

Part 1: Critical Concerns

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The epidemic of liver disease in methadone maintenance treatment (MMT) programs, lurking like a massive iceberg with only its tip exposed to public view, has been noted before in *AT Forum*.^[1,2]

Former intravenous (IV) drug addicted persons may harbor several types of hepatitis: A, B, C, and D. Hepatitis C (HCV) is perhaps the greatest threat, since most persons who contract it go on to develop chronic illness. Liver failure due to HCV results in up to 10,000 deaths annually in the United States and is the leading cause of liver transplantation nationwide.^[3]

An emerging life or death issue is refusal on the parts of many medical specialists to treat liver disorders in MMT patients and/or to allow those patients on transplant waiting lists. A critical focal point of this controversy is methadone itself.^[4,5]

Medical, ethical, legal, and economic concerns have arisen. This article is the first in a series focusing on those issues and on some possible action steps.

Prevalent Threat

Hepatitis C (HCV) is a blood-borne virus affecting approximately 4 million Americans, the majority being past or present illicit IV-drug users. This group represents the greatest proportion of new infections each year and the largest pool of persons eventually needing liver transplantation.^[6]

HCV causes inflammation of the liver that can lead to scarring and failing liver function. At later stages, HCV can cause cirrhosis, in which the liver is scarred throughout and there is the risk of complete liver failure (end-stage liver disease).

Based on a synthesis of statistics reported in the literature,^[6-9] roughly 90 of every 100 injection-drug users entering MMT programs are likely to be infected with HCV. Only 14 of those patients will recover from HCV on their own; the remaining 76 will probably develop chronic disease unless they

receive successful treatment. There is no way of predicting who will recover without treatment.

Even with treatment, about 17 of those initial 100 MMT patients will go on to develop cirrhosis and 8 will require a liver transplant for survival. Although treatments for HCV have been improving, there could be as many as 14,000 current MMT patients in America eventually needing liver transplants.

From Bad to Worse

Unfortunately, last year there were only about 5,000 liver transplants performed in 122 transplant centers across the U.S. As of September 2001, there were nearly 18,500 persons on waiting lists for liver transplants.^[10] So, in the best of circumstances, less than a third of those on wait-lists receive new livers.

Since 1988, only an estimated 180 MMT patients have had liver transplants; less than 0.5% of the 40,468 procedures performed. Today, there are merely an estimated 102 MMT patients on waiting lists, or 0.6% of the total.^[11]

Making matters worse, the MMT population is aging. Many patients who contracted HCV years ago are at stages in their illness where treatment or transplant is a do or die situation.

A majority of illicit IV-drug users with HCV may be coinfecting with HIV, which greatly accelerates the devastation of HCV. As an emerging problem, coinfecting persons are facing insurmountable obstacles to treatment or transplant for their liver disease.^[8] Furthermore, many MMT patients also use excessive alcohol, which compounds cirrhosis and related complications in those with HCV.^[9]

Treatment Barriers

Tragically, there has been an irrational withholding or delaying of available treatments for hepatitis in MMT patients and/or their rejection by liver transplant programs.

On the basis of recommended guidelines of consensus conferences held in the United States, Canada, and Europe, most specialists refuse to administer antiviral HCV treatment until all illicit-drug use has ceased for a period of time – usually 6 months. Some practitioners also require abstinence from methadone.

In actuality, these guidelines provided little explanation or justification for those practices, have been largely misinterpreted, and say nothing about methadone.[3,9]

A more recent guideline on HCV management from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) specifically states, “Patients can be successfully treated while on methadone.”[12] This message has been largely overlooked by liver treatment specialists.

According to Diana Sylvestre, MD – Executive Director of O.A.S.I.S.-Abuse (Organization to Achieve Solutions in Substance Abuse) in Oakland, California – the most serious impediment may be stigma, prejudice, and misinformation surrounding addiction and MMT. Her nonprofit clinic specializes in serving patients with HCV, particularly referrals from MMT clinics, in the San Francisco Bay Area.

“A physician can state a lot of reasons for not treating HCV in MMT patients,” she says, “but it often comes down to prejudice. Superficially, the reason usually seems justifiable, since there are so many potential barriers to treating HCV in MMT patients that a rationale can usually be derived for denial of treatment.”

Critical Timing

In general, some authors have noted that up to 36% of all HCV-infected patients never receive antiviral treatment,[9] and this proportion is greater in addiction treatment populations. Sylvestre observes that, of approximately 850 HCV-diagnosed patients seen at her clinic, only 100 have received treatment to date.

Treatment is legitimately delayed in some patients because they have active psychiatric disease, an unstable family or job situation, or a medical condition needing more immediate attention. However, Sylvestre works closely with these patients to remove the barriers to successful HCV treatment.

It also has been suggested that patients at very early stages of HCV may not benefit from treating the disease. However, a new study from Germany reported that the HCV virus became undetectable in 98% of patients treated within 3-months of becoming infected.[13]

Sylvestre points out that it is very difficult to identify acute HCV infections in opioid-addicted persons, since at the time of infection they are rarely attending to their medical needs. Furthermore, her experience has been that if the person is still injecting illicit drugs there will be extremely poor response, if any, to antiviral treatment for HCV.

Transplant Obstacles

With transplantable livers in such short supply, transplant programs jealously guard each place on their waiting lists. Only those candidates considered most likely to achieve long-term survival with a new liver are selected.

Many liver transplant centers, while claiming to evaluate patients on an individual basis, will consider only those MMT patients who withdraw from methadone.

Relatively recent survey results, encompassing 90% of liver transplant programs, depict severe discrimination against patients taking methadone.[11] The authors found that 44% of the programs denied acceptance of MMT patients on their waiting lists and nearly a third of those that did accept MMT patients required withdrawal from methadone. Essentially, 62% of liver transplant programs prohibited methadone in one way or another.

Sylvestre referred a male MMT patient with advanced cirrhosis to a major west coast transplant center for evaluation. They insisted he first withdraw from methadone, although the patient was otherwise qualified for a transplant.

Due to the stress of withdrawal the man experienced upper gastrointestinal complications, including bleeding esophageal varices. The man continued methadone withdrawal to receive a liver transplant and eventually died from a variceal bleeding crisis.

Ellen Weber, JD, Senior Vice President of the Legal Action Center (LAC) in Washington DC, tells of a female MMT patient who was listed for a liver transplant at a center in Maryland. However, when she moved to Florida, the local transplant center refused to even evaluate the woman as long as she was on methadone. The woman chose to remain in MMT and her liver disease has progressed to the point that she is currently in a nursing home.

Catch-22s

To date, there has been very little research on liver transplant outcomes in opioid-dependent per-

sons or those maintained on methadone.[3] In particular, there is no scientific evidence to support discontinuing methadone as a requirement for liver transplantation.[11] In catch-22 fashion, such a requirement may induce relapse in formerly stable patients and, because of this, would disqualify them from transplant.

Another absurdity, described by Sylvestre, is that the California Medicaid program – Medi-Cal – will pay for medications and office visits if the person has a recognized disability. Unfortunately, the criteria for being classified as disabled on the basis of HCV requires evidence of decompensated (very severe) liver disease that, under most circumstances, precludes treatment with medication; a transplant would be needed. This results in a very large population with treatable HCV in her clinic that does not qualify for financial assistance.

In one case, Sylvestre was successful in getting a patient wait-listed for a liver at an enlightened transplant center. However, Medi-Cal authorities insisted that the patient withdraw from methadone before transplant. She says those authorities have not been able to provide any medical rationale for this requirement.

Legal Pursuits

Is there a remedy in law?

The LAC's Weber comments that Section 504 of the Rehabilitation Act of 1973 prohibits discrimination on the basis of disability by institutions receiving federal financial assistance. To the extent that transplant centers are denying patients the opportunity to be considered for transplant on the basis of past addiction problems requiring methadone therapy, a legal challenge can be filed in court or with the Department of Health and Human Services (DHHS) Office of Civil Rights.

To refute discrimination claims, healthcare institutions must demonstrate a scientific or medical rationale for the denial of services. This same principle applies to individual medical practices under the Americans with Disabilities Act – treatment cannot be denied solely on the basis of methadone use, unless scientific or medical data exists to support that standard of care.

Weber believes a “Guidance” from DHHS on Section 504 nondiscrimination requirements in the delivery of health services would clarify issues relating to HCV treatment and transplant in MMT patients. Development of this could take time.

Meanwhile, Weber has made a start and is gathering information on individual cases. Regrettably, the LAC's efforts have been hampered

by a lack of funding to more actively pursue these issues.

The LAC, with offices in Washington and New York, has focused for the past 28 years on protecting individual rights and expanding access to treatment for persons with drug problems and AIDS, among others, at no charge to clients.

A Role for MMT Clinics

Sylvestre believes MMT programs can be more proactive. Programs need to become educated on HCV-treatment criteria and the barriers to treatment so they can make appropriate referrals.

If MMT programs make inappropriate referrals to liver specialists in the community, that referral base will disappear. “It doesn't do any good to send a homeless MMT patient who is actively psychotic and has little potential for successful outcomes to a hepatologist,” she says.

Programs also should become advocates for their patients needing treatment. She finds that those programs that are knowledgeable and have earned patients' trust are most successful in getting them into HCV treatment. MMT staff then need to be proactive in helping HCV-treatment providers manage these patients throughout the course of treatment.

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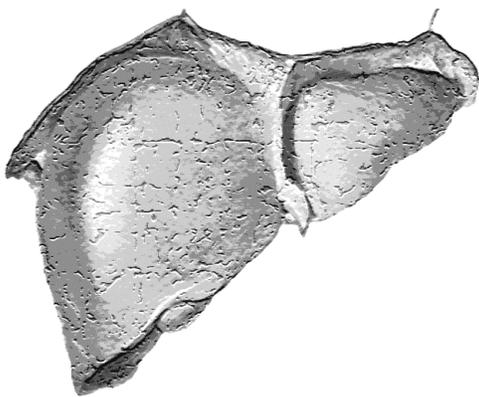
Part 2: Hepatitis C – A “Giant Silent Killer”

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In merely a decade, researchers have gone from characterizing hepatitis C (HCV) as a “sleeping giant”[1] to an “awakening giant.”[2] Meanwhile, many others have called it a “silent killer.”

The first article of this series[3] noted that about 9 out of 10 of persons entering methadone maintenance treatment (MMT) programs are likely to be infected with HCV. Of those, roughly three-quarters will develop chronic liver disease.

Although there appear to be many barriers to HCV treatment for MMT patients, there also is cause for hopeful optimism.



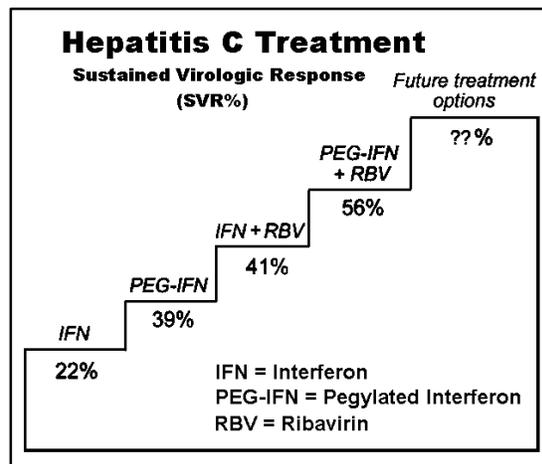
Treatments Improving

HCV treatments continue to evolve and improve, and treatment outcomes are determined by measuring virus particles in the blood. The absence of virus at the end of HCV therapy, called an end-of-treatment response (ETR), is a preliminary sign of treatment effectiveness.

However, a more accurate indicator is the sustained virologic response (SVR). This is defined as the absence of virus 6 months after the completion of treatment, which some describe as a cure.[4]

The first treatment for HCV was interferon. Injected under the skin 3 times a week for 24 to 48 weeks, it produced an SVR of up to 22% (see graph). The addition of another medication called ribavirin, which is taken by mouth twice daily, led to a near doubling of response rates to 41%.[6,7]

More recently, a longer-acting interferon, called pegylated interferon, has been developed that only requires weekly injection. It is a more effective medication than standard interferon, lead-



ing to SVRs of 39% by itself and up to 56% when combined with ribavirin.[8-10]

Success Factors

The most important predictor of treatment response is a viral characteristic called genotype, a genetic variation that has been likened to a viral “strain.” There are 6 major genotypes; in the U.S. genotypes 1, 2, and 3 are the most common, with most patients having type 1.[6]

Genotype does not affect the progression of liver disease, but it has a major impact on treatment outcome. Patients with genotypes 2 and 3 may show SVRs greater than 80% with pegylated interferon plus ribavirin, but response in those with genotype 1 is only about half that.[11,12]

Additionally, patients staying on therapy and taking nearly all of their medication have better treatment outcomes. [9,10,13] Other factors – such as age, sex, and extent of liver damage – also play a role.[14]

Although eliminating the virus is the main objective of HCV therapy, interferon may benefit the liver even in the absence of viral remission. Some studies have shown that it can slow progression of liver scarring and that it may reduce the risk of developing liver cancer.[15]

Unfounded Treatment Barriers

Even though injection drug use (IDU) accounts for the majority of HCV cases, recovering IDUs on methadone maintenance are sometimes denied treatment for HCV and have been excluded from the majority of clinical studies of HCV treat-

ments.[16] Although there is no relevant data, questions are often raised about their ability to tolerate treatment, potential relapse to drug abuse, comorbid psychiatric conditions, and possibility of reinfection.

In the general population, more than 20% of patients may discontinue HCV treatment due to intolerable side effects, including flu-like symptoms, fatigue, and anemia. Interferon can lead to severe depression, and uncontrolled depression or other psychiatric conditions usually exclude patients from starting interferon-based therapy.

An ongoing question is whether MMT patients should be withdrawn from methadone prior to HCV treatment. However, a review by Mattick and Hall [18] concluded that methadone provides stability in patients' lives, making them more receptive to adjunctive therapies. *They specifically recommended that patients need not be taken off methadone before undergoing other therapies.*

A small, prospective study in Europe by Schaefer [19] examined psychiatric complications during combination interferon/ribavirin therapy for HCV in MMT patients compared with control patients who were not former drug addicts. Depression increased equally in both groups of patients; however, the depression was mild to moderate in the methadone patients, whereas severe depression was experienced by a third of the controls. Withdrawals from treatment were equivalent in both groups; none due to depression.

Furthermore, methadone maintenance may slow the progression of HCV infection. An investigation of 285 HCV-positive IDUs [20] found that those in MMT programs were significantly less likely to develop chronic HCV infection than still-active injection-drug abusers. Furthermore, in those already chronically infected, methadone therapy was associated with more normal liver function, and methadone may allow the reversal of heroin-related immunologic impairment. Additional research is needed to better understand the natural history of HCV in MMT patients and the role of methadone in HCV treatment outcomes.

Research Supports MMT

In Schaefer's report, mentioned above, the response to interferon/ribavirin therapy after 24 weeks was 50% in MMT patients and 39% in controls. Importantly, during anti-HCV treatment, MMT patients benefited from increased methadone doses.[19]

Blechman and colleagues [17] compared interferon therapy in MMT patients and in a control

group of patients not on methadone. Disease severity, response to interferon, side effects, and treatment compliance were similar in both groups. The authors concluded that *MMT patients should not be automatically excluded from HCV-treatment trials and should be offered HCV therapy like anybody else.*

An ongoing series of clinical trials focusing on HCV therapies in MMT patients is being conducted at the Organization to Achieve Solutions in Substance Abuse (O.A.S.I.S.) in Oakland, CA, under the direction of Diana Sylvestre.[5,21,22] In a preliminary analysis of 57 MMT patients who had completed interferon/ribavirin treatment,[5] the overall ETR rate was 56%; which was comparable to results in non-opioid-dependent populations. Sustained response rates in Sylvestre's study are not yet available.

Occasional drug or alcohol use during this study produced only minor decreases in treatment outcome that were not statistically significant. However, patients using illicit drugs daily showed no virologic response at all to HCV therapy.

Interestingly, the response rate in MMT patients was unaffected by prior psychiatric diagnoses. However, by the end of treatment, 88% of subjects had received some form of psychiatric medication, primarily SSRIs, for depression. Forty-two percent increased their daily methadone dose by an average of 10 mg.

Only 22% of MMT patients discontinued from Sylvestre's study, compared with up to 21% in other studies. However, discontinuations were lower in MMT patients due solely to side effects.

Sylvestre concluded that tolerability, safety, compliance, and response rates in MMT patients were similar to those of historical controls (non-opioid-dependent patients) receiving identical therapy. This was evident despite substantial pre-existing psychiatric comorbidity in the MMT patients, and the fact that they were older, and had longer histories of HCV infection along with more liver fibrosis than subjects in other studies. *Clearly, the stabilizing effect of MMT in these studies contradicts the need for pretreatment methadone withdrawal.*

Brighter Prospects

Prospects for MMT patients with HCV are looking brighter and an HCV "giant slayer" may be on the horizon. Sylvestre and her team at O.A.S.I.S. are continuing their research in MMT patients, using the newer pegylated interferon. Clinical trials at the San Francisco VA Medical

Center also are enrolling methadone-maintained patients.

Future treatments may include anti-HCV agents that are especially useful in difficult cases. Pegylated interferon has demonstrated improved effectiveness, and a novel, bioengineered "consensus interferon" has shown promise in treating non-responders. "Triple therapies" including an interferon in various combinations with ribavirin, mycophenolate mofetil, or amantadine have been explored.[11] Unfortunately, non-interferon-based regimens are not expected in the near future, so further study is needed to improve outcomes in difficult patient populations.

Use of complementary and alternative medicines by a third of patients with chronic liver disease has been reported. Silymarin (milk thistle) compounds are frequently mentioned, as are St. John's wort, ginkgo biloba, ginseng, garlic extract, and echinacea.[23]

Most of these agents are used in hopes of minimizing liver damage caused by HCV and to manage treatment side effects. However, the 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." [24]

There is still the question of how MMT programs can participate in helping their HCV-positive patients get proper treatment. This will be addressed in the next article of this series.

AT Forum thanks Diana Sylvestre, MD (O.A.S.I.S., Oakland, CA) for her extensive contributions to this article.

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HCV Info on the Web...

The following Web sites offer important information on HCV for patients and practitioners ...

Advances in Hepatitis C:

< www.adis.com/advances_hepc/ >

American Liver Foundation:

< www.liverfoundation.org >

Hepatitis Branch, Centers for Disease Control:

< www.cdc.gov/ncidod/diseases/hepatitis >

Hepatitis Foundation International:

< www.hepfi.org >

Hepatitis Information Network:

< www.hepnet.com >

National Center for Complementary and Alternative Medicine: < <http://nccam.nih.gov/> >

National Center for Infectious Disease viral hepatitis data: < www.cdc.gov/ncidod/diseases/hepatitis/index.htm >

National Institute of Diabetes and Digestive and Kidney Diseases:

< www.niddk.nih.gov/health/digest/pubs/hep/ >

Organization to Achieve Solutions in Substance Abuse (O.A.S.I.S.): < www.oasisclinic.org/ >

Part 3: MMT Clinics' Roles in HCV Therapy

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The second article in this series [1] expressed hopeful optimism for methadone maintenance treatment (MMT) patients with hepatitis C (HCV). Treatments continue to improve, offering better outcomes for those patients who receive and complete HCV-medication regimens.

Unfortunately, it appears that a proportion of patients do not become eligible for treatment, some are denied treatment, and others are unmotivated to pursue available therapy. Consequently, many are likely to develop chronic, life-threatening liver disease.[2]

What can MMT clinics do to help?

Daunting Obstacles

At Aegis Medical Systems, which serves 5,000 MMT patients throughout California, **Allan J. Cohen**, MA, MFT, Director of Research and Development, estimates that 85% of patients are at various stages of HCV infection, with a great many needing treatment.

Similarly, at the 14th Street Clinic in Oakland, CA, **Judith Martin**, MD, Medical Director, estimates that more than 90% of their 400 MMT patients are HCV-positive.

Martin says that at patient intake, and then during yearly followup exams, liver functions are assessed to detect any problems. The county does basic testing for HCV, which is on a voluntary and confidential basis.

However, the staging of infection, typing, and viral-load testing in those who are positive for HCV antibodies is difficult. Martin says that her clinic cannot get reimbursement from Medi-Cal

(California's version of Medicaid) for these expensive tests, and referrals to outside public or private treatment providers can present daunting obstacles.

Patients themselves may be hesitant. Martin notes that patients often fear knowing more about their disease, so they don't follow up on getting tested. Even with frequent reminders and encouragement, it can take several years before they become ready to proceed with treatment.

Cohen agrees that, "Although most MMT patients are interested in taking better care of themselves, a certain percentage of patients simply decline testing and treatment. They seem to be in denial about what's going to happen to them or they don't care."

Unjustified Prejudice

Another obstacle, Martin suggests, is the reluctance of liver specialists to even examine MMT patients. "For example, many hepatologists reject patients who are on methadone outright or insist on total drug abstinence for an entire year before they will do liver tests." This limits treatment to only about 10% of her patients, since many have a pattern of occasional drug or alcohol use.

This abstinence requirement is not based on any accepted clinical guidelines, she adds. Furthermore, research data show that occasional, but not continuous, substance use does not hinder outcomes of HCV-medication therapy, so there is no scientific basis for the requirement.

Cohen concurs: "This is not simply a matter of diagnosing a person with a treatable disease and then getting immediate, adequate treatment for that

patient, as might be expected with other potentially chronic illness, such as asthma or diabetes. There are many biases and prejudices against patients in addiction treatment programs.” He believes a requirement by liver specialists that MMT patients must first withdraw from methadone to receive HCV treatment is still pervasive, but is often not overtly stated.

Fragmented System

A fragmented system of referrals and reimbursement for services poses yet another obstacle, according to Cohen. A patient’s ability to pay for treatment, if they are self-paying, or the particular county’s willingness to cover the expense are critical factors, since HCV therapy is costly.

In Bakersfield, where the Aegis corporate medical director resides, there is an arrangement with a local liver-treatment specialist who prescribes HCV medication, which is then administered to patients at the MMT clinic. However, that is not the typical arrangement.

At other clinics, liver specialists were turning away MMT patients until the clinics began arranging on their own for initial patient evaluations – eg, lab tests, liver ultrasounds, and other tests besides biopsy. Then, referrals were accepted.

Still, at county medical facilities, patients usually have long waits for HCV treatment after referral. “This can be intimidating and these persons are not good at waiting,” Cohen observes.

Addressing Psychosocial Issues

A most vital role of MMT clinics is in dealing with a continuum of psychosocial issues. According to **Joan Zweben**, PhD – Executive Director of the 14th Street Clinic and East Bay Community Recovery Project, Oakland, CA, and Clinical Professor of Psychiatry at the University of California in San Francisco – it is up to the physicians to identify medically who can benefit from treatment. But, the MMT clinic staff can provide support in dealing with this chronic illness even if a medical regimen is not immediately available or necessary.

She says the MMT program’s job is to make patients more treatment-ready, helping them overcome anything that might contribute to instability or undermine their ability to tolerate the demanding HCV-treatment regimen. For example, patients often need help with...

- shelter and a safe environment,
- a social support network,
- employment,
- treatment for other medical problems,

- psychosocial aspects of co-occurring disorders,
- transportation to medical appointments,
- staying motivated throughout treatment.

Zweben advises clinic staff to prioritize those areas needing most urgent attention. However, she says, “many of these are things that good clinics should be doing already.”

Addressing psychiatric comorbidity is critical. There are high levels of anxiety and mood disorders, including depression, in this patient population, Zweben notes, affecting perhaps 80% of patients. “These are important because if someone has distressing symptoms or emotional difficulties it effects everything you try to do to help them. Furthermore, HCV treatment causes depression in most patients, so this needs to be managed.”

Regrettably, in many parts of medicine there is a disconnect between the psychosocial component and the medical-treatment component, Zweben observes. Yet, it has been demonstrated that there is better compliance with HCV-treatment if psychosocial issues are addressed.

Educating Patients

Patient support groups are an often overlooked component of even the best HCV treatment programs around the country, Zweben believes. Also, patients should be able to attend those groups at any stage of their HCV illness; it becomes an index of their readiness for treatment.

However, Zweben concedes that having such a program doesn’t automatically mean patients will come to it. “There is a need for persistence by clinic staff and repeated exposure to the support program.”

Martin observes that MMT clinics typically have many types of support groups and these should specifically address HCV. She also stresses that a major role of the clinic staff is to provide patients with education on HCV to overcome any fears.

“We need to show patients that we think this is an important illness and encourage them.” Martin says. Her counseling staff are specifically trained in encouraging patients to get evaluated and treated for HCV.

“It’s very important to emphasize with patients that the rigorous treatment for HCV is time-limited – a year or less,” Martin continues. “It doesn’t go on indefinitely, as with treatment for HIV. I also call attention to the many patients who have done well in tolerating HCV treatment and felt it was definitely worth it.”

MMT Staff as Advocates

Adopting an active advocacy role in helping MMT patients overcome obstacles to treatment is a worthwhile goal, Cohen believes. Better communication with liver-treatment specialists could be an important first step.

In that regard, Martin proposes several ways clinics can interface between patients and outside liver-treatment specialists:

1. provide specialists with relevant data demonstrating that MMT patients are worth treating in terms of outcome success [see Part 2 in this series];
2. highlight patient strengths to the specialist in a letter or other communication;
3. provide support to specialists in managing patient compliance with treatment.

The last point involves MMT-clinic staff working closely with patients in a case-management role. This might entail having someone accompany the patient to hear the doctor's instructions and making sure the patient follows through, or arranging transportation from the clinic to the specialist's office. Martin acknowledges that most clinics do not have staff resources for this, but it is a worthy goal to work toward.

Cohen agrees that it could be useful to document the patient's performance in MMT in terms that would be meaningful to outside providers, such as treatment compliance and keeping appointments – a “report card” of sorts. This could help overcome reluctance to treat the patient.

However, what happens if an MMT patient does not appear particularly promising for HCV treatment?

While treatment might not be appropriate for everyone, or successful, merely being on methadone and in an MMT program should not be a barrier, Cohen insists. Would a person with diabetes who has not been consistently compliant with insulin therapy or reliable in keeping doctor's appointments automatically be denied HCV treatment?

Still, Martin cautions that, “it is important not to ‘burn out’ your referral base by sending them poorly qualified patients.” Yet, some flexibility is necessary; “what many specialists consider as “stability” in a patient is nearly impossible to achieve in a great many MMT patients,” she says.

Partnering with Specialists

Partnering with liver specialists in the community can be enormously helpful, Cohen believes. For example, hepatologists may not want to assume full responsibility for the patient and a close collaboration with MMT clinic medical staff could help overcome any concerns.

Cohen suggests that MMT programs might themselves take a more active role in diagnosing and treating HCV, but this could engender liability problems. MMT clinics are typically licensed only to treat opioid addiction.

But, he believes that clinics might help administer medications prescribed by specialists and dispensed at local pharmacies. In such cases, MMT staff would need a backup network of specialists. For example, if modifications of treatment are necessary someone must assume responsibility.

In a practical sense, Martin is concerned that MMT clinics are not typically staffed to assume a role in supervising or administering anti-HCV medications. Also, there is usually no provision to reimburse clinics for the extra staff time that might be required. Added support from funding agencies would be crucial.

Despite the many obstacles, Martin stresses that, “MMT programs need to become more creative in helping their patients with HCV, including those who are not yet ready for treatment.” At present, results are better for patients doing well in MMT, living essentially middle-class lives, with ample support systems and financial resources. There is the ongoing challenge of helping HCV-positive patients new in MMT, with less stable lifestyles.

In sum, MMT programs can and should take more active roles in dealing with the HCV crisis. From a public health viewpoint it can be important in helping contain this widespread infection. From a patient welfare perspective, effective medications are available to help curtail HCV progression and prolong life if patients can gain access to treatment.

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Part 4: Hope for Liver Transplantation

Summer 2002; Vol. 11, No. 3

"I've been on methadone maintenance for 24 years, with hepatitis C for at least 27 years. After treatment for hepatitis failed, I was told that I'll never get a liver transplant if I stay on methadone. ...any suggestions?"

Unfortunately, the dilemma of this methadone maintenance treatment (MMT) patient is commonplace. Yet, there is hope for him and others in MMT who are persistent in their search for needed liver transplants.

Transplantation Denied

As the first article in this series pointed out,[1] as many as 14,000 persons in U.S. MMT programs may eventually need liver transplants for survival, primarily due to chronic hepatitis C (HCV). Yet, such patients are seriously underrepresented on transplant waiting lists.

Many transplant programs, while claiming to evaluate patients on an individual basis, refuse to consider MMT patients or require that they first withdraw from methadone.[2,3] A pivotal survey by Koch and Banys reported in 2001 that 44% of liver transplant centers did not accept persons on methadone and only 180 MMT patients had ever received transplants by those that did accept them.[4] An earlier survey by Awad and Chin [5] similarly found that, while many centers said they considered MMT patients, 41% never listed such patients for transplant.

Methadone seems to be unofficially perceived as an unnecessary and potentially complicating factor in liver transplantation. This might at least partially derive from the stigma and prejudice shadowing addiction in general and methadone in particular.

Invalid Concerns

A number of concerns have been expressed about liver transplantation in MMT patients, which are summarized in the *table*. These are either unlikely to occur or can be successfully addressed if they do occur. There is no scientific rationale to support why taking methadone should rule out potentially life-saving interventions for liver disease.[6]

Unsupported Concerns About Liver Transplantation in MMT Patients

- Complications due to methadone interactions with anesthesia or posttransplant drug regimens.
- Pain management in patients already maintained on an opioid, methadone.
- Nonadherence with medication regimens after transplant.
- Unwillingness to comply with necessary followup medical care.
- Return to illicit drug use negatively affecting outcomes.

A hallmark of effective MMT programs is the aggressive promotion of abstinence from all addictive substances, strict compliance with therapeutic regimens, frequent medical follow-up, and rehabilitation of social, psychological, and vocational functioning. Hence, MMT would be invaluable for preparing former illicit-drug abusers for transplantation and in helping to maximize favorable outcomes.

Available research has demonstrated that *prior* substance-use disorders are not medically sound reasons for exclusion from liver transplantation, and pretransplant abstinence requirements are poor predictors of clinical outcomes or abstinence after transplant.[7] However, Koch and Banys most recently commented that there is an implicit assumption that former substance abusers will relapse or become noncompliant with treatment, and these social value judgments once applied to the alcoholic population appear even more stringently and unfairly directed toward recovering illicit-drug users.[8]

They note that such reservations are ethically questionable and have no supporting evidence in the scientific literature.[8] In the case of MMT, available reports indicate that posttransplant outcomes and compliance in stable methadone-maintained patients are at least comparable to the rest of the population, and these patients are no more likely to relapse to illicit-drug addiction than other formerly substance-dependent persons – usually much less so.

Favorable Evidence

To date, there have been only two published investigations of liver transplantation specifically in MMT patients. In a report from Albert Einstein Medical Center, Philadelphia,[9] 5 MMT patients underwent liver transplantation between March 1993 and May 1999, representing 2.7 percent of all liver transplants at the center during that time period. All patients were very ill prior to surgery and there were significant but manageable postoperative complications in 4 of them.

Overall, outcomes and long-term survival in the MMT patients were comparable to other patients, and none of them returned to illicit-drug or alcohol use after transplantation. The authors concluded that MMT patients with end-stage liver disease should be considered for transplantation and that “weaning completely off methadone should not be an essential requirement prior to consideration.”

In a larger study, Lau and colleagues described 34 MMT patients receiving liver transplants from 1989 to 1999 at Mount Sinai Medical Center, New York City.[10] The 1-year and 3-year survival rates (94% and 77%, respectively) were equivalent to all other liver transplant recipients at that institution. The authors concluded that continuing methadone maintenance did not complicate outcomes in any way.

In this study,[10] 4 methadone-maintained patients (about 12%) resumed illicit-drug injecting after transplant; however, according to Lawrence Liu, MD (Liver Fellow, Mount Sinai Medical Center) posttransplant drug use actually involved isolated and limited events, rather than serious relapse. Also, this 12% drug-use rate – often labeled “recidivism” – is lower than for recovering drug- or alcohol-dependent transplant recipients not in MMT.[11,12]

There is a question as to whether transplanted MMT patients were receiving adequate methadone doses. In the Mount Sinai cases, presurgical doses ranged from 5 to 100 mg/day (median 60 mg/d). Liu comments that dosing was controlled solely by the respective MMT programs rather than the transplant team, and he believes there might be a false perception that lower methadone doses are more favorable for transplantation. He recalls that, for no apparent reason, one patient had his dose reduced from 70 mg/day at the time of transplant evaluation to 5 mg/day by the day of surgery.

Similarly, Kenneth Rothstein, MD, Associate Director of the Center for Liver Disease at Albert

Einstein and a coauthor of the case series report, notes that methadone dosing – averaging only 29 mg/day – was managed entirely by the respective MMT programs. Patients’ doses might have been decreased, thinking it would better qualify them as transplant candidates. The fact that none of the patients in this report [9] relapsed to illicit-drug use might attest more to the efficacy of MMT as a supportive addiction treatment environment than to the adequacy or necessity of lower methadone doses.

Unnecessary Apprehension

As for the other concerns noted in the *table*, any apprehension regarding MMT patients seems unnecessary. Koch and Banys noted in their survey[4] that posttransplant difficulties with medication adherence (compliance) or followup care was reported by only 15% of centers experienced with MMT patients, and these were of minor significance that did not affect transplantation outcomes. In general, noncompliance to some extent may be exhibited by up to 20% of *all* posttransplant recipients, including missed clinic visits, forgotten drug doses, reducing drug doses, or even stopping one or more medications.[13]

Furthermore, interactions between posttransplant medications and methadone have not been documented in the literature. In the Koch and Banys survey,[4] none of the liver transplant centers reported immunosuppressant-drug interactions with methadone. Liu concurs that no adjustments due to methadone have been required to the standard posttransplant drug regimen at Mount Sinai.

Transplant teams unfamiliar with MMT have been concerned about managing pain in patients already taking an opioid drug (methadone). The Koch and Banys survey found that only three programs (8%) experienced any difficulties with postoperative pain management in MMT patients.[4] Rothstein observes that, in their case series, only 1 of 5 MMT patients receiving transplant required an opioid analgesic for postoperative pain; the others were managed with standard pain medications, just as all other patients. Similarly, Liu says that pain management in their MMT patients has followed usual procedures without problems.

Methadone Accepted

Liu asserts that Mount Sinai continues to consider MMT patients for liver transplantation. As of last June (2002), there were 32 methadone-maintained patients on their waiting list, and they

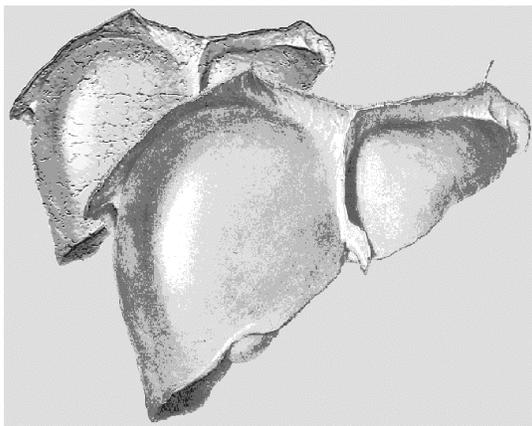
perform liver transplants in 4 to 5 such patients each year.

He further notes that, of 36 methadone-maintained liver recipients on whom they now have from 1 to 12 years of followup data, survival has been 75%, compared with typical 5-year survival of 70%. Mortality has been largely associated with recurrent HCV infection and rapid progression to cirrhosis.

Edwin Salsitz, MD, Director of Methadone Medical Maintenance (MMM) at Beth Israel Medical Center, New York, says that several of his HCV-positive patients have received liver transplants at Mount Sinai Medical Center, while others were transplanted at NYU Medical Center and one at the University of Pittsburgh.

In all, 7 of Salsitz's patients have received liver transplants and 3 were able to return to work full time. He notes that none of them encountered resistance in getting listed due to their being on methadone; however, these were long-term patients, stabilized on methadone, and with strong family and financial support.

He concedes that patients with less tenure in MMT and without such adequate support might face challenges in finding a transplant center willing to consider them. The assistance and encouragement of MMT staff can be important in overcoming any hurdles.



Better Communication Needed

To a considerable extent, there appears to be a disconnect between addiction treatment providers and the liver transplantation field. Transplant teams would benefit from a better understanding of substance dependency and the stages of addiction recovery, particularly relating to MMT. Similarly, MMT staff need to become familiar with the liver transplantation process.

Appropriate patient referrals from MMT program staff to liver transplant centers will be essential for serving the interests of patients and the respective institutions. According to Rothstein, the very small proportion of liver transplants in MMT patients at Albert Einstein was not due to any reluctance by the transplant team to consider such patients. He believes that MMT staff and referring physicians may presume that patients continuing on methadone will be automatically rejected as candidates, and he hopes to convince them otherwise in the future.

Similarly, Liu, at Mount Sinai Medical Center, expressed an interest in closer contact with patients' MMT programs. Currently, there is communication by transplant coordinators only if the referring physician is at the respective MMT clinic, which usually is not the case.

Critical Concepts

In sum, according to current evidence, methadone-maintained patients appear to be suitable candidates for liver transplantation, just as any other persons in need. MMT patients should not be expected to withdraw from methadone or reduce their dose, as this places them at high risk for illicit-drug relapse, which would disqualify them for transplant candidacy.[15,16]

Patients also should be actively participating in counseling and ongoing recovery efforts.[17] MMT patients should exhibit relatively stable psychosocial functioning and an ability to comply with their medical care, as would be expected of any patients.[18]

Additional critical concepts may be summarized:

- Considering the burden of deteriorating liver disease in large numbers of MMT patients, this population appears to be grossly underrepresented among persons eligible for and receiving liver transplants.
- Methadone does not appear to be contraindicated on the basis of harmful effects on graft function or patient survival, drug interactions, or requirements for postoperative analgesia.
- Via their active participation in an ongoing recovery program, stable MMT patients may exhibit greater adherence to treatment regimens and followup routines, and lower rates of recidivism, if any, than recovering alcoholics or formerly opioid-addicted persons not in MMT.

- A critical factor is maintaining adequate methadone serum levels both pre- and post-transplant to avert illicit-drug use.
- Long-term posttransplant outcomes in MMT patients have been as favorable as in other patient populations.

Finally, in response to the patient's plea for suggestions at the beginning of this article, the best advice might be to start looking. There are enlightened liver transplant centers that *will* consider him. Hopefully, their ranks will be increasing.

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Survey Results - Liver Disease Fates

Spring 2002; Vol. 11, No. 2

In the Fall 2001 edition of *AT Forum* (Vol. 10, No. 4) – along with the launch of the series on “Liver Disease in MMT: Treatment and Transplant” – readers were asked to comment on the fates of methadone patients seeking care for liver disease. Survey questions solicited “yes” or “no” responses to the following:

1. Do you know of patients who were denied treatment for hepatitis C (HCV) because they were on methadone?
2. Do you know of patients who were denied a liver transplant because they were on methadone?
3. Do you know of MMT patients who died because they could not get treatment or a transplant for their liver disease?

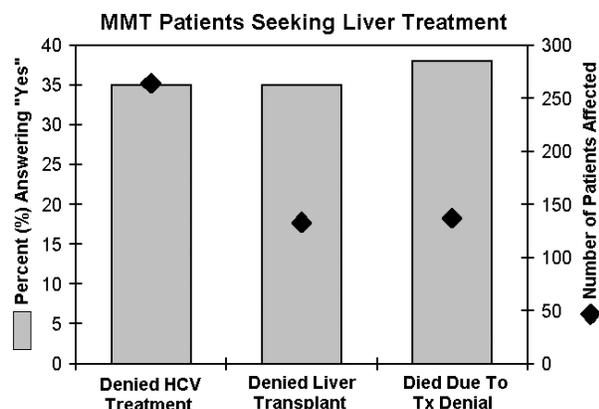
There were 150 survey responses via feedback cards and at the *AT Forum* website (www.atforum.com). The **Graph** depicts a summary of those responding “yes” to each of the statements (bars with scale on left). Between 35% and 38% of readers said they knew of patients who were denied treatment or transplant for their liver disease because of their taking methadone, and/or died as a result of such refusal.

Persons responding affirmatively to any question also were asked how many patients they knew of who were affected. Total numbers of patients mentioned are depicted on the graph with diamonds (scale on right): 264 denied treatment for HCV; 133 denied liver transplant; 137 deaths.

Tragedy Becoming Catastrophe

Even one patient being denied liver treatment or transplant simply because they are taking methadone as part of an MMT program would be a tragedy. That many patients are dying as a result of such neglect may make this a true catastrophe.

It should be noted that *AT Forum* surveys are based on informal responses, rather than systematic polls. In this case, however, it might be expected that responses grossly underestimate the actual extent of the problems.



The first article in the series observed that there is a very high prevalence of HCV among MMT patients, more than 90% in some clinics, and only about 12% receive antiviral treatment in the best of circumstances. A greater percentage of them would likely end up needing liver transplants than among HCV-positive patients in the general public. Yet, since 1988, only an estimated 180 MMT patients have had liver transplants; less than a half-percent (0.5%) of the total procedures performed during that time.

A Few Rays of Hope

As the first article in this series also described, certain MMT programs are becoming more proactive in helping their patients with hepatitis (also see the interviews in this edition). And, while nearly two-thirds of transplant centers prohibit methadone in one way or another, there are some enlightened programs around the country offering hope.

One patient responding to the survey – in MMT for 16 years and both HCV and HIV positive – wrote that he has always been treated fairly and supported by liver treatment specialists, even though they knew he was on methadone. About two years ago, he received a liver transplant at the University of Pittsburgh, which was paid for by private insurance and Medicare.

Hopefully, exceptional stories like this will become commonplace.

UPDATE ADDENDUM

New Hepatitis C Consensus Statement From NIH Panel

June 12, 2002 — A fourfold increase in persons with chronic hepatitis C (HCV) infection is projected during the next decade as a result of infection from contaminated blood and blood products (prior to routine screening starting in the early 1990s), occupational exposure, and injection drug use according to a panel convened by the National Institutes of Health (NIH). Chronic HCV is leading to significant increases in cirrhosis, end-stage liver disease, and liver cancer -- hence, it is the most common cause of liver transplants.

The independent, non-advocate, non-Federal panel issued its statement at the conclusion of a two-and-a-half-day NIH Consensus Development Conference on "Management of Hepatitis C:

2002." The meeting was convened to provide an update to a 1997 conference on the same topic.

This consensus panel broke away from its 1997 predecessors by expanding the scope of patients eligible for treatment to include those who use injected drugs, consume alcohol, suffer from comorbid conditions such as depression, or who are coinfecting with HIV. This latest guideline makes no mention of a specific drug or alcohol abstinence requirement prior to treatment, and *it also acknowledges that anti-HCV therapies have been successful in patients receiving daily methadone.*

The full text of the panel's statement is available at <<http://consensus.nih.gov>> or by calling 1-888-NIH-CONSENSUS (1-888-644-2667).

Response to Anti-HCV Therapy in MMT Patients

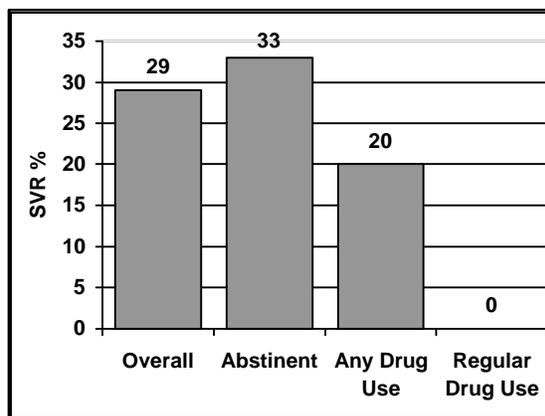
June 9, 2002 — Diana Sylvestre, MD and colleagues at the Organization to Achieve Solutions In Substance Abuse (O.A.S.I.S.-Abuse), Oakland, CA, have reported an ongoing, observational clinical trial administering standard regimens of interferon-alfa-2b plus ribavirin to HCV-positive MMT patients (See also, *AT Forum*. Part 2: Hepatitis C - A "Giant Silent Killer." 2002 [Winter];11[1]).

In an update of results for 66 cumulative patients – reported at the 64th Annual Scientific Meeting of the College on Problems of Drug Dependence; June 9, 2002; Québec City, Canada – Sylvestre et al. noted that the overall sustained viral response (SVR) rate was 29% (ITT analysis) compared with 41% in historical controls. There were preexisting psychiatric diagnoses in 62% of subjects and by the end of treatment 88% of all patients had received some form of psychiatric medication, primarily an SSRI for depression.

Twenty-four percent of patients had discontinued from the Sylvestre trial, compared with 20% in other studies; however, discontinuations were lower in MMT patients due solely to side effects, which appeared less frequent or severe than normally encountered. In more than 40% of patients the methadone dose was raised by an average of 10 mg/day to help counter side-effect symptoms.

There were trends toward higher SVR rates in the 70% of patients with 6 or more months of drug-abstinence while in MMT prior to treatment

and lower responses in 30% of subjects who used alcohol or illicit drugs during the study (heroin was used most often, although cannabis, cocaine, and methamphetamine also were implicated in some cases). In total, those who were abstinent from illicit drugs and alcohol throughout HCV treatment had a 33% SVR, compared with 20% in those who used any drugs (See **graph**). Of importance, 7 patients using illicit drugs and alcohol on a daily basis exhibited no response to anti-HCV therapy.



The 29% overall SVR in this trial was considered a favorable outcome in view of the many negative prognostic factors in this nonselect group of patients who were older, with more advanced liver disease, and had a greater prevalence of psychiatric comorbidity than more select groups of

non-MMT patients in past clinical trials. There appeared to be significant negative effects of psychiatric illness, possibly in combination with continued drug and/or alcohol abuse during and after treatment, which lowered SVR rates. Conversely, 15 subjects without preexisting psychiatric illness or any drug/alcohol use during treatment exhibited an SVR of 40%, which is equivalent to results in general population trials.

In sum, Sylvestre and colleagues found that MMT patients receiving pharmacotherapy for HCV demonstrated overall tolerability, safety, and compliance rates similar to those of historical con-

trols in the general population receiving identical therapy. This was evident despite substantial preexisting psychiatric comorbidity in a majority of the methadone-maintained patients; however, the aggressive management of psychiatric illness may help lessen its impact on treatment outcomes. At least a short period of illicit-drug abstinence in MMT prior to starting treatment for HCV was beneficial, although rare use of drugs did not appear detrimental to successful treatment outcomes. On the other hand, continued alcohol and other drug use appeared to render anti-HCV therapy unproductive.

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