

## Antiviral therapy for hepatitis C: why are so few patients being treated?

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Despite the long-term morbidity associated with hepatitis C and the availability of effective treatment, fewer than a quarter of infected individuals are treated with antiviral therapy. While this is partly related to inherent limitations of currently available medications and the underlying patient population, numerous health system barriers also exist. Fewer than half of chronic hepatitis C infections are diagnosed, relatively few are referred for treatment, and misperceptions about the disease and its treatment abound amongst patients and physicians alike. This article will discuss patient and physician factors that contribute to the undertreatment of chronic hepatitis C.

**Keywords:** interferon, ribavirin, treatment, viral hepatitis, public health

Hepatitis C is an RNA virus that is transmitted primarily via blood contact, such as intravenous drug use or blood transfusion prior to 1992. Nearly 80% of infections result in chronic hepatitis C, which is asymptomatic in most cases. However, over a period of 25–30 years approximately one-fifth of individuals will develop cirrhosis, and consequently be at high risk for liver failure and hepatocellular carcinoma.<sup>1</sup> In the USA and Europe, hepatitis C affects >1% of the population and is the leading indication for liver transplantation.<sup>2,3</sup> Although the incidence of new infections has declined, the number of deaths related to hepatitis C is projected to increase over the next 20 years due to prevalent cases with long-standing infection.<sup>4</sup>

In the last two decades there have been dramatic improvements in treatment of hepatitis C. The benefit of adding ribavirin to interferon was demonstrated in a series of studies in the late 1990s,<sup>5</sup> and then pegylated interferon was approved at the end of 2001. Combination therapy with pegylated interferon and ribavirin can now achieve sustained virological response (SVR) in 50% of patients.<sup>6</sup> Patients who achieve SVR enjoy long-term remission of disease,<sup>7</sup> with liver-related mortality rates comparable to those of the general population.<sup>8–10</sup>

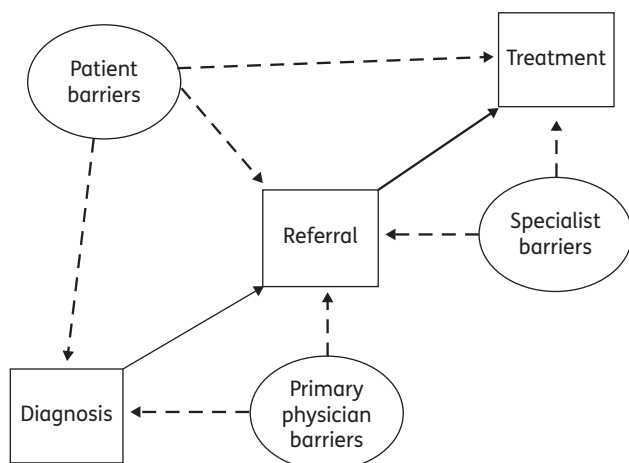
Despite the efficacy of antiviral therapy and the long-term morbidity and mortality associated with untreated hepatitis C, recent data suggest that relatively few patients are being treated. In Europe only 3.5% of individuals with hepatitis C had received antiviral therapy by the end of 2005, with treatment rates ranging from 16% in France to <1% in countries such as Poland.<sup>2</sup> In the USA only 21% of infected individuals had cumulatively received antiviral therapy by the end of 2007, and treatment rates appear to be declining.<sup>11</sup>

In order to understand why so few patients are being treated, let us examine the pathway patients follow from diagnosis to

referral to treatment, and the multiple barriers that exist along the way (Figure 1). First, fewer than half of individuals with chronic hepatitis C in many countries are even aware that they are infected.<sup>11</sup> These individuals are more likely than the general population to lack health insurance and a usual source of medical care.<sup>12</sup> Additionally, hepatitis C is usually asymptomatic and requires physicians to actively screen for the disease in patients with risk factors. This may be low priority during a busy primary care appointment—it has been estimated that provision of all recommended preventative care would consume 7.4 h of each primary doctor's day, leaving no time for other tasks.<sup>13</sup> Furthermore, physicians may not realize the value of diagnosing hepatitis C, as studies have identified misconceptions about the disease and treatment efficacy among primary care physicians.<sup>14</sup> Thus, underdiagnosis is the first and largest barrier to treatment of hepatitis C.

Once the diagnosis of hepatitis C is made, patients must then be referred to a specialist experienced with the administration of antiviral therapy. Such referrals may not always be made. In one survey of primary care physicians, 72% would not refer a patient with normal liver enzymes for treatment,<sup>14</sup> despite evidence that such patients can develop progressive disease.<sup>15</sup> An additional problem is the paucity of specialists interested in treating hepatitis C. Antiviral therapy with interferon is labour intensive and the reimbursement rates are relatively low, and many patients have to travel long distances to find an experienced specialist.<sup>16</sup>

Even among patients who see a specialist to discuss antiviral therapy, fewer than one-third receive treatment.<sup>11,17</sup> This is mostly related to the inherent limitations in currently available medications, which cannot be used in patients with decompensated cirrhosis, severe depression or cardiopulmonary disease.<sup>1,18</sup> Additionally, given the medication toxicity and



**Figure 1.** The pathway patients follow in order to be diagnosed and treated for hepatitis C prior to developing symptoms of liver failure. Numerous barriers exist along the way, including low rates of diagnosis and referral, limited access to specialists, and patient fears and misconceptions. Continuous lines indicate the pathway patients follow to treatment, while broken lines indicate barriers to treatment.

concerns about safety and adherence, most providers will not treat patients who are still active substance abusers. In addition to these inherent limitations, considerable variability exists between providers in the decision to offer treatment. For example, one study found that receipt of antiviral therapy was determined more strongly by which provider was seeing the patient than by characteristics of the patient themselves.<sup>17</sup>

As anyone who treats hepatitis C is well aware, patient preferences also strongly influence the decision to undertake antiviral therapy. While many patients are overly concerned about their disease and are willing to take almost any steps to eradicate the virus, an equal number of patients are quite resistant to being treated. Numerous patient misperceptions and cognitive biases have been documented that may contribute to this resistance. For example, many patients reason that because their disease is asymptomatic, it does not need to be treated.<sup>19</sup> Other patients express inordinate concern about side effects, incorrectly perceive that a liver biopsy is required prior to treatment, or anticipate feeling regret if they undergo treatment and do not achieve a response.<sup>20</sup> A final problem is discontinuation of treatment due to side effects, which occurs in 15% of cases even in clinical trials,<sup>1</sup> and is probably even more common in general practice. Clinical experience has demonstrated that a proactive approach to educating patients and monitoring for side effects can decrease dropout rates, especially during the first month when side effects are the most severe.

It is anticipated that the long-awaited approval of protease inhibitors for treatment of hepatitis C will occur within the next year or two. In conjunction with pegylated interferon and ribavirin, the protease inhibitor telaprevir demonstrates improved rates of SVR for patients with genotype 1 virus.<sup>21</sup> Therefore, it may be reasonable for the time being to defer therapy in selected patients. However, this gain in efficacy is offset by an increase in side effects from triple therapy. Thus, many of the barriers discussed above, such as patient resistance and paucity of providers comfortable managing these complicated regimens, will remain.

In summary, despite the long-term morbidity associated with hepatitis C and the availability of effective treatment, fewer than a quarter of infected individuals are treated with antiviral therapy. Some of the barriers to treatment are currently unavoidable and relate to the patient population and inherent limitations of currently available medications. However, an even larger role appears to be played by non-clinical factors such as access to healthcare, under-diagnosis and misperceptions by physicians and patients. A report recently released by the Institute of Medicine highlighted the failure of current public health efforts in controlling the epidemic of viral hepatitis in the USA, and this report may stimulate educational campaigns to promote awareness about the disease.<sup>22</sup> In the future, targeted screening campaigns may increase rates of diagnosis, and development of patient decision aids may overcome some barriers at the patient and primary physician level. In the meantime, those involved in caring for patients with hepatitis C should continue to educate their referring physicians and the general public about the availability and efficacy of antiviral therapy.

## Transparency declarations

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