Barriers to hepatitis C virus treatment in a Canadian HIV-hepatitis C virus coinfection tertiary care clinic

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BACKGROUND: Despite demonstrated efficacy in HIV-hepatitis C virus (HCV) coinfection, not all patients initiate, complete or achieve success with HCV antiviral therapy.

PATIENTS AND METHODS: All HIV-HCV coinfected patient consults received at The Ottawa Hospital Viral Hepatitis Clinic (Ottawa, Ontario) between June 2000 and September 2006 were identified using a clinical database. A descriptive analysis of primary and contributing factors accounting for why patients did not initiate HCV therapy, as well as the therapeutic outcomes of treated patients, was conducted.

RESULTS: One hundred two consults were received. Sixty-seven per cent of patients did not initiate HCV therapy. The key primary reasons included: HIV therapy was more urgently needed (22%), loss to follow-up (12%), patients were deemed unlikely to progress to advanced liver disease (18%) and patient refusal (12%). Many patients had secondary factors contributing to the decision not to treat, including substance abuse (23%) and psychiatric illness (14%). Overall, 59% of untreated patients (40 of 68) were eventually lost to follow-up. Thirty-three per cent of referred patients started HCV therapy. Twenty-seven of 42 courses (64%) were interrupted prematurely for reasons such as virological nonresponse (48%), psychiatric complications (10%) and physical side effects (7%). Of all treatment recipients, 12 of 42 full courses of therapy were completed and three remained on HCV medication. Overall, eight of the 102 coinfected patients studied (8%) achieved a sustained virological response.

DISCUSSION: Not all HIV-HCV coinfected patients who are deemed to be in need of HCV treatment are initiating therapy. Only a minority of patients who do receive treatment achieve success. Implementation of HIV treatment, patient retention, attention to substance abuse and mental health care should be the focus of efforts designed to increase HCV treatment uptake and success. This can be best achieved within a multidisciplinary model of health care delivery.

Key Words: *Antiviral therapy; HCV; HIV; Liver*

Des obstacles au traitement du virus de l'hépatite C dans une clinique de soins tertiaires de la co-infection du VIH et du virus de l'hépatite C

HISTORIQUE : Malgré son efficacité démontrée en cas de co-infection par le VIH et le virus de l'hépatite C (VHC), les patients n'entreprennent et ne terminent pas tous l'antivirothérapie du VHC et ils n'en obtiennent pas tous des résultats.

PATIENTS ET MÉTHODOLOGIE : Les auteurs ont repéré toutes les consultations de patients co-infectés par le VIH et le VHC ayant eu lieu à la clinique d'hépatite virale de l'Hôpital d'Ottawa (Ottawa, Ontario) entre juin 2000 et septembre 2006, au moyen d'une base de données cliniques. Ils ont procédé à une analyse descriptive des facteurs primaires et contributifs déterminant les raisons pour lesquelles des patients n'ont pas entrepris la thérapie contre le VHC, de même que les issues thérapeutiques des patients traités.

RÉSULTATS : Cent deux consultations ont eu lieu. Soixante-sept pour cent des patients n'ont pas entrepris la thérapie contre le VHC. Les principales raisons s'établissaient comme suit : la thérapie contre le VIH était plus urgente (22 %), perte au suivi (12 %), l'état des patients était réputé peu susceptible de se détériorer vers une maladie hépatique avancée (18 %) et refus des patients (12 %). De nombreux patients présentaient des facteurs secondaires contribuant à la décision de ne pas traiter, y compris l'abus de drogues ou d'alcool (23 %) et les maladies psychiatriques (14 %). Dans l'ensemble, 59 % des patients non traités (40 des 68) ont fini par être perdus au suivi. Trente-trois pour cent des patients aiguillés ont entrepris la thérapie contre le VHC. Vingt-sept de ces 42 thérapies (64 %) ont pris fin prématurément pour des raisons comme une non-réponse virologique (48 %), des complications psychiatriques (10 %) et des effets secondaires physiques (7 %). Chez tous les receveurs d'un traitement, 12 des 42 thérapies ont été menées jusqu'au bout, et trois patients ont continué de prendre des médicaments contre le VHC. En tout, huit des 102 patients co-infectés à l'étude (8 %) ont obtenu une réponse virologique soutenue.

DISCUSSION : Les patients co-infectés par le VIH et le VHC réputés avoir besoin d'un traitement contre le VHC n'entreprennent pas tous une thérapie. Seule une minorité des patients traités ont des résultats probants. L'implantation du traitement contre le VIH, la rétention des patients, l'attention aux soins de l'abus de drogues et d'alcool et des problèmes de santé mentale doivent être au centre des efforts visant à accroître la mise en œuvre et la réussite du traitement contre le VHC. On y parviendra mieux au sein d'un modèle multidisciplinaire de prestation des soins.

As a result of common risk factors for exposure, HIV and the hepatitis C virus (HCV) are often found concurrently. Approximately 20% of HIV seropositive Canadians are HCV coinfected (1-3). Liver disease has emerged as a major cause of morbidity and mortality in HIV-HCV coinfected patients. HIV negatively impacts HCV-induced liver disease, resulting in accelerated progression to cirrhosis, liver failure and liver-specific death (4-8).

Although the likelihood of achieving a sustained virological response (SVR) is diminished in patients with HIV-HCV coinfection (9,10), successful clearance of chronic HCV infection with antiviral therapy reduces liver fibrosis and inflammation, which presumably prevents cirrhosis, liver failure and liver-specific death. The risk of antiretroviral-related hepatotoxicity may also be reduced (11). Despite these potential benefits, many patients do not initiate or

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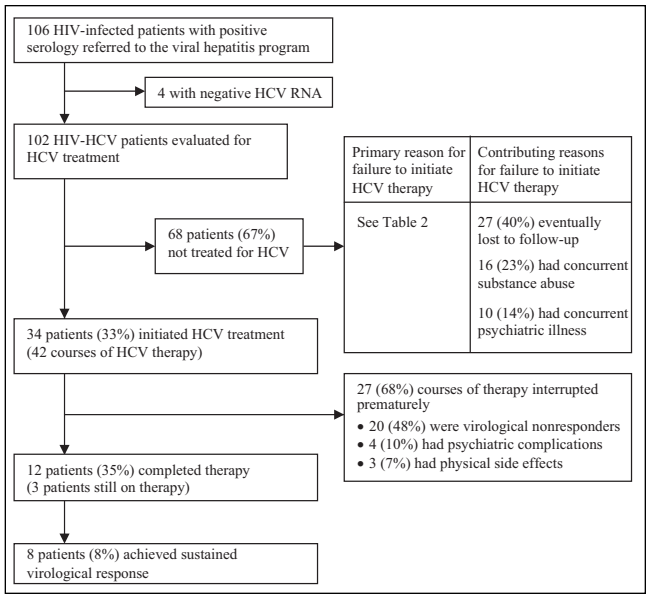

Figure 1) *Flow chart describing the evaluation of 106 HIV-hepatitis C virus (HCV) coinfected patients who were seen at The Ottawa General Hospital Viral Hepatitis Clinic (Ottawa, Ontario)*

complete HCV antiviral therapy and, consequently, do not clear their HCV infection. In the present paper, we describe medical, social and psychological reasons why HIV-HCV coinfected patients are not initiating HCV antiviral therapy despite their referral to a Canadian tertiary care centre dedicated to HCV care provision.

PATIENTS AND METHODS

A retrospective review was conducted of all HIV-HCV coinfected patients referred to The Ottawa Hospital Viral Hepatitis Clinic (Ottawa, Ontario) between June 2000 and September 2006. The program offers clinical care by infectious diseases specialists and nurses who are knowledgeable in the management of HIV and HCV. Hepatology and psychiatric assessment are available by referral. Access to social work and psychologists is very limited. Patients were identified using a computerized clinical database (SPSS Version 13.0, SPSS Inc, USA). A supplemental chart review was performed to gather information on patient characteristics, attendance records, baseline HIV RNA level and CD4 count, and antiretroviral use, as well as to identify the primary and contributing factors responsible for patient failure to initiate HCV antiviral treatment. The collection and analysis of clinical data from consenting patients managed at The Ottawa Hospital Viral Hepatitis Clinic were reviewed and approved by The Ottawa Hospital Research Ethics Board. Informed consent was obtained for participation in the database at the patient's first visit to the clinic. Participation rates exceed 99%.

A descriptive analysis was performed to tabulate the primary and contributing factors accounting for why patients did not initiate HCV therapy. Those who did commence therapy were analyzed for their therapeutic outcomes.

RESULTS

One hundred six consultations for HIV-HCV coinfection assessment were seen at The Ottawa General Hospital Viral Hepatitis Clinic between June 2000 and September 2006.

TABLE 1
Characteristics of 102 HIV-hepatitis C virus (HCV) coinfected patients on their first visit to The Ottawa General Hospital Viral Hepatitis Clinic (Ottawa, Ontario)

Characteristic	Nontreated HCV patients (n=68)	Treated HCV patients (n=34)
Male, n (%)	60 (88)	29 (85)
Age, years, mean ± SD	42±7	43±7
Caucasians*, n (%)	66 (97)	31 (91)
HBsAg positive, n (%)	3 (4)	1 (3)
History of injection drug use, n (%)	43/58† (74)	21 (62)
History of excessive alcohol use‡, n (%)	31/53† (58)	22 (65)
HAART use at initial assessment, n (%)	35 (51)	25 (74)
CD4 count, cells/μL, mean ± SD	404±260	543±284
HIV RNA, copies/mL, median (IQR)	1458 (49 to 48,400)	<50 (49 to 3709)
Log_{10} HCV RNA, copies/mL, mean ± SD	$1.65\times10^6\pm1.83\times10^6$ (n=56)†	$0.97\times10^6\pm0.80\times10^6$ (n=31)†
Genotype, n (%)		
1	45 (66)	23 (68)
2	1 (1)	3 (9)
3	16 (24)	5 (15)
4	1 (1)	3 (9)
Genotype missing	5 (8)	0 (0)
ALT, U/mL, mean ± SD	78±73 (n=63)†	98±32 (n=74)†
Advanced fibrosis stage§, n (%)	10/27 (37)	10/22 (45)

**Non-Caucasians are African Canadians; †Not all patients are included because of missing data; ‡Defined as greater than 50 g/day; §Defined as Stage 3 or 4 by the METAVIR scoring system. ALT Alanine aminotransferase; HAART Highly active antiretroviral therapy; HBsAg Hepatitis B surface antigen; IQR Interquartile range*

Four patients were HCV antibody-positive but RNA-negative, and as such, were excluded from the analysis. The remaining 102 HIV-HCV coinfected patients were evaluated in detail (Figure 1).

The cohort was predominantly male (87%) and Caucasian (95%) (Table 1). The mean age was 43 years. Seventy per cent of referred patients reported a history of injection drug use, 41% had a history of tattooing and 61% reported a history of excessive alcohol consumption. Baseline characteristics were similar between treated and untreated groups for most key parameters. Treated HCV patients did have better control of their HIV disease, with greater HIV RNA suppression (HIV RNA level below 50 copies/mL) and higher mean CD4 cell count. They also had lower rates of injection drug use and incarceration.

Sixty-eight patients (67%) did not initiate HCV therapy. The key primary reasons for not initiating HCV therapy are reported in Figure 1 and Table 2. HIV therapy was deemed to be more urgently required than HCV treatment in 22% of referrals. Nineteen per cent never came to the clinic or were lost to follow-up before completion of their initial workup. Eighteen per cent were deemed unlikely to progress to advanced liver disease based on their clinical evaluation, liver studies and estimated rate of fibrosis progression calculated from liver biopsy results. These patients were advised not to

commence HCV treatment but were asked to follow up in the clinic every six to 12 months. Twelve per cent of patients (n=8) declined treatment for HCV despite recommendations to the contrary. Most cited treatment side effect concerns. Therapy was not initiated in 14% of patients as a consequence of substance abuse issues, and in 7% because of psychiatric illnesses including needle phobia, depression, bipolar condition and anxiety. Other concurrent factors that were not identified as the key reason for not starting HCV therapy, but nevertheless contributed to this decision, were identified. These factors related predominantly to substance abuse (23%) and psychiatric illness (14%) (Figure 1).

A portion of patients who did not initiate therapy (27 of 68 [40%]), but who were advised to be followed serially over the long term, were also eventually lost to follow-up. Overall, 59% of untreated patients (40 of 68) were lost to follow-up during this period of evaluation.

Five of the coinfected patients who did not receive treatment for their HCV (7%) died. Causes of death included untreated HCV due to concomitant untreated psychiatric disorder and subsequent liver failure, death in the hospital with an admission diagnosis of alcoholic hepatitis and untreated HIV, septic shock in a patient with controlled HIV (CD4 level 323 cells/μL, viral load less than 50 copies/mL) and unknown (n=2). The outcomes of untreated patients lost to follow-up are not known.

Thirty-four of the original 102 HIV-HCV coinfected patients (33%) received 42 courses of HCV therapy (Table 1). Treatment initiation years were as follows: 2000 (n=2), 2001 (n=6), 2002 (n=5), 2003 (n=8), 2004 (n=6), 2005 (n=3) and 2006 (n=4). Regimens consisted of ribavirin plus interferon-alpha-2B (n=14), pegylated interferon-alpha-2B (n=23) or pegylated interferon-alpha-2A (n=4). Twenty-seven courses of therapy (64%) were interrupted prematurely for reasons including virological nonresponse, defined as failure to achieve a $2\log_{10}$ reduction at week 12 or detectable HCV viremia at week 24 (n=20); psychiatrical complications (n=4); and physical side effects (n=3). Of the 34 patients who received therapy, 12 completed full courses and three were being treated at the time of analysis. Eight of these 34 patients achieved a SVR, which represents 24% of those starting therapy and only 8% of the original 102 referrals. Three of 24 patients (13%) with genotype 1/4 and five of eight patients (63%) with genotype 2/3 achieved a SVR.

TABLE 2
Primary reasons why patients did not initiate hepatitis C virus (HCV) therapy (n=68)

Reason	Patients, n (%)
Medical	
HIV identified as priority for treatment	15 (22)
HCV therapy not recommended based on minimal liver disease	12 (18)
Medical contraindication	1 (1)
End-stage liver disease precluding HCV therapy	1 (1)
Psychiatric	
Psychiatric comorbidity	4 (6)
Needle phobia precluding HCV therapy	1 (1)
Patient-related	
HCV therapy recommended but patient declined	8 (12)
Lost to follow-up	8 (12)
Referred to viral hepatitis clinic but did not attend scheduled appointment	5 (7)
Predicted poor adherence	1 (1)
Social circumstances – incarceration	1 (1)
Social circumstances – poor housing	1 (1)
Substance abuse	
Alcohol abuse	7 (10)
Illicit drug use	3 (4)

DISCUSSION

Despite effective HCV treatment and access to a dedicated viral hepatitis clinic based within a Canadian tertiary care centre, two-thirds of referred HCV-HIV coinfected patients did not initiate therapy. Only a few patients were ineligible for treatment based on nonmodifiable criteria, including comorbid medical contraindications, end-stage liver disease and advanced HIV disease. Many patients were identified as having multiple concurrent barriers to treatment, including substance abuse, psychiatric illness, anxiety related to workup or treatment, and poor social circumstances. These are challenging obstacles but they can be overcome.

Several studies have demonstrated comparably low rates of treatment uptake in the setting of HIV-HCV coinfection (12-17). The barriers to treatment were remarkably similar. In an urban American cohort (18), two-thirds of HIV-HCV patients were ineligible for HCV treatment by virtue of nonadherence to medical visits (23%), active psychiatric disease (21%), ongoing drug or alcohol abuse (23%), decompensated liver disease (12%), advanced HIV disease (13%) and other medical comorbidities (8%). In another American study (19), only 15% of eligible coinfected patients initiated HCV therapy. Reasons included noncompliance (40%), alcohol and injection drug use (15%), decompensated cirrhosis (13%), psychiatric diseases (8%) and comorbid diseases (24%). In a prospective American-based analysis (20), only 12% of patients were free of contraindications to HCV treatment. Alcohol use was the most frequently identified contraindication, but most patients had multiple barriers, including depressive symptoms, injection drug use, poorly controlled HIV and decompensated liver disease. Canadian physicians based at the Northern Alberta HIV Program at the University of Alberta (Edmonton, Alberta) deemed 85% of their coinfected patients to be ineligible for HCV treatment (21). Contraindications included nonadherence or nonattendance (50%), unstable or chaotic lifestyle (46%), active injection drug use (26%), psychiatric comorbidity (18%), low CD4 counts (15%), minimal liver disease based on enzymes (15%) or biopsy (6%), and advanced liver disease (3%).

Our analysis, and that of others, demonstrates that coinfection treatment requires expertise in the management of mental illness, addictions, poverty and patient retention. Like most Canadian HCV clinics, our program has very limited access to these services and is, in our opinion, a major reason why so few of our HIV-HCV coinfected patients ended up on HCV treatment. To achieve success with currently available therapies, a multidisciplinary clinical care model is well suited to enable the coordination of primary health care with specialty HIV and HCV care, alongside integrated support from addiction

medicine, mental health and social work. The holistic focus should be on providing ongoing support to engage and retain coinfected patients with complex social and medical health care needs. Multidisciplinary models for the treatment of HIV have been proven to be successful (22). These models should be applied to HCV and coinfected patients.

Several studies have shown the potential effectiveness of a multidisciplinary approach to HIV-HCV care (23,24). In one study (23), HCV care was transferred from a liver clinic to a HIV primary care program. Key features of this program included the establishment of a coinfection clinic within the HIV clinic, assignment of a full-time nurse to monitor and support patients, and creation of a coinfection patient peer group. As a result, appointment attendance improved from less than 10% of referred patients to more than 70%. At another American urban centre, a coinfection clinic – consisting of a physician who specialized in HIV and HCV, a hepatologist, a coinfection nurse, a clinical coordinator, psychiatric care, counselling, coinfection group therapy, addiction treatment and home care – was established. Patients received directly administered interferon in conjunction with concurrent mental health and addiction care. In this case, treatment outcomes were improved. Adherence to weekly interferon dosing was nearly complete, and no patient interrupted treatment as a consequence of psychiatrical complications, drug use or relapse (25).

One important component of a comprehensive care program is education. In our experience, many of the patients who decline treatment do so as a consequence of misinformation related to HCV disease and/or treatment. A previous HCV knowledge questionnaire at our site (26) found that 52% of patients rated knowledge of HCV as poor at their first visit. These patients self-identified HCV education and psychological counselling as important needs. After nearly one year of interactions with our HCV clinic team, these patients indicated that they felt better informed, and were more satisfied with their care and more actively involved in their treatment (26). Another study conducted at The Ottawa Hospital (27) found that patient readiness for successfully starting antiretroviral medications for HIV can be enhanced by providing a psychoeducational readiness adherence intervention. HIV treatment, similar to HCV treatment, can be difficult, and a similar model of pretreatment intervention could be applied to patients with HCV.

HIV care is centralized in the Ottawa region, with the vast majority of HIV and HIV-HCV coinfected patients followed entirely or at least in part by the immunodeficiency clinic based at The Ottawa Hospital. As such, we believe that the approximately 350 HIV-HCVcoinfected patients followed at the Immunodeficiency Clinic represent the large majority of patients in the region. We acknowledge that the proportion of treatment-eligible, coinfected patients in our region may have been overestimated as a consequence of referral bias, both from our own immunodeficiency clinic and the small number of HIV-HCV coinfected patients followed elsewhere. This may explain why, in our clinic, 33% of patients started therapy, which is higher than the rates reported at other sites (18-21). Socioeconomic status impacts treatment uptake and outcomes. However, this information was not available for analysis. Of note, economic factors are not a major barrier to obtaining HCV medication in Canada, because economically disadvantaged patients are eligible for a drug benefit card that covers this specific expense.

Despite the concerns described above, our study demonstrated multiple but consistent barriers to HCV treatment in a Canadian HIV-HCV coinfected population. Our current approach to HCV care is fractured. Mounting evidence suggests that a multidisciplinary model of care could address the social and psychiatric issues frequently encountered in this population, reduce the loss of patients to follow-up, effectively educate and prepare patients, and treat a larger proportion of the HIV-HCV coinfected population.

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