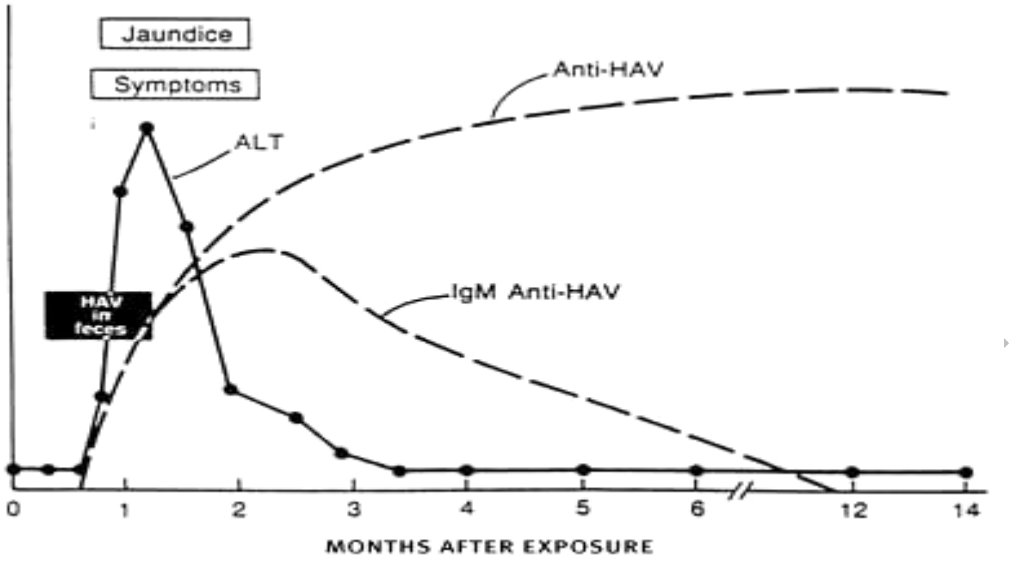

Figure 2: **The time course of an uncomplicated HAV infection** (From Larson et al. 2005)

HAV infection can be prevented by vaccination, and all household contacts should be vaccinated on serologic diagnosis of HAV infection in a household member. Up to a third of all persons in the country are estimated to have been infected at some time, usually during childhood. The estimated annual incidence of HAV infection has dropped substantially since introduction of vaccine in 1995-1996, but 61,000 new infections were estimated to have occurred in 2003. Computer models have estimated the annual incidence of hepatitis A to be 270,000 cases in the United States, which is more than 10 times the reported number (Armstrong and Bell 2002).

Treatment and Prevention. HAV is a small (27 nm.) ribonucleic acid picornavirus that is transmitted mainly through the fecal-oral route and produces either asymptomatic or

symptomatic infection followed by recovery. For injection drug users, HAV can be transmitted intravenously, rarely, by contaminated injection practices: either through equipment shared with an individual who is viremic during acute HAV infection or through use of HAV-contaminated water. But, HAV is most commonly transmitted fecal-orally to injection drug users through poor hygienic practices. There is no specific treatment for HAV infection, and most people recover without medical intervention, although supportive measures such as intravenous fluids are occasionally needed. The case-fatality rate for HAV infection is generally low (less than one percent or about 100 persons per year), although injection drug users with preexisting chronic liver disease (such as alcoholic liver disease or other hepatitis virus infections) are at increased risk of fulminant hepatic failure and death. Death from HAV infection is extremely rare in infants and young persons, and the risk of dying increases with age, particularly in persons who become infected over the age of 40 years. Nearly 20% of reported hepatitis A cases have occurred among injection drug users (CDC 1999), and approximately 6% of reported HAV cases occurred among injection drug users during 2002 (CDC 2004). The CDC recommends that all injection drug users not previously exposed to or infected with HAV be immunized with the hepatitis A vaccine to protect from severe liver disease. Vaccination is not harmful for persons who have been infected with HAV. If pre-vaccination testing for anti-HAV antibodies is being considered as a cost-saving measure, a first dose of the vaccine can be administered at the time of blood draw, especially if the at-risk individual may not return for the test result.

Two hepatitis A vaccines, comprised of inactivated virus, are licensed for use in the United States. The HAVRIX (GlaxoSmith Kline) and VAQTA (Merck) vaccines are

well tolerated, immunogenic and effective in preventing HAV infection. A two-dose series of either vaccine produces detectable protective antibodies in the serum that can last life-long in 98-100% of individuals (Levy et al. 1998). More recently, a combined vaccine for protection from HAV infection and HBV infection has been approved and is called Twinrix (GlaxoSmithKline Vaccines; see www.twinrix.com). Twinrix combines the antigenic components contained in Havrix® (Hepatitis A Vaccine, Inactivated) and Engerix-B® [Hepatitis B Vaccine (Recombinant)]. Twinrix is immunogenic against both HAV and HBV, and provides comparable immunity to the monovalent vaccines when administered in a standard 3-dose schedule.

Hepatitis B Virus

Injection drug users infected with HBV are at high-risk for serious liver disease through the development of cirrhosis or hepatocellular carcinoma. An estimated 2-6% of adults who are infected with HBV will become chronically infected. In addition, persons with chronic liver disease from other causes (for example, chronic HCV infection) may be more likely to develop fulminant liver failure from acute HBV infection. In a recent series of case studies of injection drug users with acute HBV infection, all patients identified with fulminant liver failure died (Garfein et al. 2004). These patients also had chronic HCV infection. Thus, prevention of HBV infection by vaccinating injection drug users is critically important. CDC recommends that all injection drug users who have not been previously vaccinated or exposed to HBV be vaccinated. Vaccination is not harmful for persons who have been infected with HBV. If pre-vaccination testing for anti-HBV antibodies is being considered as a cost-saving measure, a first dose vaccine can be administered at the time of blood draw, especially if the at-risk individual may not

return for the test result. Two hepatitis B vaccines that comprise inactivated virus are licensed for use in the United States. The Recombivax (Merck) and Engerix (GlaxoSmithKline) vaccines are well tolerated, immunogenic, and effective in preventing chronic HBV infection. A three dose series of either vaccine produces protective antibodies in the serum that can last life-long in up to 90% of individuals. As noted above, a three dose series combination hepatitis A and hepatitis B vaccine (Twinrix, GlaxoSmith Kline) is also licensed for use in adults. Education of injection drug users on HBV infection and vaccination is paramount, since a recent study has shown that 52% of injection drug users questioned were not able to accurately self-report their vaccination status (Kuo et al. 2004a). Studies have shown that a hepatitis B vaccination program targeting injection drug users is both feasible and effective (Altice et al. 2005; Kuo et al. 2004; Quaglio et al. 2002).

Biology, Epidemiology, and Transmission. HBV is a small deoxyribonucleic acid virus (42 nm.) with a complex structure. The viral genome, comprised of a circular double-stranded DNA, replicates within infected hepatocytes. Liver disease occurs through an immune response to viral replication in the liver. Individuals infected with HBV can have virus particles in their blood, saliva, and semen. HBV envelope (HBsAg) protein and the secreted protein of the nucleocapsid core (HBeAg) are important viral molecules used as serological markers of infection (see Figure 3; Beers and Berkow 1999; Lok 2004). Antibodies to HBV viral markers appear in the serum of individuals approximately 4 weeks after the signs and symptoms of liver disease, jaundice, and elevated liver enzymes appear. Antibodies to core and surface antigens remain in the serum for years. Acute HBV infection is a self-limited illness, in most immunocompetent

individuals, and resolves in approximately 6 months. Monitoring of a reduction in liver enzymes and the loss of expression of viral antigen in the serum over a six month period is evidence of improvement and resolution of acute infection.

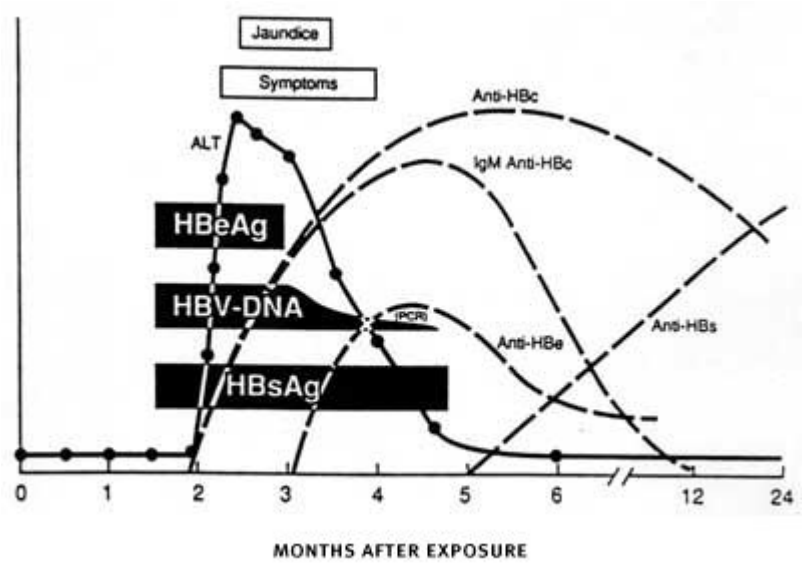

Figure 3: Time course of acute HBV infection showing the expression of viral markers of infection and the immune response to infection (From Larson et al. 2005)

There are eight genotypes and nine subtypes of HBV based on the viral genomic sequence of HBV derived from HBV infected patients from different geographical regions. In the United States, genotypes A and C are highly prevalent, but genotypes B and D can also be found (Fung and Lok 2004). About five percent of persons in the United States have serological evidence of exposure to HBV, and an estimated 73,000 new cases of acute HBV infection occurred in 2003. Because of the success of infant and childhood hepatitis B vaccination programs in the United States, the vast majority of acute HBV infections occur in adults, with most resulting in complete recovery and

immunity from future infection. HBV infection may become chronic in only 5-10% of persons infected as adults (Figure 4); but the infection becomes chronic more frequently in non-immune children (up to 90%) or in immunocompromised patients (30 to 100%). The natural history of HBV chronic infection is characterized by variations of viral replication with spontaneous reactivations or discontinuations. Chronic HBV infection pathology is seen mainly in the liver and is immune-mediated, resulting from not only the host-virus interactions, but also from the complexity of the natural history of chronic HBV infection. Liver pathology leads over time to compensated cirrhosis (yearly incidence of 1.3 to 5.9%). Cirrhosis may result in complications of portal hypertension and liver failure or hepatocellular carcinoma which explain 80% of the morbidity and mortality of HBV infection. The 5-year survival rate of patients with HBV-related cirrhosis ranges from 52 to 82%. Immunosuppression, HDV co-infection, HIV co-infection or chronic alcohol consumption are the main factors which modify and exacerbate the natural history of chronic HBV infection. HBV infection is highly prevalent in immigrant/migrant populations, and epidemiology studies in the United States have shown a race-ethnicity association for HBV infection (Celona et al. 2004). In population studies, Asians are most likely to be infected, compared to African Americans and Caucasians, with Latinos least likely to be seropositive for HBV.

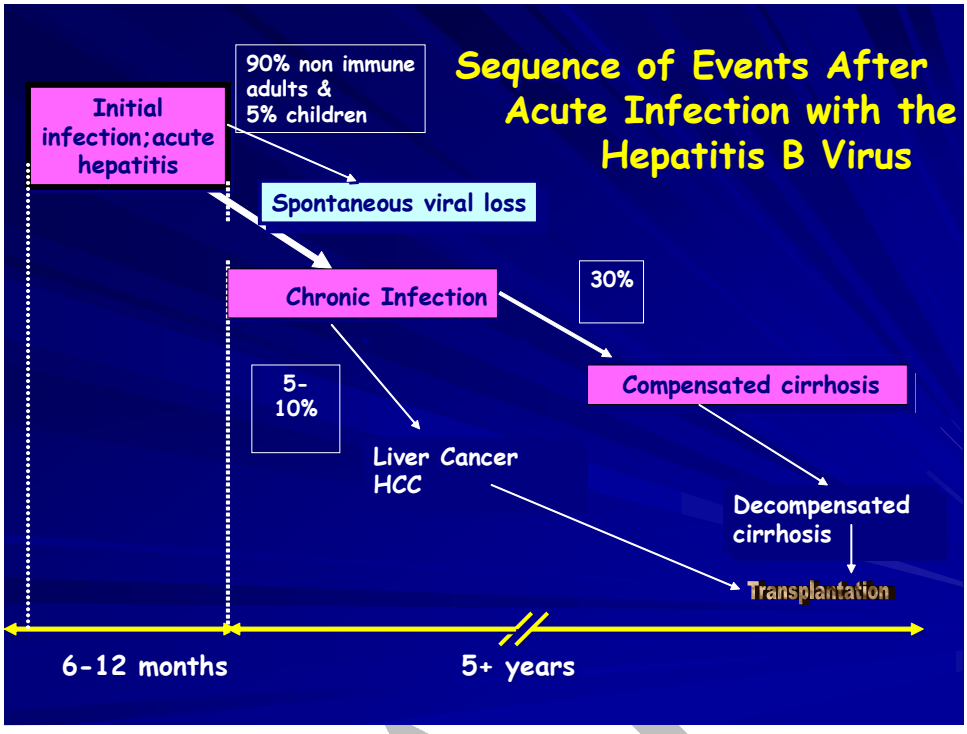

Figure 4 - Diagram of the natural history of infection with the hepatitis B virus

As shown in Table 4, it is estimated that more than one million persons in the United States are chronically infected with HBV. It is also estimated that 15-25% of persons with chronic HBV infection will die prematurely from the consequences of chronic liver disease. Approximately 4,000 persons die each year of hepatitis B-related liver cirrhosis and 1,500 die of hepatocellular cancer related to HBV infection each year (CDC 2002; Fattovitich et al. 2004). Only approximately 15% of individuals with end-stage liver disease meet medical criteria to qualify for liver transplantation (Wong et al. 2004). Individuals with a measurable serum level of HBV DNA, indicative of current HBV replication, and who express HBeAg are at higher risk for progressive liver disease and hepatocellular carcinoma (Lok 2004).

Although sexual contact with an individual chronically infected with HBV is the most common route of transmission, sharing IDU equipment contaminated with HBV can

also lead to infection. Injection drug users accounted for approximately 12% of all cases in 2002, with 40% becoming infected with HBV after one year of IDU and more than 80% becoming infected after 10 years (CDC 2002). Sexual transmission, accounting for half of all HBV infections (41% heterosexual, 9% men having sex with men [MSM]; CDC 2002), also may be an important basis for infection among addicted persons as a result of lifestyle factors (for example, exchanging or selling sex for drugs). The CDC recommends that all injection drug users who have not been exposed to HBV be vaccinated.

Pharmacotherapy. Current pharmacotherapy of chronic HBV infection has limited long-term efficacy (AASLD 2003). A careful assessment of patient age, severity of liver disease, HBeAg status, likelihood of a treatment response, and potential adverse events and complications is needed before treatment begins. Except for patients with contraindications or who previously were non-responsive to therapy, interferon-alfa, lamivudine or adefovir may be used as an initial therapy.

Interferon-alfa, usually prescribed for a 16-week course of therapy, may be an effective treatment for chronic HBV infection with positive HBe-antigen, producing a sustained viral response (SVR) in 25% to 50% of patients (CDC 2002). The use of long-acting pegylated interferon in chronic HBV infection may lead to further improvements in virologic response rates (Janssen et al. 2005). The nucleoside analog lamivudine, an inhibitor of HBV DNA polymerase, is an oral medication that has been shown to be similar in efficacy to standard interferon treatment, but leads to fewer side effects. Prescribed as a long-term oral maintenance therapy, it unfortunately usually leads to the emergence of drug-resistant viral mutations (Raj 2001). Another oral nucleoside

analogue, adefovir dipivoxil, has been recently approved for treatment of HBV infection. It appears to have a very low rate of inducing viral resistance and may be effective in persons developing lamivudine-resistant strains (Mutimer et al. 2001; Walsh et al. 2001). Combination therapy, using two or more approved drugs for chronic HBV infection, may be on the horizon in an effort to enhance treatment outcomes.

In choosing an anti-viral agent to use as a first-line therapy, consideration should be given to long term safety, efficacy, medication cost, monitoring tests, clinic visits, and patient and provider preferences (AASLD 2003). While viral clearance is the ultimate objective of all therapies for hepatitis, additional benefits may accrue from antiviral treatment. For patients who fail to clear the virus, ongoing pharmacotherapy has been shown to improve liver histology and reduce the risk of progressive liver disease, thus lowering rates of cirrhosis and/or hepatocellular carcinoma in some patients (Raj 2001; Straley and Terrault 2004).

Hepatitis B Virus and Hepatitis D Virus Co-infection

HBV infection may be accompanied by the presence of HDV, which has an incomplete RNA virion that requires a helper function of HBV in order to replicate. Because HDV undergoes viral replication in the liver utilizing HBV genes (Beers and Berkow 1999; Tennant 2001), HDV cannot exist in the absence of chronic infection with HBV. The prevalence of hepatitis D in the United States is relatively low, although injection drug users may be at high risk. HDV infection compounds the liver disease associated with HBV infection and increases the risk of liver cancer 2-6 fold compared to HBV infection alone (Fattovitch et al. 2004). HBV/HDV co-infection should be suspected in a patient who presents with severe acute HBV infection, since co-infection is

associated with fulminant hepatitis. The diagnosis of acute HDV infection is based on the determination of serum IgM or seroconverstion to IgG HDV antibodies (see Figure 5). However, HDV serology can be unreliable in staging HDV infection. In a recent outbreak of HBV infection in injection drug users with a high prevalence of HDV infection, risk factors for co-infection were having more than one sex partner, injecting more than four times a day, and sharing injection equipment with more than two persons. The important public health issue of exacerbated liver disease in HBV/HDV co-infection can be seen in this outbreak since all individuals co-infected died of fulminant liver failure (Bialek et al. 2005).

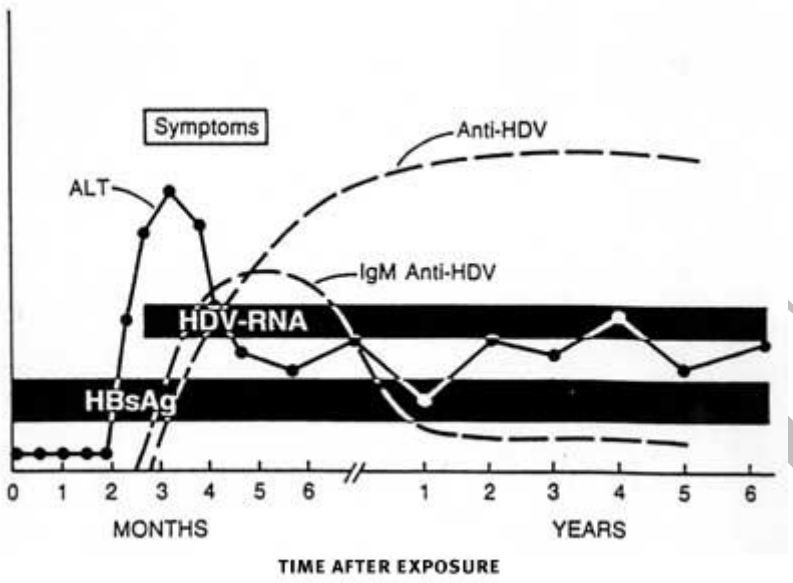

Figure 5: Time course of acute (months) and chronic (years) HDV superinfection (HBV/HDV co-infection) (From Larson et al. 2005)

Treatment. Interferon therapy in persons co-infected with HBV and HDV is less effective because of the complications associated with this type of infection. While treatment decreases liver enzyme levels and suppresses HBV replication, the virus is not eradicated and, typically, HBV infection reasserts itself if treatment is stopped.

Hepatitis C Virus

IDU is the major high-risk activity for the acquisition of HCV infection. Through the implementation of hepatitis C prevention interventions, including hepatitis C education, the spread of HCV infection within the IDU risk group has slowed. However, the morbidity and mortality of HCV infection has been estimated to cost $5.46 billion annually in the United States (Leigh et al. 2001). Current public health efforts addressing the spread of hepatitis C in the injection drug user community have included computer modeling of the transmission dynamics of the epidemic (Pybus et al. 2005).

Biology, epidemiology, and transmission. HCV is a small (40 to 60 nm. diameter), enveloped, single-stranded RNA virus of the family Flaviviridae. To date, six different genotypes and up to 90 subtypes of HCV have been identified. The virus undergoes continuous mutation leading to the development of quasispecies. The development of genetic diversity during viral replication is one of the primary factors responsible for its resistance to eradication by the immune system and resultant chronicity of infection. The HCV is grouped into six genetic "families," or genotypes. HCV genotype 1 predominates in the United States, accounting for 65 to 75% of infections, with genotypes 2 or 3 comprising most other HCV infections. Although the extent of liver disease does not differ among the different genotypes, SVR to current pharmacotherapies are significantly lower in patients with genotype 1 compared with genotypes 2 or 3. Hence, the current recommended length of treatment for interferon-based combination therapy is less for genotypes 2 and 3 compared to genotype 1. However, genotype alone does not provide sufficient predictive value for assessing treatment eligibility (AASLD 2004; Chitturi and George 2000; NIH 2002).

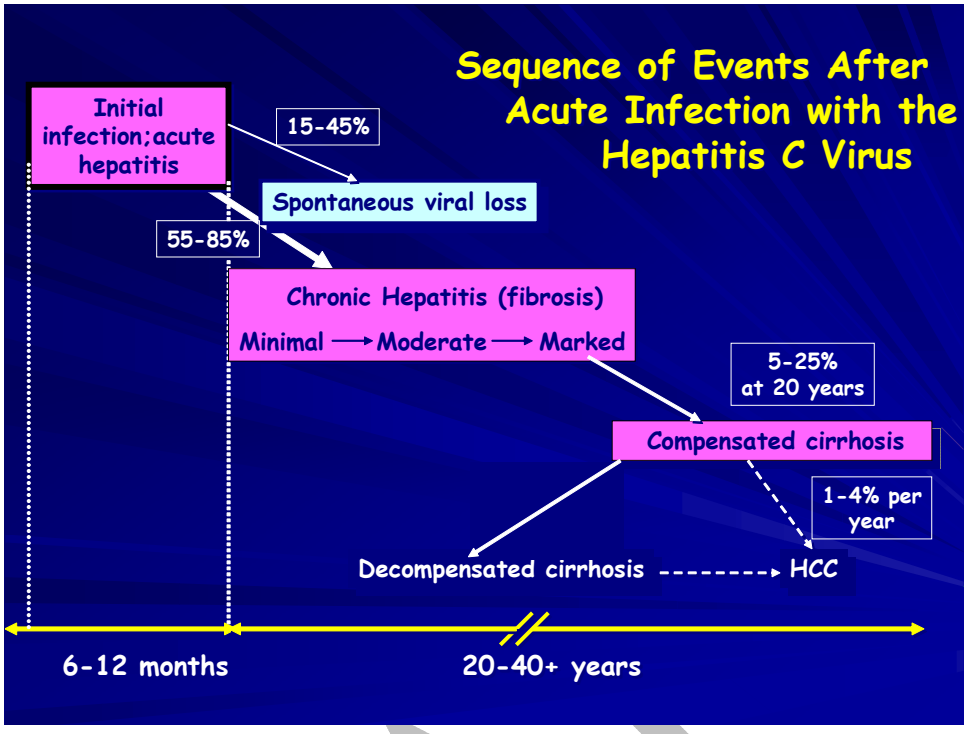

Figure 6 - Diagram of the natural history of infection with the hepatitis C virus

HCV infection is the most common chronic blood-borne infection in the United States, although the exact prevalence of this infection may be underestimated since many infected persons are asymptomatic. According to a population-based, household survey, the National Health and Nutrition Examination Survey (NHANES III), nearly four million Americans are estimated to have been exposed to HCV and therefore exhibit antibodies to the virus. This is approximately four times the number infected with HIV. Infection with HCV typically leads to chronic viremia. A diagram of the natural history of chronic hepatitis C infection is presented in Figure 6. A recent review of longitudinal studies of HCV infection indicated that spontaneous clearance of virus occurs in approximately one in four individuals during acute HCV infection (Micallef et al. 2005). Studies have also shown that HCV viral sequences can be detected in approximately 69%

of persons who are antibody-positive, corresponding to an estimated 2.7 million persons in the United States with active chronic HCV infection (Table 4). This viremic infection is prominent in males and non-Hispanic African-Americans. The peak prevalence at the time of NHANES III, conducted from 1988-1994, was in persons 30 to 49 years of age (Alter et al. 1999). Given the decreasing incidence of new infection and high persistence of infection in those exposed, it is likely that the highest prevalence of chronic infection is now in persons 40-59 years of age.

Alone or in combination with alcohol consumption, HCV infections account for about 60% of all newly diagnosed cases of chronic liver disease and are the leading reason for liver transplantation and a major etiology of hepatocellular carcinoma in Americans (Chitturi and George 2000; NIDA 2000). Overall, hepatitis C is responsible for up to 70% of chronic hepatitis cases, 30 to 40% of cases of cirrhosis and end stage liver disease (ESLD), and 60% of liver cancer cases (CDC 1998).

While prospective studies have shown that approximately 55-85% of exposed persons will develop a chronic infection with the virus, up to 50% of patients including injection drug users may clear the virus (spontaneous self cure) during acute infection (Jauncey et al. 2004). In a recent study of viral clearance in drug abusing veterans, increasing age at the time of HCV infection, alcohol consumption and HIV co-infection were negatively associated with spontaneous HCV infection clearance (Piasecki et al. 2004). Individuals not clearing HCV infection may develop progressive liver disease and hepatitis C-induced cirrhosis, which occurs in up to 20% of persons after approximately 20 years of chronic infection (Figure 6). Approximately one quarter of persons progressing to cirrhosis may develop ESLD and become candidates for liver

transplantation. ESLD, or hepatic decompensation, is characterized by: 1) ascites (diuretic sensitive or diuretic refractory), or 2) variceal hemorrhage, or 3) hepatic encephalopathy. Assessing patients for comorbid conditions, such as concurrent HIV or HBV infections or alcoholic liver disease, and preventing the development of additional comorbidities--by vaccinating against HAV and HBV infections as well as referring for substance abuse treatment--are fundamental to the medical management of chronic hepatitis C. For injection drug users this can best be achieved by integrating care and treatment for both substance abuse and HCV infection (Edlin et al. 2005).

Patients who develop decompensated cirrhosis have a high likelihood of dying from complications of liver disease. Currently, approximately 8,000 to 10,000 persons in the United States are estimated to die from liver disease as a result of HCV infection each year, and the CDC has predicted that HCV-related mortality could double or triple during the next decade or two (CDC 1998).

IDU accounts for the majority of HCV infections, greatly exceeding all other transmission factors (see Figure 7). Sexual exposure is estimated to account for approximately 15% of cases of HCV infection, and transmission by this route is associated with multiple sexual partners and sexually-transmitted diseases. Almost all blood transfusion-related cases occurred prior to initiation of blood product screening in 1992. Other transmission routes, as shown in Figure 7, include healthcare-related cases (for example, accidental needle-stick, or unclean medical procedure equipment), hemodialysis, tattooing, and mother-to-child transmission during birth. In a small but significant number of cases the etiology cannot be identified (Alter et al. 1999; CDC 1998).

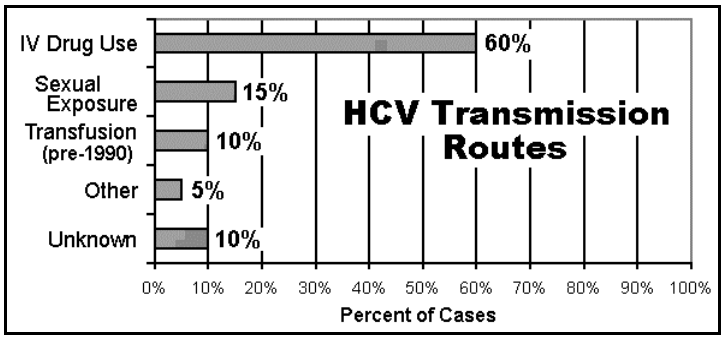

Figure 7 - **Injection-drug use accounts for the majority of HCV cases**.

Treatment of HCV Infection. According to current hepatitis C treatment guidelines, all patients with chronic HCV infection are potential candidates for antiviral therapy. Drug users, individuals with a history of drug use, or individuals in drug addiction treatment should not be excluded from needed hepatitis C treatment, as a result of drug use issues (AASLD 2004; Scott 2005). Generally, patients with biopsy-proven liver disease who are at increased risk for progression to cirrhosis and ESLD are considered to be treatment candidates. In addition, those with factors associated with increased risk of rapidly progressive liver disease such as HIV/HCV or HBV/HCV co-infection are also candidates for treatment. Because individuals with acute HCV infection may be highly responsive to interferon therapy, consideration should be given to early treatment when the infection is diagnosed acutely. Individuals with cirrhosis, determined through liver biopsy or through surrogate biochemical markers, can be offered pharmacotherapy for HCV. However, those with signs of hepatic decompensation--including ascites, persistent jaundice, wasting, variceal hemorrhage, or hepatic encephalopathy--are at high risk for treatment-related complications and death, and therefore should be referred for clinical trials or liver transplantation.

During the past decade with the introduction of new pharmacologic agents and combination treatments for hepatitis C, the treatment of chronic HCV infection continues to evolve and has become increasingly effective. The SVR is the benchmark of treatment success and is defined as an undetectable HCV RNA six months after the end of treatment. While therapy once achieved SVRs of less than 20%, approximately 55% of uncomplicated patients treated with current antiviral regimens today can expect an SVR. In follow-up studies of these patients virtually all have remained virus free (Kjaergard et al. 2001). Responses as high as 90% have been achieved in select populations. However, the development of similarly effective treatment options for patient groups at high risk for treatment-related complications and progressive liver failure remains an ongoing challenge (Davis and Rodrigue 2001; Manns and Wedemeyer 2001).

To date, the standard therapy for chronic hepatitis C infection is the combination of peginterferon and ribavirin. Peginterferon with ribavirin has improved overall SVRs to greater than 50% (Davis and Rodrigue 2001). Maximium SVRs may occur in treatment with peginterferon and weight-based ribavirin (Torriani et al. 2004). However, hepatitis therapies will continue to evolve every few years, providing greater efficacy (Shad and McHutchison 2001).

A number of factors have been described as major influences on the outcomes in interferon-based treatment regimens. They include both host factors as well as viral factors and are summarized in Table 5 (McHutchison and Poynard 1999; Ryder and Beckingham 2001). A significant factor associated with successful SVR is HCV

Table 5: Factors Influencing HCV Treatment Outcomes	
Host Factors	**Viral Factors**
• High degree of fibrosis • Age > 40 or 50 at time of infection • Male sex • Weight > 75 kg.; 165 lbs. • African-American • Long duration of infection • HIV co-infection	• Genotype 1 • Viral load > 2 million copies/ml. • Large number of quasispecies

genotype. Genotype 1 infections are substantially less responsive to interferon-based pharmacotherapy. Typically, overall SVR in the range of 40-55% can be expected with peginterferon/ribavirin combination therapy. By contrast an SVR of about 80% or more has been consistently reported in clinical trials of patients with HCV genotype 2 or 3 treated with peginterferon/ribavirin regimens. In efforts to enhance SVRs for patients with HCV genotype 1, a number of clinical trials of other agents and dosing strategies are underway. Induction regimens, lengthier treatment regimens, consensus interferon, and gamma interferon have all shown efficacy in preliminary trials. The use of mycophenolate mofetil and amantadine as adjunctive agents is also currently under study. Recent reports at the 2004 meeting of the American Association for the Study of Liver Disease in Boston indicated that phase II clinical trials are beginning for HCV protease inhibitors as well as HCV polymerase inhibitors (Afdhal et al. 2004; Chu et al. 2004). Other potential therapies are in development such as antisense oligonucleotides to inhibit viral replication; anti-fibrotic compounds; and inhibitors of the enzyme inosine monophosphate dehydrogenase, which deplete intracellular guanosine triphosphate levels

(Di Bisceglie et al. 2002). However, it will likely be a number of years before the efficacy of these newer products can be determined through clinical trials and become standard treatment regimens.

Hepatitis C Treatment: Complementary & Alternative Medicine

Approximately one-third of patients with chronic liver disease have been reported to use complementary and alternative medicines, and many use them without the knowledge of their physicians (Seeff et al. 2001). Silymarin (milk thistle) is the complementary medication most frequently used, but St. John's wort, ginkgo biloba, ginseng, garlic extract, echinacea, and "Liverite" (a liver hydrolysate containing amino acids, vitamin B_{12}, choline, inositol, lecithin, phosphatidylethanolamine, and phosphatidylinositol) are also commonly taken in an attempt to minimize the liver damage caused by HCV infection (NCCAM 2000). The NIH's National Center for Complementary and Alternative Medicine is careful to note that, "no complementary medicine or alternative medicine therapies have been scientifically proven to cure or even ease symptoms of hepatitis C." (NCCAM 2000, p. 2) The interactions of these agents with interferon-based treatment regimens and adjunctive medications (for example, methadone, antidepressants, etc.) are not known, but such "drug-drug interactions" may be significant, and certain alternative medications such as kava-kava have been associated with the development of fulminant liver failure.

Hepatitis and HIV Co-infection

Biology, Epidemiology, and Transmission. Viral hepatitis and HIV infections are intersecting epidemics among injection drug users in the United States and in other

countries and possess many shared public health and treatment concerns (Bonacini 2002; Peters 2005). It is estimated that 750,000 to 1.5 million persons in the United States are infected with HIV and approximately 40,000 new cases occur annually. Up to 60% of injection drug users are infected with HIV. One survey of 295 patients entering an OTP found a prevalence of markers for HCV, HBV, and HIV of 80, 65, and 32%, respectively. Among the HIV-positive patients, 88% also were positive for HCV or HBV exposure (Chamot et al. 1992). Thus, viral hepatitis and HIV co-infection may be common among patients seeking or receiving treatment for opioid addiction.

HBV-HIV Co-infection Among patients infected with HIV, rates of chronic HBV infection range from 7-10%, with IDU cohorts reporting rates approaching 70% (Shire and Sherman 2005). A study of HBV and HIV transmission has shown that HBV is sexually transmitted nearly nine times more efficiently than HIV (Kingsley et al. 1990). Therefore, sexual transmission of HBV and the intravenous inoculation of HBV through IDU need to be considered as potential transmission routes.

HIV infection modifies the natural history of HBV infection. Individuals with HIV infection are more likely not to spontaneously clear or resolve HBV infection and, thus, become chronic carriers of HBV. The ability to spontaneously clear HBV infection is dependent on generating an immune response to infection. For individuals infected with HIV, immune competence is a function of their CD4 count. Thus, managing HIV infection and maintaining elevated CD counts can be keys to managing the early stages of HIV/HBV co-infection. However, HIV induced immunodeficiency can reduce the immune mediated liver disease induced by HBV infection, but promote HBV replication. Reconstituting an immune response in HIV/HBV chronically co-infected patients through

the use of antiretroviral therapy may result in enhanced liver damage and an initial flare up in liver enzymes. Recent cohort studies of HBV/HIV infected patients show higher rates of liver-related mortality than in patients with HIV-monoinfection (Thio et al. 2002).

Treatment of HBV-HIV Co-infection. There has been a renewed interest in the medical management of HBV/HIV co-infection with the advances seen in anti-retroviral therapy (Alberti et al. 2005; Nunez and Soriano 2005; Peters 2005; Shire and Sherman 2005; Soriano et al. 2005). For co-infected patients, control of HIV infection is the priority. With the control of HIV, patients who are candidates for HBV therapy have the same treatment goals as individuals infected with HBV alone: loss of hepatitis B surface antigen, production of innate immunity to hepatitis, hepatitis B e antigen (HBeAg) seroconversion, normalization of elevated liver enzymes, reduced liver disease progression, prevention of the appearance of hepatocellular carcinoma, as well as, suppression of HBV replication. Although there are currently no FDA approved drugs for the treatment of HBV/HIV co-infection, pharmacotherapy options include interferon-a (pegylated), lamivudine, adefovir, tenofovir, emtricitabine, and entecavir. The multiple anti-viral options available allow for combination regimens and salvage therapy once drug resistant virus develops. Table 6 provides representative treatment options targeting specific aspects of co-infection for patients with HBV/HIV co-infection based on either the United States Public Health Service Treatment Guidelines (Benson et al. 2004), the Spanish Consensus Conference recommendations (Soriano et al. 2004), the European Consensus Conference Guidelines (Alberti et al. 2005) or the recommendations of an International Panel of Experts (Soriano et al. 2005).

- **Table 6: Treatment Targets and Possible Options for Patients with HBV/HIV Co-infection**

Co-infection Target	Treatment Option
Hepatitis B virus ($HBeAg^+$)	interferon-a (pegylated); entecavir; or Adefovir
Hepatitis B virus ($HBeAg^-$)	Interferon-a (pegylated); Entecavir; Adefovir
Hepatitis B virus and HIV	anti-retroviral (HIV) regimen including lamivudine or emtricitabine with tenofovir or adefovir
To control HIV	anti-retroviral (HIV) regime adefovir or entecavir anti-retroviral (HIV) regimen + one HBV anti-viral drug to avoid immune reconstitution induced liver disease

HCV-HIV Co-infection. Eighty percent or more of injection drug users infected with HIV have concurrently tested positive for exposure to HCV. The mode of transmission is through sharing of injection equipment resulting in the intravenous inoculation of virus. The majority (80-85%) of those exposed to HCV will become chronically infected (see Figure 8).

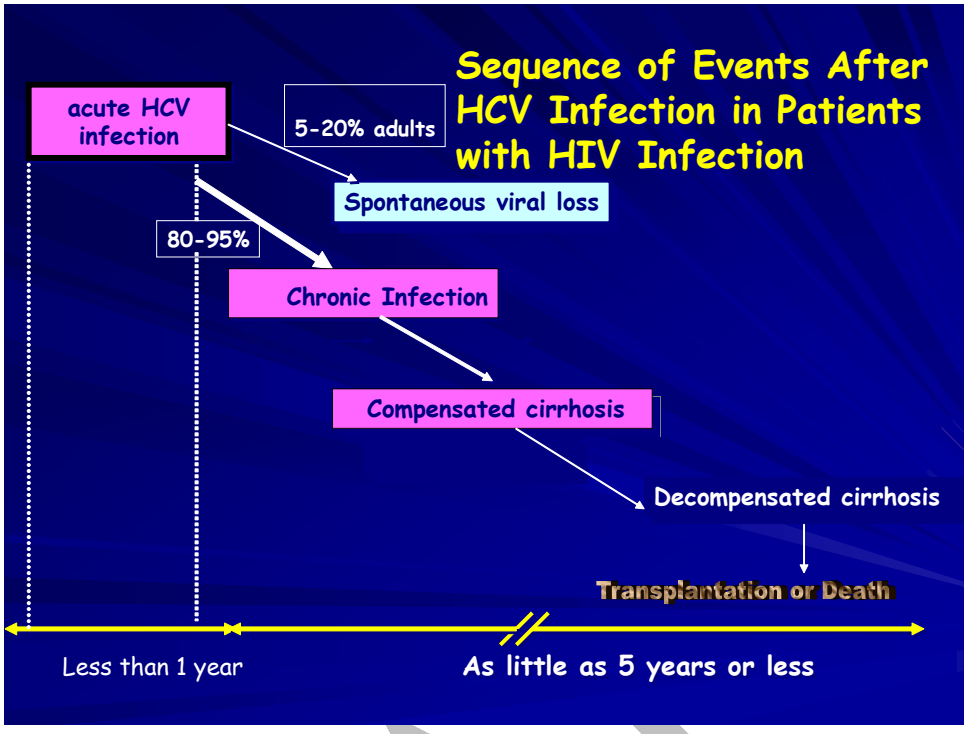

Figure 8: Diagram of the natural history of HCV infection in patients with HIV infection

Most research studies indicate that HCV-positive persons co-infected with HIV tend to have more rapid declines in health, even when they receive antiretroviral therapy for HIV infection (Alvarez and Latorre 2004; Greub et al. 2000). HIV co-infection has also been shown to shorten the survival time of patients with HCV-related decompensated cirrhosis (Pineda et al. 2005). In contrast, other investigators have found in their population of patients that HCV co-infection did not alter the risk of dying, developing acquired immune deficiency syndrome, or responding immunologically to antiretroviral therapy (Sulkowski et al. 2002).

Prior to implementation of anti-retroviral therapy, life expectancies were shorter and progressive liver disease was less evident in co-infected injection drug users. In the anti-retroviral therapy era, life spans of patients with HIV infection are increasing, and end-stage liver disease is emerging as a major cause of morbidity and mortality in this

population. There is growing experience with treating HCV infection in HIV co-infected persons (Dore and Thomas 2005; Mauss and Rockstroh 2005; Sulkowski 2004).

Treatment of HCV-HIV Co-infection. The medical management of patients infected with HIV and HCV remains a significant medical problem. Medical management and treatment recommendations for HCV infection in HIV infected individuals are available from the Hepatitis C Resource Centers (Department of Veterans Affairs 2005). HCV-related liver disease in patients with HCV/HIV co-infection is a significant medical management issue. Thus, treatment guidelines for the management of HCV recommend that patients with HIV/HCV undergo medical evaluation for HCV-related liver disease. Currently, liver biopsy remains the gold standard for the evaluation of liver disease (Sterling 2005), but efforts are underway to develop non-invasive surrogate markers to accurately stage mild *versus* advanced liver disease in patients with HIV/HCV co-infection (Kelleher et al. 2005). The level of liver disease is a consideration for HCV treatment as well as a correlate for anti-retroviral associated hepatoxicity in the treatment of HIV for co-infected patients (Aranzabal et al. 2005). In addition, the treatment of patients with HIV/HCV co-infection is further complicated by the relatively high prevalence of other medical and psychiatric comorbidities as well as the influence of each infection on the natural history of the other. Compared to HCV monoinfected individuals, HCV/HIV co-infection results in a shorted interval for the appearance of clinically relevant liver disease, accelerated progression of liver disease and increased mortality as a result of HCV-induced liver disease (Figure 8). The treatment of HIV with antiretroviral regimens may result in an increase of HCV viral load and liver toxicity. Elevated HCV viral loads are commonly found in HCV/HIV co-infected individuals

compared to monoinfected individuals, and do not predict good outcomes for HCV treatment. Efficacy of interferon-based treatment of HCV infected individuals is inversely related to HCV viral load and level of liver disease. Thus, HCV/HIV co-infected individuals who are in most need of efficacious treatment regimens are least likely to respond to current HCV treatment.

A reduced response to HCV treatment in HCV/HIV populations is clearly evident from the data of three large-scale treatment trials (Carrat et al. 2004; Chung et al. 2004; Torriani et al. 2004). These three clinical trials reported similar SVR despite having diverse clinical trials designs. The APRICOT international clinical trial provided the best SVR to HCV treatment of HCV/HIV co-infected patients at 40% (Carrat et al. 2004). This study shows the importance of maximizing ribavirin concentration in combination with interferon treatment for patients with minimal liver disease to produce a SVR. The NIH supported AIDS Clinical Trials Group (ACTG5071) study reported a 27% SVR for co-infected patients with a history of drug use and minimal liver disease (Chung et al. 2004). This study reported a SVR of 15% for the patients infected with HCV genotype 1, the major HCV genotype observed in injection drug users. The RIBAVIC study, a European study with a majority of injection drug users, reported a 27% SVR in patients who completed treatment, with an SVR for genotype 1 of less than 10% (Torriani et al. 2004). In this study, almost one of every two patients was unable to complete the treatment regimen. This latter study indicated the difficulty facing health care providers in providing HCV treatment for co-infected individuals and the need for support services for these patients to maximize successful outcomes.

An important parameter in the response to treatment in HCV/HIV co-infected patients may be immune competence (Graham et al. 2005). However, the hallmark of HIV infection is the gradual loss of $CD4^+$ cells as the infection progresses from acute to chronic. Progression of liver disease in the immunocompromised host is accelerated, but the immunopathogenic events that take place during this progression are poorly understood. The presence of $CD4^+$ cells may be required for HCV clearance and self-limited disease (Post et al. 2004). A weak or limited $CD4^+$ response to HCV antigens has been shown to be associated with a rapid progression of liver disease related to HCV infection, both in transplantation and non-transplantation setting. In patients with HCV/HIV co-infection, $CD4^+$ T cell proliferative immune responses to HCV antigens are lower than in HCV monoinfected patients. Thus, in HCV/HIV co-infection, there may be a loss of recognition of HCV antigens and/or the loss of $CD4^+$ helper function to induce $CD8^+$ cytolytic cells which neutralize cells infected with HCV (Einav and Koziel 2002). Immune enhancement strategies may be important in HCV/HIV co-infection to reduce the depletion of $CD4^+$ cells thereby promoting both host defense mechanisms and enhanced responses to therapeutic regimens.

Viral Hepatitis Infection, Pharmacologic Therapy and Opioid Treatment Programs

Integration of Addiction Treatment with Hepatitis Prevention, Screening and Treatment

OTPs can provide comprehensive therapeutic milieus comprised of primary medical care, psychosocial counseling, vocational rehabilitation, HIV testing and counseling, HCV education and testing, and other vital medical and social services. Noting the complex medical management issues related to substance abuse, addiction and its associated comorbidities, comprehensive medical and social programs are needed to address the health issues of injection drug users. As noted earlier, substance abuse treatment programs that offer a broader array and greater frequency of services have reported improved retention times and treatment outcomes. Programs responsive to the severity of drug abuse during the initial stages of drug treatment have been shown to produce positive treatment outcomes based on greater retention time in treatment and patient satisfaction with treatment services (Hser et al. 2004). Maximum retention time in methadone treatment is associated with comprehensive treatment, provision of frequent health services, and appropriate methadone dosing (Booth et al. 2004).

Comprehensive services for hepatitis infection include both hepatitis care and treatment. Elements of hepatitis care for drug users include screening for at-risk behavior; HAV, HBV, HCV and HIV testing; prevention counseling and education; vaccination against HAV and HBV infections; and evaluation for comorbidities,

including the need for substance abuse services, psychiatric care, social support, liver disease evaluation, and interferon-based hepatitis C treatment.

Reports indicate that injection drug users tend to become infected with HCV rapidly. From 50 to 80% of individuals comprising IDU cohorts have been shown to be infected within 6 to 12 months of beginning IDU (NIDA 2000). Thus, potentially all injection drug users may be found to be HCV infected if they enter drug treatment and are screened for HCV infection after years of drug use (CDC 1998; Davis and Rodrigue 2001). Prevalence estimates of HCV infection in former and current injection drug users, usually derived from surveys of patients in methadone treatment programs, range from 72% to greater than 90% (CDC 1998; Inglesby 1999; McCarthy and Flynn 2001; NIDA 2000; Stein et al. 2001), as compared with 1.8% in the overall U.S. population (Alter et al. 1999; CDC 1998). In one study of 306 OTP patients, a high seroprevalence of antibody to HCV (87%) was detected, yet 82% had not received prior testing for the infection (Stein et al. 2001). The CDC has recommended routine HCV testing for individuals who have ever injected illegal drugs, as part of a national strategy to identify HCV-infected individuals and prevent the consequences of their infection (CDC 1998). In addition, peer driven counseling and testing for hepatitis infection has been shown to change risky behaviors of injection drug users associated with the transmission of HCV (Aitken et al. 2002).

Hepatitis C treatment studies have reported that approximately one fifth of current alcohol and/or drug abusers do not comply with hepatitis C treatment monitoring or are lost to follow-up, and ongoing drug use may increase viral load and reduce virologic response to treatment (Davis and Rodrigue 2001; Sylvestre 2002) . However, patients

with co-occurring HCV infection and substance use can complete interferon-based treatment with careful monitoring and aggressive intervention. Hepatitis C treatment providers who integrate early interventions for drug use and other comorbidities into their hepatitis C treatment algorithm promote good outcomes. Using this hepatitis C treatment paradigm, studies show that patients with current or past histories of significant substance use disorders can successfully complete a course of interferon-based therapy and obtain an SVR (Sylvestre et al. 2005).

Clinical studies of hepatitis C treatments have not targeted patients receiving methadone or other substance abuse treatments. Methadone treatment has been considered a confounding factor in determining treatment efficacy, and the OTP population has been viewed as atypical hepatitis C patients. Medication adherence in former and current injection drug users is also a concern. However a growing number of studies (Mauss et al. 2004; Schaefer et al. 2003; Sylvestre et al. 2005; Van Thiel et al. 2003) have found that interferon-based treatment regimens are safe and effective for patients receiving methadone treatment, that dosing of interferon or ribavirin is not altered by methadone, and that patients who discontinue hepatitis C therapy while receiving methadone do so early in the course of hepatitis C treatment. Patients receiving methadone treatment should not be withdrawn from methadone prior to hepatitis C treatment, since continued methadone maintenance can be helpful in enhancing quality of life through stabilization during hepatitis C treatment. However, additional research is needed to better understand the natural history of HCV infection in patients receiving pharmacotherapy for substance use. There is a growing base of data indicating that interferon-based therapy is effective in substance abuse treatment settings. Therefore,

AASLD Clinical Practice Guidelines recommend that hepatitis C treatment not be withheld from individuals attending and seeking treatment for HCV infection in OTPs (Strader et al. 2004).

Early Screening, Testing and Treatment for HCV infection

The optimal methods for detecting HCV infection are to screen populations for a history of at-risk behaviors and to test selected individuals for HCV exposure who have an identified risk behavior or factor (AASLD 2004). As stated earlier, IDU is the chief mode of HCV transmission in the United States and anyone with a history of injecting drugs should be tested for HCV infection (CDC 1998). However, there is no specific diagnostic test for acute HCV infection and no treatment recommendations about the timing of hepatitis C treatment, other than to assess whether chronic HCV infection has developed prior to treatment. Nevertheless, this does not preclude health care providers from screening individuals for risk factors, offering HCV testing to those at increased risk for HCV infection as well as providing infected individuals with hepatitis C counseling, medical evaluation, care, and treatment (Alter et al. 2004). Testing for HCV infection and treating patients who test positive is an effective approach. An SVR of 98% was obtained with patients treated within three months of testing positive for HCV infection (Jaeckel et al. 2001). In addition, the only controlled clinical trial of initiation of interferon-based treatment in acute HCV infection (8 weeks post exposure) showed an SVR of 100% (Normura et al. 2004). Based on these studies, some researchers and clinicians propose treating acute HCV infection expeditiously because it is likely to prevent complications, such as cirrhosis, and to be cost-effective (Santantonio 2004). However, treating acute HCV infection is a controversial topic, and additional studies to

support such a recommendation are needed. Early screening, HCV testing and treatment of hepatitis C may be problematic, since acute infections are mostly asymptomatic and rarely recognized clinically. Thus, diagnostic testing of all at-risk individuals would be necessary (Villano et al. 1999). This includes the use of elevated levels of liver enzymes in identifying at-risk individuals (see Figure 9). However, liver function tests typically exhibit high variability over time in HCV-infected patients, so their predictive value is somewhat ambiguous (Inglesby et al. 1999).

Without appropriate laboratory tests, it is difficult to identify recent or acute HCV infection in opioid-addicted persons first entering OTPs because concurrent morbidity can mask any hepatitis C symptoms (Chitturri and George 2000; Leavitt 2001; Sylvestre 2002). Exposure to HCV is determined by the presence of serum antibody to HCV through use of an enzyme immunoassay (EIA). HCV infection is determined by identifying HCV virus in serum samples using molecular tests such as polymerase chain reaction (PCR) and/or transcription-mediated amplification (NIH 2002). In a recent study of 493 patients exposed to HCV who were in opioid treatment, 77% were found to have HCV infection as determined by PCR analysis. The only statistically significant clinical feature distinguishing those with HCV infection from others were abnormal serum ALT levels (Sylvestre et al. 2005).

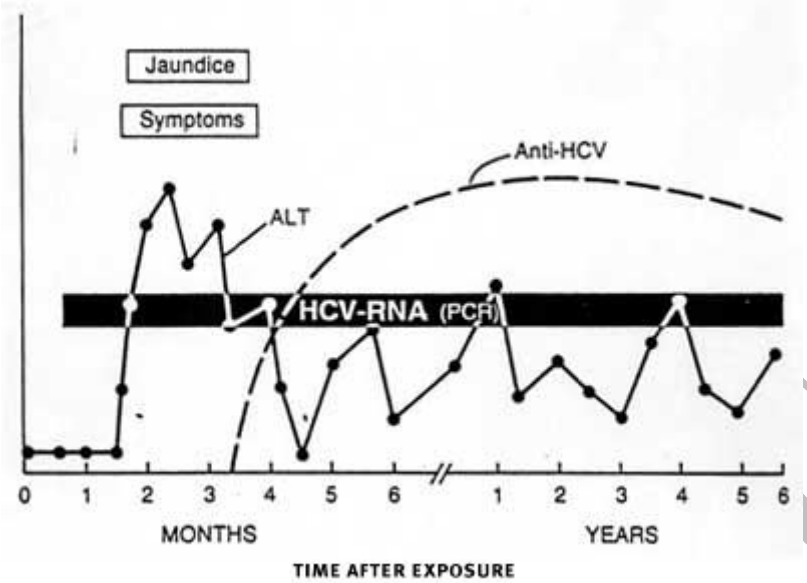

Figure 9 : Time course of acute (months) and chronic (years) HCV infection (from Larson et al. 2005)

The clinical presentation of acute HCV infection is complex, with 30-40% of patients presenting with clinical symptoms prior to testing positive for HCV exposure. Thus, the initial marker for HCV exposure may not be present in symptomatic patients. For asymptomatic patients, acute HCV infection occurs without any signs or symptoms and it may not be until cirrhosis develops that any symptoms appear. Once end stage liver disease emerges, prospects for survival are limited because of both the shortage of and the restricted access to donor livers for transplantation (Wong et al. 2004). Although there may be important benefits of starting treatment during early or acute stages of HCV infection, an accurate evaluation using appropriate laboratory screening techniques is needed, although laboratory methods to identify early HCV infection are not readily available.

Hepatitis Education

OTPs, compared to drug-free treatment programs, are more likely to provide hepatitis education materials to patients and to educate most or all staff about hepatitis

infection (Astone et al. 2003; Strauss et al. 2003). These education materials are also more comprehensive in OTPs and encompass topics such as viral transmission, testing, treatment options, and HIV co-infection (Strauss et al. 2004). SAMHSA has supported a hepatitis education program for OTPs, and the American Association for the Treatment of Opioid Dependence (AATOD) has developed a curriculum for hepatitis education and participated in its dissemination through The Hepatitis Education Training for Opioid Treatment Providers Program (www.AATOD.org/hepatitis.html). Other hepatitis curricula, developed by Federal and State agencies are available (see Table 7) and emphasize differing aspects of hepatitis C infection. For instance, the New York State Department of Health curriculum comprises a two day workshop with an emphasis on integrating hepatitis C into substance abuse treatment settings. Alternatively, the Veterans Administration curriculum is vast and provides great detail regarding hepatitis C and alcohol consumption. The Health Resources and Services Administration is developing a curriculum as technical assistance for HIV care providers that treat patients with co-occurring HCV infection.

Peer driven counseling/education, comprising a brief behavioral intervention coupled to testing for hepatitis infection, has been shown to change risky behavior of injection drug users associated with the transmission of HCV virus (Aitken et al. 2002; Tucker et al. 2004). These curricula and counseling education efforts are important components of a comprehensive substance abuse treatment plan for injection drug users because, when implemented, they meet the need of increasing the patient's knowledge of hepatitis C and promote treatment readiness (Evans et al. 2005; Walley et al. 2005).

However, not every substance abuse treatment program serving injection drug users provides these needed services (Vassilev et al. 2004).

Table 7: Salient Hepatitis C Curricula Developed by Federal and State Agencies

Agency	Program & Website
Substance Abuse and Mental Health Services Administration (SAMHSA)	HIV and Hepatitis Matrix www.samhsa.gov/Matrix/matrix_HIV.aspx American Association for the Treatment of Opioid Dependence web site www.AATOD.org/hepatitis.html
Centers for Disease Control and Prevention (CDC)	The Division of Viral Hepatitis - Hepatitis C Toolkit, brochures, posters, Counseling and Training resources www.cdc.gov/ncidod/diseases/hepatitis/c/#materials The National Commission on Correctional Health Care Curriculum www.cdc.gov/ncidod/diseases/hepatitis/resources/training/ncchc_man.htm
Department of Veterans Affairs (VA)	VA National Hepatitis C Program Educational resources. Patients corner, VA information www.hepatitis.va.gov
Health Resources and Services Administration (HRSA)	Integrating HIV & HCV services www.hab.hrsa.gov/catie/list.asp?ref=256
New York City Department of Health and Mental Hygiene	Understanding Hepatitis C www.nyc.gov/health
Massachusetts Department of Health	Massachusetts Hepatitis C Program www.mass.gov/dph/cdc/masshepc/default.htm
New York State Department of Health	National Virus Hepatitis Training
Texas Department of State Health Services	Texas Hepatitis C Initiative Counselor Training Manual www.tdh.state.tx.us/ideas/hepatitis Also required continuing nursing education through the CDC, Texas Nurses Association or National Center of Continuing Education www.tdh.state.tx.us/ideas/hepatitis/heaptitis_c/professional/cne

Clinical Research: Hepatitis C Treatment Studies and Pharmacotherapy

Clinical investigations of hepatitis C treatments have not included patients receiving methadone treatment. Generally, as stated earlier, methadone administration has been considered a potentially confounding factor for good treatment outcomes and the OTP population has been viewed as atypical (Stephenson 2001). However, available data suggest that hepatitis C treatment outcomes of patients receiving methadone treatment can be equivalent to those reported in studies of patient populations that exclude patients receiving methadone treatment. Schafer (2001) found that 50% of patients receiving methadone experienced a viral response to interferon-ribavirin treatment after six months compared to 39% of patients in a control population. Schafer concluded that patient compliance and retention in therapy were critical factors, and that an interdisciplinary OTP setting with adequate patient support facilitated safe and successful treatment.

Blechman et al. (1999) compared interferon therapy for chronic HCV infection in 26 patients receiving methadone treatment with a control group of 22 patients not receiving methadone. In this retrospective chart-analysis, disease severity, response to interferon, side-effect profile, and treatment compliance were equivalent in both groups. The authors concluded that stable patients receiving methadone treatment should not be excluded from hepatitis C treatment trials and are candidates for antiviral therapy as noted in current Clinical Practice Guidelines (AASLD 2004).

Hagan and colleagues (1999) examined interferon therapy administered to 19 HCV-infected patients in an OTP. Of the14 (74%) who completed the study, 79% had a treatment response at three months. Only two patients were discontinued because of medication non-adherence; two left the OTP; and one discontinued interferon. This study showed delivering interferon-based therapy in the OTP clinic setting is a feasible option.

Sylvestre et al. reported on an ongoing, observational clinical trial administering standard regimens of interferon-alfa-2b plus ribavirin to HCV-infected patients receiving methadone treatment (2005). To date, in 76 cumulative patients the reported overall SVR was 28% (intention to treat analysis) compared with 41% in historical controls. There were preexisting psychiatric diagnoses in 59% of subjects, and by the end of hepatitis C treatment 86% of all patients had received some form of psychiatric medication, primarily a selective serotonin reuptake inhibitor (SSRI) for depression. Twenty-four percent of patients were discontinued from the trial. However, treatment discontinuations were lower in patients receiving methadone treatment attributable solely to hepatitis C treatment side effects, and these side effects appeared less frequent or severe than encountered in the historical control group. In 45% of patients, the methadone dose was raised by a median of 15 mg. (the range being 0-180 mg.) to counter side-effect symptoms. The 70% of patients who had six or more months of drug-abstinence during which they received methadone treatment prior to beginning hepatitis C treatment had a higher SVR rate. A lower SVR rate was noted in the 30% of subjects who used alcohol or illicit drugs during the study; heroin use was most often reported, although cannabis, cocaine, and methamphetamine use were also reported. In total, those who were abstinent

from illicit drugs and alcohol throughout hepatitis C treatment had a 35% SVR, compared with an SVR of 21% in those who used any drugs (Figure 10). Of importance, seven

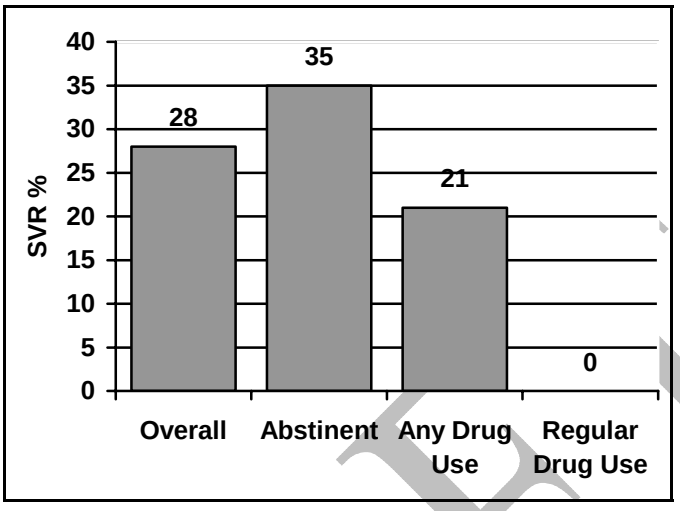

Figure 10 - Response to interferon-ribavirin treatment in 66 HCV-positive patients receiving methadone treatment (Sylvestre et al. 2005).

patients using illicit drugs (stimulants) and alcohol on a daily basis exhibited no response to interferon-based therapy.

The 28% overall SVR in this trial was considered a favorable outcome, given the multiple comorbidities in this particular group of patients who were older, had more advanced liver disease, and had a greater prevalence of psychiatric illness than select groups of patients without comorbidities in other hepatitis C treatment trials. In this trial, a subgroup of fifteen subjects without preexisting mental illness or any drug/alcohol use during treatment exhibited an SVR of 40%, which is equivalent to results in selected cohort hepatitis C treatment trials.

This study shows patients receiving methadone treatment and pharmacotherapy for HCV infection have an overall tolerance, safety, and compliance rate similar to those of historical controls in selected cohort hepatitis C treatment trials. This is despite substantial preexisting psychiatric comorbidity in a majority of the patients receiving

methadone treatment. Thus, hepatitis C treatment paradigms that aggressively manage psychiatric illness result in enhanced treatment outcomes (Sylvestre et al. 2004). Participation in an OTP prior to starting treatment for chronic HCV infection was beneficial, although rare use of drugs (relapse) did not appear detrimental to successful treatment outcomes. On the other hand, daily, ongoing stimulant and/or alcohol use during the course of interferon treatment did not result in any successful hepatitis C treatment outcomes, even in the most supportive environments. Of interest, although 40% of subjects required a modest methadone increase, there was no analysis of baseline methadone dose levels in this population. Suboptimal doses for some of the patients may have been an important factor influencing recidivism.

In another study, Backmund et al. (2001) investigated whether persons actively injecting opioids and infected with hepatitis C could be withdrawn (detoxified) from opioids and successfully treated with 24- to 48-week interferon-ribavirin combination therapy. Fifty of 100 qualified injection drug users, including a majority variously dependent on alcohol, cocaine, and/or benzodiazepines, consented to undergo a 28-day medically-supervised opioid-withdrawal program and receive treatment for HCV infection. Overall, there was an SVR in 36% (n=18) of subjects who exhibited excellent medication compliance and clinic attendance. However, after completing the 28-day inpatient opioid-detoxification program, 80% of subjects had one or more injection-drug relapses, including 10 of the 18 patients with an SVR. Thirty percent of the patients who relapsed had entered treatment at an OTP, and 53% of these patients receiving methadone treatment had an SVR. This SVR was 17% higher than the overall group, and 13% better than the SVR rate (40%) in those patients who remained abstinent without a drug relapse

who did not enter an OTP (Figure 11). While apparently substantial, these differences did not reach statistical significance, possibly because of the small numbers of subjects involved and the low statistical power.

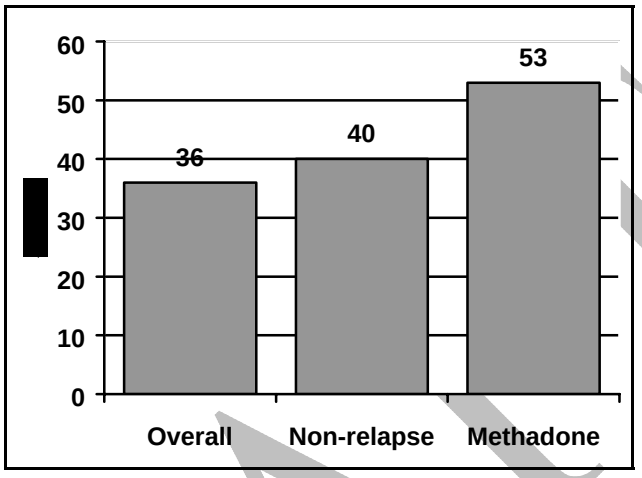

Figure 11 - **Sustained virologic response among HCV-positive injection drug users (Data from Backmund et al. 2001).**

Although this study indicates that injection drug users may be treated successfully for HCV infection in the face of continuing drug abuse, the authors emphasize that this select group of subjects was younger, had a higher percentage of non-genotype-1 HCV infection, and had a relatively shorter duration of HCV infection than in other comparative studies. This hepatitis C treatment study involving substance use detoxification reported high relapse rates with no HCV re-infections. This observation may be due, in part, to subjects reusing the sterile syringes and needles provided for home injection of interferon. Recent reports by Dalgard and colleagues in Norway (2002) and Backmund et al. (2004) suggest that re-infection may not be as rapid as previously thought. Dalgard reported on 27 former injection drug users not in an OTP who had been treated successfully for HCV infection. One-third of the patients had returned to injecting drugs and only one became re-infected (with a different strain of the

virus) at 64-months' (median) follow-up. In addition, the study followed 18 injection drug users for a mean of 33.8 months with 15 remaining HCV RNA-negative. Further studies are needed to identify the risk of HCV re-infection in patients who undergo recidivism.

In contrast to issues regarding treatment of HCV infection in injection drug users who are not in substance abuse treatment, Stein and colleagues (2001) observed that the typical stability of persons in an OTP makes them good candidates for the rigors of interferon-based therapy. Of 306 HCV-positive patients in an OTP that they surveyed, more than half (53%) were eager to participate in interferon therapy. This was in the face of knowing that interferon-based treatment requires injections, is only partially efficacious, may produce adverse reactions, and may require a liver biopsy.

A growing body of evidence to date strongly indicates that participation in treatment in OTPs results in better hepatitis C treatment outcomes for patients with opioid addiction and hepatitis infection. Patients receiving treatment at OTPs may exhibit good hepatitis C treatment adherence and retention, with limited side effects or adverse events. AALSD Clinical Treatment Guidelines recommend that hepatitis C treatment not be withheld from patients participating in OTPs. A period of prior abstinence from alcohol and illicit drugs resulting from being treated in an OTP may be beneficial for maximizing treatment responses but is not necessary or required to initiate interferon-based treatment of chronic HCV infection. Two critical factors regarding methadone treatment and concurrent hepatitis C treatment are: (1) maintaining adequate methadone serum levels to avert potential drug-relapse both prior to, during, and following treatment

for HCV infection; and (2) conducting ongoing supportive psychotherapies for patients with psychiatric diagnoses.

Viral Hepatitis and the Health Care Provider: Occupational and Nosocomial Exposure to Viral Hepatitis

An implicit concern for treating patients who are at-risk for hepatitis infection is the possibility that the transmission of virus may occur in the health care setting. For substance abuse treatment programs, both the health care provider and patient must be aware of the personal risk and possible courses of action if viral transmission should occur.

The route of transmission for approximately 10-15% (Figure 7) of all hepatitis infections remains undetermined. An important issue for substance abuse treatment programs is the nosocomial transmission of hepatitis virus as well as patient-to-patient transmission during treatment. Both HBV and HCV have been documented to be transmitted from an infected health care worker or patient through percutaneous or mucosal exposure to blood and other body fluids (CDC 2003). The opportunity for occupational or nosocomial exposure to hepatitis in a substance abuse treatment program increases as more wrap-around services, such as infectious disease testing, immunizations, and pain management, as well as treatment clinical trials are performed at the treatment site as part of the comprehensive substance abuse treatment plan (Comstock et al. 2004; Krause et al. 2003; Larghi et al. 2002). This transmission poses personal, legal, and professional risks to patients, health care workers and treatment programs. Fundamental to the prevention of transmission are education provided particularly to health care staff on the Occupational and Safety and Health Administration's Blood Borne Pathogens Standard (www.osha.gov/SLTC/bloodbornepathogens/index.html) and

use of the latest safety devices. Strict adherence to universal safety precautions is important to prevent transmission. Dedicated space, equipment, and staff for wrap-around services can significantly reduce hepatitis transmission as well (Saxena et al. 2003). Vaccination of health care workers and all non-immune individuals in the substance abuse treatment setting against both HAV and HBV infections is also an important prevention measure and has been shown to be cost effective (Jacobs et al. 2004).

Protocols for post-exposure treatment and follow-up have been developed (CDC 2001; Delwaide 2003; Sounder et al. 2005; West 2001). For exposure to HBV, the exposed individuals should undergo serological testing. Active (immunization) and passive (anti-HBV antibody) immunoprophylaxis is effective against HBV infection, if the individual is not vaccine immune. Immunoprophylaxis should be provided within 24 hours of exposure, based on the HBV surface antigen status of the source and vaccine-response of the exposed person. On diagnosis of acute hepatitis B infection, anti-viral treatment is not recommended for immunocompetent individuals because of the high percentage of spontaneous viral loss. For exposure to HCV, immune globulin and interferon-based anti-viral treatment are not recommended. Recommended post-exposure management for HCV is to determine the HCV status of the source and the exposed person and to follow-up HCV testing to determine if infection has occurred (CDC 2001). HCV is detectable as early as one to two weeks after exposure, while hepatitis C antibodies may be detected in the serum at approximately eight weeks post exposure. Elevations of liver enzymes may be detected in the 6-12 week post-exposure time frame (Kim and Saab 2005). Studies have shown that individuals who present with

symptomatic acute HCV infection have a high likelihood of self clearance of virus or self-cure. The only controlled clinical trial of initiation of interferon-based treatment in acute HCV infection (8 weeks post exposure) showed an SVR of 100% (Normura et al. 2004). Thus, addressing HCV exposure in acute infection predicts a good outcome either through self cure or short-term interferon-based treatment.

Psychiatric and Medical Complications of Hepatitis Infection, Treatment, and Addiction

Psychiatric Illness Comorbidity

Treatment side effects associated with hepatitis C pharmacotherapies have been found to impair quality of life during treatment and to result in treatment discontinuation in approximately 15 to 20% of treated patients. However, up to 15% of all patients may not experience any side-effects whatsoever (Ryder and Beckingham 2001). Interferon therapy may be associated with systemic side effects, such as fatigue, muscle aches, nausea, vomiting, headaches, low-grade fever, and low platelet and neutrophil counts. Although such adverse reactions usually are mild to moderate and can be managed, they may be sufficiently troublesome to influence patient noncompliance or withdrawal from treatment (See Table 8; Strader et al. 2004).

Table 8 -- Common Side Effects of Interferon-alpha and Ribavirin
Flu-like Symptoms- fever, headache, myalgia, fatigue, asthenia, rigors, dizziness, influenza-like symptoms
Gastrointestinal- diarrhea, anorexia, nausea, vomiting, abdominal pain
Neuropsychiatric- depression, impaired concentration, irritability, insomnia
Skin/Appendages- alopecia, pruritus, rash
Hematologic- decreased hemoglobin, decreased white blood cell count, decreased platelet count

Adapted from Physician's Desk Reference, Fifty-first Ed., 1999

Natural and recombinant interferons have short biological half-lives, requiring daily or three-times-weekly subcutaneous injections. Fluctuations in serum concentrations may undermine both efficacy and tolerance. Pegylated interferon has a prolonged serum half-life that improves tolerance and permits less frequent subcutaneous dosing. Compared with interferon monotherapy, interferon plus ribavirin combinations typically result in reduced side effects and treatment discontinuations (McHutchison et al. 1998).

Manufacturers' package inserts for interferon warn of the potential for neuropsychiatric adverse events, including depression, and the possibility of psychiatric relapse after beginning therapy. Dose-dependent and reversible neuropsychiatric effects have been reported to occur in 30 to 40% of patients during interferon treatment. These may be severe, limiting treatment in 10 to 20% of cases, and are greater than two-times more frequent in persons with histories of psychiatric disorders than in those without (Davis and Rodrigue 2001; Ho et al. 2001). Psychiatric diagnoses, other than substance-abuse disorders, are a prominent reason for treatment ineligibility unless the patient has treated and stabilized (Muir et al. 1999; Sylvestre at al. 2004). Psychiatric support including the use of antidepressants, such as selective serotonin reuptake inhibitors, or anxiolytics during interferon-based therapy are frequently required.

Preexisting psychiatric comorbidity has been observed in roughly half of persons entering OTPs (Brooner et al. 1997; SAMHSA 2005a). The management of these

illnesses is an important component of the OTPs therapeutic milieu that can help reduce adverse reactions and risks of drug relapse associated with interferon-based treatments (Ho et al. 2001; SAMHSA 2005). Furthermore, prospective clinical studies have demonstrated that a concurrent diagnosis of mental disorder does not preclude effective interferon-based treatment, provided the patient is receiving appropriate psychiatric care and psychotropic drug therapy (Pariante et al. 1999; Sylvestre et al. 2004). A recent study of patients treated with peginterferon alfa-2b and ribavirin while in methadone treatment showed no serious psychiatric events due to interferon-based treatment (Mauss et al. 2004). An earlier small, prospective, controlled study in Europe examined psychiatric complications during interferon-based combination therapy (Schafer 2001). Depression increased from baseline in only 16% of patients receiving methadone treatment and was found to be mild or moderate. However, during interferon-based treatment, many OTP patients requested increased methadone doses. The Hepatitis C Resource Centers of the Veterans Administration have produced a monograph entitled "Management of Psychiatric and Substance Use Disorders in Patients with Hepatitis C: A Reference for Hepatitis C Care Providers". The full text may be found at www.hepatitis.va.gov and it provides an algorithm for screening for psychiatric and substance use disorders, as well as addressing suicidal ideation, depression, and post-traumatic stress disorder in the context of substance use and abuse and treatment for hepatitis C virus infection.

Medication Adherence

As with all prescribed medications, adherence to the treatment regimen is fundamental to a positive treatment outcome. In maximizing positive treatment outcomes for interferon-based treatments, medication adherence is an important factor in the

observation of an SVR (McHutchison et al. 2001). In a recent study of treatment outcomes in a hepatitis C clinical practice, a significantly higher SVR (53% *versus* 20%) was observed in patients who received greater than 80% of the recommended dose of interferon-based therapy (Shehab et al. 2004). Newly described 80/80/80 analyses depict protocol-adherent patients who took at least 80 percent of two study drugs in combination for at least 80 percent of the study duration, and treatment dropouts are excluded. Such analyses produce improved results and better demonstrate potential outcome success.

In an analysis of hepatitis C treatment studies published to date in which patients were treated for HCV infection in combination with substance abuse treatment, SVR and adherence data in HCV-infected methadone treated patients were comparable to control groups (Schaefer et al. 2004). However, patients with former or current drug abuse were more likely to discontinue treatment early compared to control groups. Patients in methadone treatment have also been shown to discontinue hepatitis C treatment early in the course of treatment (Mauss et al. 2004). Patients who are likely to discontinue treatment early need supportive interventions, including medication adherence interventions (Bacon 2004). These may include the management of drug-drug interactions and treatment side effects as well as interventions to enhance medication adherence in drug users, such as taking into account lifestyle factors and daily activities or using directly observed treatment protocols (Conway et al. 2004; Kresina et al. 2004; Wagner and Ryan 2004).

Medication adherence interventions are particularly important in the early phase of interferon-based combination therapies. A stronger predictor of an SVR to combination therapy is the dynamic change in HCV RNA during the first 12 weeks of

treatment (Fried 2004). Defined as the early virologic response (EVR), the determination of HCV viremia at week 12 of treatment can predict those patients who will obtain an SVR. A decrease of greater than 2 logs of HCV-RNA levels at 12 weeks of treatment, compared to the HCV-RNA level at the start of treatment, predicts an SVR. For HIV/HCV co-infected patients, two recent studies have shown an EVR to have a near 100% negative predictive value and thereby predict patients that will not obtain an SVR through hepatitis C treatment (Ballesteros et al. 2004; Soriano et al. 2004a). Thus, supportive interventions initiated during the first 12 weeks of HCV treatment, such as medication adherence interventions, are particularly important in the medical management of patients with chronic hepatitis C.

Medication adherence interventions are important and necessary in the treatment of co-morbidities associated with substance abuse. Non-adherence with antiviral treatment regimens is common in persons actively using illicit drugs, particularly alcohol and/or cocaine, who do not receive adherence interventions (Samet et al. 2004; Weiss 2004). However, research has demonstrated that drug use is not a predictor of noncompliance with treatment regimens and that past drug addiction does not preclude favorable adherence to antiviral therapies (Lucas et al. 2001; Murphy et al. 2004). A prospective longitudinal study of 74 HCV-infected patients receiving interferon treatment, with and without ribavirin, found that adherence was not influenced by sociodemographic factors or mode of hepatitis acquisition. In particular, a history of injection-drug abuse was not linked significantly with compliance difficulties (Kraus et al. 2001).

Experience with populations in OTPs indicates that stabilized patients tend to be exceptionally compliant, even with unusually burdensome requirements, such as reporting to a clinic multiple times each week to receive methadone or to attend therapy groups. Patients in OTPs tend to be resilient, possibly resulting from the rigors of former addictive lifestyles. With adequate preparation and motivation, they appear to readily endure difficult therapeutic regimens. Furthermore, these patients' frequent contacts with the healthcare system through the OTP also promote ongoing compliance monitoring and long-term follow-up (Backmund et al. 2001; Borg et al. 1999).

Drug- -Drug Interactions: Addiction Pharmacotherapy and HCV Treatment

Concerns about drug interactions with methadone have also been used as medical justification to exclude patients in OTPs from receiving treatment for hepatitis and from pharmaceutical trials. Pharmacokinetic interactions, when anticipated and monitored, can be managed by medication dosage adjustments. Monitoring adequate serum methadone levels (SMLs) are critical to achieving and continuing drug-abstinence in OTPs. Any medication that could alter methadone pharmacokinetics might underlie drug relapse and modify treatment outcomes.

Methadone and currently used interferon-based treatments would not be expected to interact significantly with each other, although the full extent of such interactions has not been investigated rigorously. A study evaluating interaction between methadone and peginterferon-alpha 2a in 24 HCV monoinfected patients receiving methadone showed that serum methadone concentrations were elevated 10-15% but were not clinically significant and no dose reductions occurred (Sulkowski et al. 2005). There is some evidence that interferon-alfa may mildly inhibit P450 enzymes, and it has been

demonstrated to strongly inhibit clearance of theophylline, which is primarily metabolized by CYP1A2 enzymes (Intron 1998). Since this is only a minor route of methadone metabolism, interferon-alfa disposition would not likely be affected. Pegylated interferon does not appear to affect drug metabolism by liver enzymes in patients with hepatitis C (PEG-Intron 2001), although continuing investigation is warranted. Ribavirin is not metabolized through P450 pathways, so enzyme-based drug interactions would not be problematic (Rebetron 1998).

Most patients in OTPs who receive methadone also receive prescribed medications for various co-occurring disorders and treatment side effects. Psychotropic agents also often are prescribed to counter the side effects of interferon. Potential drug interactions should be considered carefully to help avoid unintended increases or decreases in serum methadone concentrations. The number of compounds known to interact with the CYP450 system is large and, as noted above, co-medications that induce CYP450 activity may foster subtherapeutic methadone concentrations and produce acute opioid withdrawal symptoms. Conversely, CYP450 inhibitors may cause abnormally high methadone levels precipitating toxic adverse reactions (Wolff et al. 2000). For a list of common CYP450 enzyme substrates, inhibitors, and inducers see http://medicine.iupui.edu/flockhart .

Diseases with hepatic involvement could disrupt hepatic metabolic function, down-regulate CYP450 enzymes, and result in slower rates of drug clearance. Viral infections also stimulate cytokine production, which has been associated with suppressed CYP enzyme activity. Thus, conditions suppressing CYP function could produce higher than expected methadone serum levels in HCV infected patients receiving methadone

treatment. However, studies of patient dosing of methadone at OTPs has shown that patients with HCV infection receive higher methadone doses (Maxwell et al. 2002).

However, it should be noted that in one examination of 228 patients receiving methadone treatment, of whom 149 (65%) were HCV infected, no significant differences in dose were found between those who had or did not have HCV (overall mean 90 mg/day methadone; Litwin and Gourevitch 2001).

Further research is needed to define the interaction of HCV and subsequent liver damage with methadone dose variability. Few studies specifically have measured the effects of hepatitis virus on methadone serum levels. It also may be important for future investigations to determine whether selective effects occur on the disposition of the active R-enantiomer of methadone. Meanwhile, appropriate serum level monitoring and individualization of methadone dose appear to be essential in patients with HCV infection who are receiving methadone treatment.

Hepatototoxicity, Liver Disease, and Liver Function Tests

There are numerous laboratory tests, referred to as liver function tests, which are useful in providing information on liver function/dysfunction. The liver function tests serve as non-invasive markers of liver function and can be used as screening tools to assess liver dysfunction in patients who have unsuspected liver disorders, such as acute viral hepatitis, cirrhosis, or partial bile obstruction. Liver function tests, when performed over time, can also detect a change in liver function or characterize a patterned liver dysfunction. For example, liver function tests can distinguish between liver disorders such as viral hepatitis and cholestatic syndromes. But, liver function tests alone can not be diagnostic for a specific liver disease (Knight 2005). However, when performed

serially, liver function tests allow the health care provider to characterize and follow the course of the liver disease. Liver function tests lack sensitivity, in that some patients with serious liver disease can have normal test values. But, in the assessment of the severity of liver dysfunction, liver function tests can be a component of data that may allow the health care provider to predict an outcome early in course of the disease (Peng et al. 2005). Thus, laboratory based liver function tests are fundamental to the medical management of patients with liver disease and in the treatment of liver disease (Korenblat and Berk 2005).

The liver performs hundreds of biochemical/biological functions and, thus, one liver function test can not accurately assess the total functional capacity of the liver. There are many tests for liver function that can be grouped as follows: tests for the liver's capacity to transport organic anions and metabolize drugs; tests that detect injury or death of hepatocytes (hepatic necrosis); tests of the liver's biosynthetic capacity; as well as tests that detect chronic inflammation in the liver, altered immunoregulation or viral hepatitis markers (Kaplan 1993). A listing of salient liver function tests and their clinical use is presented in Table 9.

Table 9 -- Common Liver Function Tests and Their Clinical Value

Liver Function Test	Normal Value*	Clinical Value
Alanine aminotransferase (ALT)	10 - 31 U/L	ALT lower than AST in alcoholism
Albumin	3.5 - 5.2 g/dL.	assess severity/chronicity measures liver protein synthesis
Alkaline phosphatase	25 - 112 U/L	Diagnose cholestasis & hepatic infiltrations
Aspartate aminotransferase	10 - 44 U/L	Early diagnosis & monitoring

(AST)		of hepatic necrosis
Bilirubin (Total)	0.1 - 1.0 mg/dL.	assess severity of cholestatic liver disease
Gamma glutamyl transpeptidase	16 - 74 U/L	Diagnose alcohol abuse Marker of cholestasis
Prothrombin time	11.3 - 16.5 sec.	assesses severity of liver disease; measure of liver protein synthesis

* Normal values vary with the laboratory reporting them (adapted form Larson et al. 2005)

Liver function tests are used in multiple ways in the medical management of addiction and the pharmacologic treatment of opioid addiction. As noted earlier, methadone and buprenorphine are metabolized in the liver. Thus, tests that measure liver drug metabolism are important in identifying and maintaining a therapeutic SML, as well as, drug-drug interactions that may influence the SML and promote relapse to heroin abuse (Ferrari et al. 2004). Therapeutic drug monitoring for methadone in plasma is being investigated for establishing adequate dosing and for monitoring drug diversion. It is routine for determining individual drug pharmacokinetics for patients taking anti-retroviral medication for HIV infection (Cone and Preston, 2002; Fraaji et al. 2004).

For injection drug users, the determination of the presence of viral hepatitis and other "underlying liver disease" is important in the medical management of opioid addiction. Tests that identify antibodies to hepatitis viruses indicate past exposure of the patient to infection or vaccination.

Tests that determine the presence of virus, viral replication or viral genes and their gene products indicate a current infection with hepatitis virus. Although the liver contains thousand of enzymes, indicators of liver cell injury and acute hepatocellular diseases are the serum levels of aminotransferase enzymes found in hepatocytes: alanine

aminotransferase (ALT) and aspartate aminotransferase (AST). A routine chemistry liver function panel consists of determinations of AST, ALT, alkaline phosphatase, lactate dehydrogenase, gamma glutamyl transpeptidase, bilirubin (total and conjugated), and albumin levels in a blood sample. The ALT and AST (and their ratio) are the most frequently measured indicators of liver disease. The measure of serum ALT and AST are an indication of enzyme leakage from tissues rich in the enzymes into the blood. In the case of the liver, the enzymes leak through the damaged cellular (hepatocyte) plasma membrane and, thus, measure cellular damage or death in the liver. Tissues rich in AST are the liver, heart, skeletal muscle, pancreas, and lungs. ALT is primarily present in the liver and kidney, thus elevated levels of enzymes are not necessarily specific for liver injury or necrosis. However, both AST and ALT are typically elevated in all liver disorders which include acute and chronic hepatitis, cirrhosis, alcoholic liver disease, and liver cancer. Elevations up to eight times the upper limit of normal serum concentrations (see Table 9) are nonspecific, in that they can be found in any of the liver disorders or found in specific patient populations (Celona et al. 2004). The highest elevations occur with liver insults and associated hepatocellular injury, such as drug and alcohol hepatotoxicity or viral hepatitis. Seventy to ninety percent of patients can present with determinations over eight times normal values in liver enzymes. However, as shown in Figure 9, the elevated values may not occur constantly over time in acute or chronic liver disease. Thus, single determinations of liver enzymes may not reflect the level of liver disease. Elevated liver enzymes are considered consistently elevated with a pattern of at least three consecutive monthly elevated readings.

There is a poor correlation between the extent of liver cell necrosis and the elevation of AST and ALT, with the absolute elevation of AST and ALT not a prognostic indicator of liver disease outcome. However, decreases in AST and ALT levels may indicate a liver disease recovery process. In most liver disease, AST and ALT are equally elevated with ALT usually slightly higher than AST. The exception to this observation is alcoholic liver disease in which an AST/ALT ratio of 2 or greater is suggestive of alcoholic liver disease. This is the result of an alcohol-induced deficiency of ALT. Thus, alcohol as a hepatotoxin enhances AST levels but may also reduce ALT levels through cellular metabolic deficiencies (Kaplan 1993).

Since there is a poor correlation between the extent of liver cell necrosis and the elevation of liver enzymes, other laboratory tests have been studied to identify clinical chemistry markers as non-invasive markers of progressive liver disease, especially hepatitis fibrosis (Lichtinghagen and Bahr 2004; Poynard et al. 2005). These clinical chemistry markers are combined to form multiparameter scores or combined with measures of products of the hepatic extracellular matrix such as hyaluronic acid, laminin, matrix metalloproteases, or their inhibitors, or collagen degradation products. These studies seek to find biological scores for routine clinical use that are easily obtainable, specific for liver disease, and accurately reflect the stage of liver fibrosis. At a minimum, scores need to accurately differentiate minimal liver disease from advanced liver cirrhosis (Kelleher et al. 2005). With the ability to accurately stage liver disease, biomarkers may replace the current use of liver biopsy in the assessment of liver inflammation and fibrosis due to chronic liver disease (Afdahl 2004). In addition, serum markers, at that

point in the future, may also be used to determine responses to therapy for hepatitis as well as to evaluate disease progression over time (Colletta et al. 2005).

Liver Biopsy and Methadone Treatment

Liver biopsy remains the "gold standard" or only scientifically proven assessment of liver inflammation and fibrosis resulting from chronic liver disease, including HBV infection or HCV infection (Gebo et al. 2002a). Thus, liver biopsy is used by medical care providers to determine the grade and stage of liver disease. There are both risks and benefits of a liver biopsy. As with any invasive procedure, the benefits gained from an accurate assessment of liver disease must outweigh the small but definitive risks associated with the biopsy. Risks include bleeding, pain, and puncture of organs, sampling error, patient anxiety, costs, and a low risk of adverse events including death (Sterling 2005). Contraindications for liver biopsy are an uncooperative patient, impaired coagulation, thrombocytopenia, ascites, biliary obstruction and vascular tumors. Methadone treatment is not a contraindication for liver biopsy, and studies of hepatitis C and substance abuse have routinely utilized liver biopsy to assess the level of liver disease of patients in methadone treatment (Cournot et al. 2004;. Jowett et al. 2001; VanThiel et al. 2003).

Current hepatitis C treatment recommendations approved by the American Association for the Study of Liver Disease (AASLD 2004) are that therapy should be individualized for persons with liver biopsy evidence of no or minimal-to-mild fibrosis, while treatment is indicated for persons with more than portal fibrosis. Since between 14-24% of individuals have normal aminotransferases values on liver enzyme panels but show greater than portal fibrosis on liver biopsy, the current hepatitis C treatment

recommendations are the following: regardless of the level of aminotransferases, a liver biopsy should be performed when the results will influence whether treatment is recommended, but a biopsy is not mandatory in order to initiate therapy. The value (risk *versus* benefit) of a liver biopsy has been questioned, particularly for hepatitis C treatment decisions for individuals infected with HCV genotypes 2 or 3, since there is a high likelihood of an SVR using current standard-of-care treatment regimens (Andriulli et al. 2004; AASLD 2004).

Continued Alcohol Use

Alcohol use and alcoholism is a serious medical problem among individuals with opioid addiction (Kosten and O'Connor 2003). Heavy alcohol use has been shown in a substantial number of persons first entering OTPs (Chatham et al. 1995, NIAAA 1988). The Treatment Episode Data Set (TEDS) which summarizes data on admissions to substance abuse treatment programs reported in 2000, that 23.3% of patients entering an OTP indicated the use of alcohol along with heroin (SAMHSA 2002b). Continued alcohol use can result in decreased medication adherence, drug-drug interactions that modify treatment pharmacokinetics, progressive liver disease and continued at-risk behavior for infectious disease co-morbidity. Consensus recommendations for medication-assisted treatment are for staff of opioid treatment programs to be trained to recognize the pharmacologic and psychosocial effects of both opioid and nonopioid substances of abuse, including alcohol (SAMHSA 2005). Thus, patients seeking, entering, or receiving substance abuse treatment for opioid addiction should be carefully screened for alcohol dependence using a validated instrument such as the CAGE

questionnaire, with OTP's having treatment options available either directly or through referral.

Treatment for alcohol dependence which maximizes good treatment outcomes consists of pharmacotherapy, counseling interventions, and participation in social mutual-help groups (Boothby and Doering 2005; SAMHSA 2005). The medical management of withdrawal from alcohol and opiates is complex, and there are substantial differences in severe complications (Kosten and O'Connor 2003). Medications used in detoxification from one class of addictive drug may mask symptoms of another class of drug. Depending on the emergence of serious complications, detoxification of a polysubstance dependent individual may require inpatient treatment. For individuals who casually use alcohol and who are opioid dependent, once the patient receives methadone treatment alcohol use has been shown to decrease with time (Caputo et al. 2002). Patients participating in OTP's have frequently been excluded from fully participating in Alcoholic Anonymous meetings and denied admission and treatment in traditional addiction and chemical dependency programs (Kipnis et al. 2001). Pilot programs that educate the medical and counseling staff at Addiction Treatment Centers (ATCs) on integrating methadone treatment into the traditional addiction treatment framework have met with success. Thus, patients receiving methadone can complete traditional chemical dependency treatment programs through integration of services at the ATC (Kipnis et al. 2001).

Alcohol consumption is also a medical issue for patients who are opioid dependent and have a viral hepatitis infection. Research studies, to date, have not been able to determine a safe level of alcohol consumption for individuals infected with viral

hepatitis. Alcohol consumption of greater than 30 grams/day in men (3-4 drinks, with an average drink comprising 13 grams of alcohol) and 20 grams/day in women increases the risk of liver disease progression and reduces responses to interferon therapy; more than 80 grams/day may seriously compromise hepatitis C treatment (NIH 2002; Schiff 1997). For individuals with HBV infection, alcohol consumption has been shown to increase the risk of the development of hepatocellular carcinoma (liver cancer). For individuals who are successfully cured of HCV infection, moderate alcohol consumption has been shown to increase the risk of developing liver cancer (Tokita et al. 2005). Alcohol-induced enhancement of viral replication or increased susceptibility of liver cells to viral injury has been suggested as the means through which liver disease may progress (CDC 1998). The Consensus Conference Statement of the European Association for the Study of the Liver (EASL 1999) notes that heavy alcohol intake increases HCV viremia and decreases medication adherence with injection drug users at-risk of HCV re-infection.

The most recent NIH and AASLD guidelines acknowledge that hepatitis C treatment for infected injection drug users is feasible and can be effective. However, the guidelines recommend that interferon-based therapy be performed in the context of efforts to address drug/alcohol use, abuse or dependence (AASLD 2004). This includes participation in OTPs (AASLD 2004; NIH 2002). However, continued drug or alcohol use is not a medically valid (or ethically valid; Scott 2005) reason for withholding hepatitis C treatment to individuals in immediate need (AASLD 2004). As with all medical interventions, hepatitis C treatment decisions need to be made based on an assessment of risks and benefits to the patient. The risk, in this case, is that ongoing alcohol use/abuse enhances liver toxicity resulting in decompensated liver disease or end-

stage liver disease. The benefit is amelioration of HCV infection and potential reversal of progressive liver disease.

Hepatitis C treatment studies have reported that approximately one fifth of current alcohol/drug abusers do not comply with hepatitis C treatment monitoring or are lost to follow-up, and ongoing drug use may increase viral load and reduce virologic response to treatment (Davis and Rodrigue 2001; Sylvestre 2002). However, patients with co-occurring HCV infection and substance use may complete IFN treatment with careful monitoring and aggressive intervention. Treatment providers must integrate early interventions for drug use and other comorbidities into their hepatitis C treatment algorithm. Using this treatment paradigm, studies show that patients with current and past histories of significant substance use disorders are able to successfully complete a course of interferon-based therapy, and that SVR rates are similar to those without such difficulties (Sylvestre et al. 2004).

Orthotopic Liver Transplantation

Orthotopic liver transplantation is standard treatment for individuals with end-stage liver disease. A substance abuse-related diagnosis, either hepatitis C or alcoholic liver disease, is the leading cause (in 46% of cases) and next leading cause (in 25% of cases) for liver transplantation, respectively. The current use of addictive drugs is an absolute contraindication for acceptance into liver transplantation programs (Keeffe 2000). An abstinence period of at-least six months is required and patients fully recovered from drug use can be considered for liver transplantation. In a survey of liver transplantation programs in 2001, 32% of programs required patients to discontinue methadone treatment (Koch and Banys 2001). It is estimated that approximately 6% of

all individuals with HCV infection are prescribed methadone. However, 85% of all methadone patients are HCV infected. Studies to date providing data on patients who undergo liver transplantation while receiving methadone do show these patients have substantial medical complications, but the studies do not support withholding the provision of liver transplantation from patients receiving methadone (Di Martini and Weinrieb 2003; Kanchana et al. 2002; Liu et al. 2003; Weinrieb et al. 2004).

The initial report (Kanchana et al. 2002) described the outcomes of five patients receiving methadone who had been abstinent from illicit drugs and alcohol for at least six months. Three patients had end-stage liver disease resulting from HCV infection, one from HBV infection and one from alcoholic liver disease. No patient returned to illicit drug use post transplantation and mean patient survival time, at publication, was 1,250 days (over three years). The study concluded that acceptable patient survival rates can be achieved in patients receiving methadone as long as patients receive counseling, psychotherapy, and services post transplantation to enhance retention in care.

The largest reported series of patients (Liu et al. 2003) provided outcomes for 35 patients receiving methadone. The study reported a higher than normal rate, (69%), of acute cellular rejection, but patient graft and survival times were comparable to national averages. Eleven percent of patients relapsed to isolated episodes of heroin use post-transplant. In a recent report (Weinrieb et al. 2004), ten patients receiving methadone were matched with 19 non-methadone, non-opioid dependent, patients, post transplantation. Patients receiving methadone required significantly more intraoperative anesthesia and postoperative analgesia as well as a methadone dose increases (preoperatively compared to post operatively). Mean survival time post-transplantation

was not different between groups. However, post transplantation 20% of patients used alcohol or illicit drugs. The authors conclude that liver transplantation patients receiving methadone pose a greater challenge to their medical management, but should not be withheld from liver transplantation waiting lists. Information regarding the organ transplantation process and waiting lists for transplantation can be found at the United Network for Organ Sharing web site www.unos.org.

Hepatitis-HIV Coinfected Patients. Coinfection of hepatitis and HIV viruses greatly accelerates the progression of liver disease associated with viral hepatitis. As an emerging problem, persons with coinfection face insurmountable obstacles to treatment or transplantation for their liver disease (Nadler 2001). Life expectancy in HIV-infected individuals has been extended due to advances in antiretroviral therapy, and HIV infection now can be considered a chronic illness, rather than an absolute exclusion to organ transplantation. Liver transplantation is being evaluated as a therapeutic option for patients with controlled HIV infection and end-stage liver disease resulting from HCV infection, HBV infection or drug-induced hepatotoxicity (acute liver failure). Liver transplants have been successfully performed in 41 HIV-positive patients at 11 centers worldwide between 1990 and 2001. The one caveat has been the potential for drug interactions between anti-retroviral agents and immunosuppressive drugs and the need for dose adjustments. Clinical trials at 10 centers in the United States are underway to assess the impact of HIV infection (and coinfection with HCV or HBV in some patients) on liver transplant outcomes. Initial reports (Neff et al. 2003) indicate that orthotopic liver transplantation is effective in selected HIV positive patients suffering from end-stage liver disease.

Internationally, liver transplantation for patients with HIV infection and end-stage liver disease has occurred in Great Britain, Sweden, Belgium, France, The Netherlands, Germany and Spain (reviewed in Neff et al. 2004; Miro et al. 2004). The accumulated experience in Europe and the United States indicates that the three year survival in HIV-positive liver transplantation recipients is similar to that of HIV-negative recipients. Guidelines for the selection of patients with HIV-infection for liver transplantation have been generated in the United Kingdom and Spain (O'Grady et al. 2005; Miro et al. 2005). Briefly, they include no opportunistic infections, CD4 count above 200, undetectable HIV viral load, and an abstinence period (up to two years) from heroin and cocaine use. Methadone treatment is not an exclusion criterion.

Diabetes, Renal Disease, Opioids, and Renal Transplantation

IDU, HCV infection, and type 2 diabetes mellitus each independently and, in concert together, can result in chronic renal disease and the need for renal transplantation. A chronic complication of type 2 diabetes mellitus is diabetic nephropathy. An extra-hepatic manifestation of HCV infection can be type 2 diabetes (Howard et al. 2003). Using the NHANES III national data set, the prevalence of type 2 diabetes in adults aged 20-59 with HCV infection was 3.4% (Behrendt and Ruiz 2005). In this cohort, HCV infection and type 2 diabetes was associated with a family history of diabetes, as well as advanced liver fibrosis, but not the classical phenotype for diabetes (overweight individuals with coronary heart disease). Opium addiction has been shown to enhance the metabolic abnormalities associated in patients with type 2 diabetes (Karam et al. 2004). Numerous studies have described the clinical and pathological features of renal disease associated with injection drug use of heroin, cocaine, morphine, amphetamine and other

narcotics (reviewed in Dettmeyer et al. 2005). Drug addiction neuropathy, including renal failure associated with oxycodone addiction, constitutes an important cause of end-stage renal disease that can be augmented by a genetic predisposition to diabetes as well as HCV infection (Hill et al. 2002). Thus, for the injection drug user seeking treatment, there is a spectrum of diseases and infections that can exacerbate addiction-associated renal disease leading to end-stage renal disease (see Figure 12)

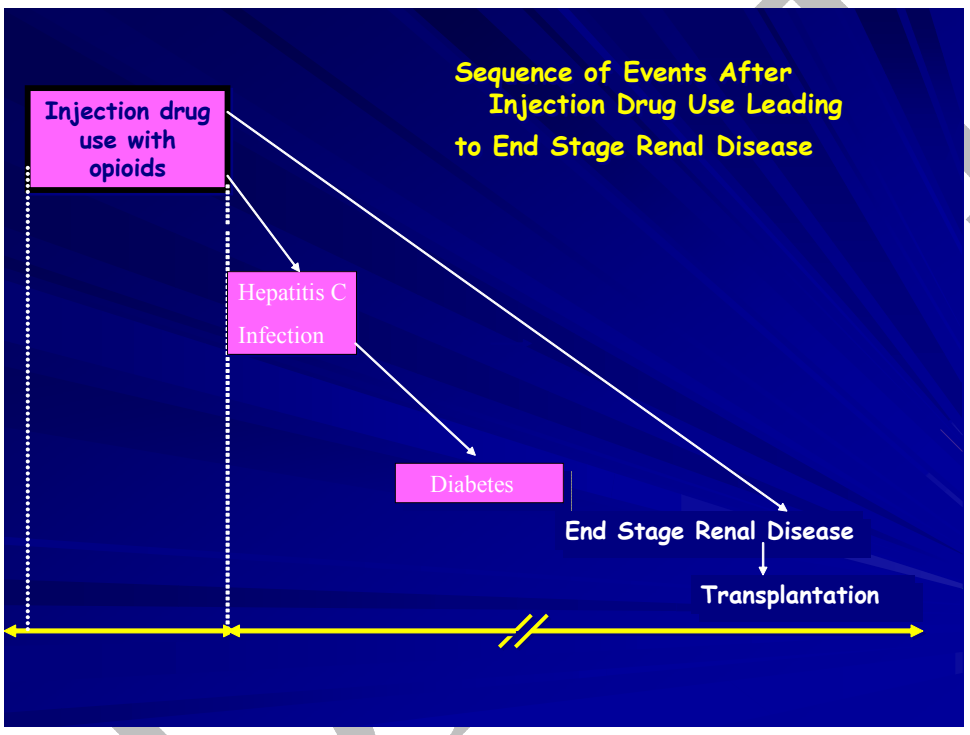

Figure 12. Enhancement of heroin-associated nephropathy by HCV infection and diabetes

Methadone has been shown to be safe and effective in patients with renal disease undergoing dialysis (Dean 2004). Renal transplantation of HIV+ patients has been performed (Kumar et al. 2005; Roland 2004). Post transplant survival has improved in these individuals with the use of antiretroviral therapy to control HIV infection. Current

experience in renal transplantation in HIV-infected patients in the United States indicates that the three-year survival rate is similar to that of HIV-negative transplant recipients, with virological and immunological control of the infection by anti-retroviral treatment. There has been no increase in the number of opportunistic infections or tumors, due to immunosuppression post-transplantation. The criteria for selecting HIV+ renal transplantation candidates include no opportunistic infections, CD4 cell counts greater than 200 per ul., and control of HIV infection with an undetectable viral load. In Spain, where most of these patients are former drug abusers, a two-year period of abstinence from cocaine and heroine abuse is also required, although patients are permitted to participate in methadone treatment (Trullas et al. 2005). Problems post-transplantation include interactions between anti-retroviral drugs and immunosuppressive drugs, management of HCV coinfection and progressive liver disease, as well as acute graft rejection.

Addiction and Immune Modulation

Both basic research studies and clinical observational studies indicate that opiates and opiate abuse has a broad influence on immune networks and their function (Donahoe and Vlahov 1998; Sharp 2003). Exogenous opioids may alter immune function, associating pathogenic susceptibility with opioid use, as well as with immunomodulatory activities (Alonzo and Bayer 2002; Ryan et al. 2004). Since the 1950's abnormalities have been observed in immune responses of heroin injection drug users, including diseased lymph glands, elevated white cell counts, increased antibodies, and false-positive tests for syphilis, rheumatoid arthritis, and other illness. T cells, mediators of

cell-mediated immunity, have been shown to express cell surface opioid receptors (Sharp 2003). These receptors, when bound, would reduce the immune response induced by T cells, thereby suppressing overall immune responses.

Clinical investigations have demonstrated that immune response abnormalities can be moderated or eliminated by methadone treatment (Donahoe 1993; Novick et al. 1991: SAMHSA 1993). Methadone treatment has been reported to normalize immune function and stress responses in former injection drug users (Zajicova et al. 2004). Research also suggests however, that inadequate methadone-maintenance doses or withdrawal from methadone may create extraordinary stress, potentially altering immune system function (McLachlan et al. 1993).

Addiction and Cancer

In the United States, cancer is highly prevalent with one out of every two men and one in three women developing cancer at some point in their lifetime (DHHS 2005). Cancer arises from a loss of the normal regulatory events that control how and when cells grow, divide and proliferate. The loss of the regulatory control of cellular growth and division is a multi-step process called carcinogenesis and has a strong genetic component (Hall et al. 2001). However, research studies have shown that environmental factors, such as lifestyle behaviors, can contribute to the process of carcinogenesis and for instance, trigger the malignant transformation of a pre-cancerous lesion to form cancer. A well recognized behavior that is closely associated with an increased risk of cancers in various organs of the body is cigarette smoking (Nishikawa et al. 2004). Chronic alcoholic beverage consumption is also a significant risk factor for cancer of the digestive tract (oral-pharynx, larynx, esophagus, liver, and colon) as well as breast (Poschl et al. 2004).

Alcohol consumption in association with cigarette smoking, which may occur in a significant number of individuals receiving treatment in an OTP, may significantly impact the process of carcinogenesis (Poschl and Sietz 2004). The additive or synergistic effect of two or more agents leading to cancer is termed co-carcinogenesis. Co-carcinogenesis has been proposed for virus-chemical interactions to cause cancer. Thus, addiction to nicotine and/or alcohol may be important co-carcinogens in patients who attend an OTP, particularly, if these patients are infected with HBV or HCV. The Eleventh Edition of the Report on Carcinogens (DHHS 2005; available at http://ntp.niehs.nih.gov) was recently released and has for the first time, listed HCV and HBV as known human carcinogens. Both HBV infection and HCV infections are listed as a cause of liver cancer. Thus, OTP's that address lifestyle behaviors such as smoking and alcohol consumption, as well as infections related to IDU such as HBV and HCV, are preventing the occurrence of additional comorbidities in their patient population. Primary prevention programs for cancer are focusing on lifestyle changes, which include diet and exercise, to promote better health for their patients (Festi et al. 2004; Martinez 2005)

Chronic Pain Management

The management of either acute or chronic pain of patients enrolled in OTPs is important due to the prevalence of chronic severe pain found in these patients (Rosenblum et al. 2003). Chronic severe pain, defined as moderate to severe pain that is persistent for more than six months, has been reported to be experienced in 37% of OTP patients. Acute pain has been reported in 80% of patients. Sixty-five percent of patients reported pain levels sufficient to impede function. However, patients in OTPs were less likely than in drug-free programs to self medicate for pain. But, aberrant drug-taking

behaviors may occur in patients who are undergoing treatment for chronic pain, especially if opioid therapy is involved. Patients with pain may unilaterally escalate doses of opioids or use medications to treat other symptoms and, thus, divert the use of prescription medications. These complex behaviors may be indicative of addiction or may be simply a reaction to under-medicated pain. Optimal medical management of chronic pain in patients with addiction problems or who engage in problematic behaviors involves careful, ongoing assessment by the care provider as well as a tailored, individual management approach (Layson-Wolf et al. 2002; New York State Dept Health AIDS Institute 2005). This approach should use multiple structures to maximize the likelihood of a good outcome, including strict contracts, prudent drug selection, and frequent follow-ups to pain and addiction treatments, including the use of urine toxicology screening (Passik and Kirsh 2004).

Assessing the psychological status of a substance using patient with pain is essential. Chronic pain is associated with psychological problems including depression, anxiety, and social isolation as well as feelings of powerlessness, hopelessness, or low self-esteem (Sproule et al. 1999). Any of these potentially could promote drug use or relapse (ASAM 1997). The Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) requires that daily medical practice incorporate effective, individualized pain assessment and treatment, essentially weaving pain management into the fabric of all accredited organizations (Dahl 1999; Summers 2001).

Principles of pain management in persons who are in recovery from addiction and in methadone treatment have been updated (2004 Public Policy Statement). Close communication between medical staff in OTP programs is recommended. It is important

that patients receive their usual oral daily methadone dose prior to surgery and that arrangements be made for continuation of methadone treatment dosing both during the hospital stay and upon return home. Several key points regarding pain management for patients in OTPs are summarized in Table 10 (Leavitt 1998).

Table 10 - Pain Management Principles for Patients in OTPs

- Patients in OTPs experience pain normally and thus, benefit from appropriate analgesia in the same manner any other persons with acute or chronic pain.
- Patients in OTPs may need analgesics (including opioids) more frequently and in larger doses.
- Blockade effects of adequate methadone treatment doses help protect the patient from any euphoric effects, drug craving, and/or respiratory depression associated with opioid analgesics.
- The regular methadone treatment dose should be continued while adequate short-acting opioids are prescribed, if necessary.
- Withdrawal from or reducing methadone is counterproductive and can negatively affect patient health.
- Patients' fears of drug relapse should be acknowledged and appropriate supervision, follow-up, and relapse prevention support provided.

Patients in OTPs may receive inadequate doses of opioid analgesics because of mistaken perceptions that methadone treatment provides pain relief and that more opioid medication may induce overdose or drug relapse. Medical staff may be influenced by misunderstandings surrounding addiction rather than pain management guidelines. Patients in methadone treatment can have a greater sensitivity to pain (hyperalgesia) or be refractory to the analgesic effects of other opioids, thereby requiring aggressive management for chronic pain, such as larger analgesic doses at more frequent intervals (Compton and Ling 1998; Manfredi et al. 2001). A patient receiving adequate methadone

treatment doses would be blocked against the euphoric effects of opioid-class analgesics; but sufficient doses of such agents are still required for pain reduction. Due to the cross-tolerance effects of methadone, risk of opioid overdose is minimized. Spinal and epidural narcotics however, can be problematic in opioid tolerant patients, since the greater doses required may increase adverse effects.

Patients receiving methadone treatment for addiction do not experience increased drug craving when given adjunctive opioid analgesics for pain. Patients may be titrated off of adjunctive analgesics just as with opioid-naïve patients once the pain is resolved (Leavitt 1998). Still, it is common for many former substance-dependent persons to be fearful of losing control and, thus, refuse or seek to minimize analgesia with drugs having addictive potential. Patient education may be required and reassurances by medical staff should be supported by close supervision and follow-up with patients, possibly including relapse prevention counseling (SAMHSA 1993) or periodic urine testing as a supportive tool in confirming abstinence from substance use. A patient-provider written treatment agreement may be useful in detailing the functional goals of treatment, duration of medication, management of refills and lost prescriptions and/or medications, and define the number of medical providers for pain medication. Provider legal concerns present an additional barrier and as in all aspects of medical care, appropriate documentation and adherence to published clinical guidelines should be practiced (New York Department of Health AIDS Institute 2005).

The Koch and Banys survey (2001) found that only three OTPs (8 percent of the study) experienced any difficulties with postoperative pain management with patients. In a case series study of 36 patients in methadone treatment, the standard postoperative

analgesia protocols were suitable for OLT (Liu et al. 2003). Certain analgesic agents need to be avoided in patients receiving methadone treatment. Since methadone is a μ-receptor agonist, patients treated with methadone are likely to suffer precipitated withdrawal if given mixed opioid agonist/antagonist or partial opioid agonist analgesics, such as buprenorphine (Buprenex®), butorphanol (Stadol®), nalbuphine (Nubain®), or pentazocine (Talwin®). Additionally, opioid agonists, such as meperidine and propoxyphene, which are N-demethylated to long-acting, neuro-excitatory metabolites, should be avoided in patients taking methadone, since they would be ineffective unless given in such high doses that the risk of toxic effects from the metabolites becomes unacceptable.

Resources for Care and Treatment

Furthering Medical Education

Hepatologists, gastroenterologists, infectious disease specialists, primary care providers, general and family practitioners, psychiatrists, and addiction treatment specialists would benefit from continuing medical education related to the care and treatment of chronic HCV infection in injection drug users. A further understanding of substance dependency and the stages of addiction recovery, particularly with respect to methadone treatment, are needed. OTPs need to address hepatitis infection, liver disease and community resources to support patient care and treatment. In addition to this monograph, information and education resources are readily available on the Internet. A listing of salient resources is provided in (Table 11).

Table11 - Salient Internet Resources: Methadone, Hepatitis, Coinfection

- Addiction Treatment Forum
  www.ATForum.com
- American Association for the Study of Liver Diseases (AASLD)
  www.aasld.org
- American Association for the Treatment of Opioid Dependence (AATOD)
  www.AATOD.org/
- American College of Gastroenterology (ACG)
  www.acg.gi.org
- American Gastroenterological Association
  www.gastro.org/
- American Liver Foundation (ALF)
  www.liverfoundation.org
- American Society of Addiction Medicine (ASAM)
  www.asam.org
- Centers for Dis. Control and Prevention (CDC)
  www.cdc.gov/ncidod/diseases/hepatitis
- Infectious Disease Society of America.
  www.idsociety.org/content/navigationMenu/Practice_Guidelines/Guidelines_by_topic/hepatitisc

Library, Alcohol and Drug Abuse Institute, University of Washington

http://lib.ada.washington.edu

- Matrix Institute on Addictions
  www.matrixinstitute.org
- Medscape HIV/AIDS from WebMD

www.medscape.com

- National Alliance of Methadone Advocates
  www.methadone.org/
- National Center for Complementary and Alternative Medicine (NCCAM), NIH
  nccam.nih.gov
- National Digestive Diseases Information Clearinghouse (NDDIC), NIDDK, NIH
  www.niddk.nih.gov

- Center for Substance Abuse Treatment (CSAT), SAMHSA
  www.samhsa.gov/centers/csat2002/csat_frame.html
- Cleveland Clinic Foundation. Hepatitis C Management
  www.clevelandclinicmeded.com/hcv
- Department of Veterans Affairs. Hepatitis C Resource Centers.
  www.hepatitis.va.gov
- Division of Pharmacologic Therapies, CSAT, SAMHSA
  www.samhsa.gov/centers/csat/content/dpt/index.html
- GastroHep.com
  www.gastrohep.com
- Hepatitis B Foundation
  www.hepb.org
- Hepatitis c Advocacy
  www.hepcadovcacy.org
- Hepatitis C Connection
  www.hepc-connection.org
- Hepatitis C in Me (Maine)
  www.hepatitiscnme.org
- Hepatitis Foundation International (HFI)
  www.hepfi.org
- HIV and Hepatitis.
  www.hivandhepatitis.com
- Natl. Foundation for Infectious Diseases (NFID)
  www.nfid.org/
- National Institute of Diabetes and Digestive and Kidney Disease (NIDDK), NIH:www.niddk.nih.gov/health/digest/pubs/hep/
- National Institute on Alcohol Abuse & Alcoholism, NIH
  www.niaaa.nih.gov/
- National Institute on Drug Addiction, NIH
  www.nida.nih.gov/
- National Institutes of Health (NIH)
  www.nih.gov/
- New York Department of Health AIDS Institute Substance Use Guidelines
  ttp://hivguidelines.org/public_html/center/clincial-guidelines/sub-gl/substance.html
- Organization to Achieve Solutions in Substance Abuse (O.A.S.I.S.)
  www.oasisclinic.org/
- Projects in Knowledge. Initiatives in Gastroenterology
  ww.projectsinknowledge.com/recent/indexG.html
- Texas Department of State Health Services- Public Information kit- Hepatitis C Initiative
  www.tdh.state.tx.us/ideas/hepatitis/hepatitis_c/overview/public_info_kit/
- University of California, San Francisco Center for Information. Coinfection with hepatitis & HIV
  http://hivinsite.ucsf.edu/

All sites were accessed and active as of September 2005.

Regular interaction among addiction-treatment providers, liver-treatment specialists, infectious disease specialists and primary care providers has been recommended to better coordinate patient care. To foster improved treatment for hepatitis, a cooperative approach may promote adherence to medication regimens, treatment for coexisting physical and psychiatric conditions, and implementation of strategies to prevent relapse during and following treatment (Davis and Rodrigue 2001; NIH 2002). Integrating delivery of pharmacotherapy for liver disease with multidisciplinary substance abuse care at a single site, such as an OTP, has been

demonstrated as an important strategy for improving attendance at medical visits and optimizing treatment outcomes (Litwin et al. 2005; Muir et al. 1999; Willenbring et al. 2004).

Referral Networks and Co-location of Care and Treatment

As noted earlier, methadone treatment programs may provide a comprehensive therapeutic milieu, often including primary medical care, psychosocial counseling, vocational rehabilitation, ongoing performance monitoring, and other vital services. OTPs can also provide buprenorphine pharmacotherapy to clients under the DATA 2000 regulations. Comprehensive care and treatment programs are being developed that integrate general and HCV and/or HIV-related medical, substance abuse, and mental health services at a single site (Litwin et al. 2005; Strauss et al. 2005; Sylvestre et al. 2004; Taylor 2005). Health care provider teams include a physician (internist or family practitioner), a mid-level provider (PA or NP), psychiatrist, a social worker, nurse, and substance abuse treatment counselors. Weekly interdisciplinary meetings can foster communication between staff regarding diverse aspects of patients' care. Subspecialty care, advanced diagnostics and acute care can be provided through a linkage with a nearby tertiary care system. Physicians at methadone treatment sites serve as patients' inpatient attending physicians if they are hospitalized for medical care, thereby providing continuity of care. Co-location of hepatitis C and HIV care services in the substance abuse treatment settings fosters access to care for patients with multiple comorbidities, many of whom likely would not be accessing needed care (Dore and Thomas 2005;

Gunn et al. 2005; Kresina et al. 2005). Co-location of care has also been shown to lead to high rates of adherence with liver biopsy and initiation of antiviral therapy (Litwin et al. 2005). To significantly improve patient outcomes for this difficult to treat patient population, more programs will need to adopt such co-location models as the standard of care. A manual entitled "HIT'M" for training staff into integrate hepatitis prevention into HIV/AIDS, STD and drug treatment programs is available from the American Liver Foundation. The Departments of Health of various states as well as County Health Departments are providing resources in support of hepatitis C service integration. For example in Oregon, the Multnomah County Health Department Viral Hepatitis C Integration Program (VHIP) is dedicated to building capacity within the county health department and in the community through integrating services and creating community services and resource linkages. Five primary areas are targeted HIV Prevention and Outreach to build street outreach and education for hepatitis; Sexually Transmitted Disease Clinics--to implement HCV testing, post-test counseling, and hepatitis A and B vaccinations; Social Work--for HCV test positive individuals, short term case management and social service support; development of a referral system among primary care and family services addiction specialists; Health Education--for the development and dissemination to the community of hepatitis curricula; and Community Planning Processes--to establish community planning groups for development and implementation of a hepatitis C strategic plan. In this program, consumers of hepatitis services are part of the community planning process and interface with institutional decision makers and the county health department policy makers.

Community planning and health services referral networks are fundamental to providing needed medical and social services not available at OTPs (Fletcher et al. 2003). To help achieve a viable referral network, OTPs need to identify health care providers in the community willing and trained to provide medical and social services to their patients (Novick 2000; Sweeney et al. 2004). Greater improvement in post-treatment outcomes has been shown in programs that tailor frequency and type of service to unique client needs (Rowan-Szal et al. 2000). Substance abuse treatment programs should be advocates for their patients needing and seeking care and treatment thereby providing a support network throughout the course of therapy.

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