The demand for definitive management of end-stage organ disease in HIV-infected Canadians is growing. Until recently, despite international evidence of good clinical outcomes, HIV-infected Canadians with end-stage liver disease were ineligible for transplantation, except in British Columbia (BC), where the liver transplant program of BC Transplant has accepted these patients for referral, assessment, listing and provision of liver allograft. There is a need to evaluate the experience in BC to determine the issues surrounding liver transplantation in HIV-infected patients.

**METHODS:** The present study was a chart review of 28 HIV-infected patients who were referred to BC Transplant for liver transplantation between 2004 and 2013. Data regarding HIV and liver disease status, initial transplant assessment and clinical outcomes were collected.

**RESULTS:** Most patients were BC residents and were assessed by the multidisciplinary team at the BC clinic. The majority had undetectable HIV viral loads, were receiving antiretroviral treatments and were infected with hepatitis C virus (n=16). The most common comorbidities were anxiety and mood disorders (n=4), and hemophilia (n=4). Of the patients eligible for transplantation, four were transplanted for autoimmune hepatitis (5.67 years post-transplant), nonalcoholic steatohepatitis (2.33 years), hepatitis C virus (2.25 years) and hepatitis B-delta virus coinfection (recent transplant). One patient died from acute renal failure while waiting for transplantation. Ten patients died during preassessment and 10 were unsuitable transplant candidates. The most common reason for unsuitability was stable disease not requiring transplantation (n=4).

**CONCLUSIONS:** To date, interdisciplinary care and careful selection of patients have resulted in successful outcomes including the longest living HIV-infected post-liver transplant recipient in Canada.

**Key Words:** Hepatitis; HIV; Liver; Transplant

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Le VIH et la transplantation hépatique : l’expérience britanno-colombienne de 2004 à 2013

Jusqu’à récemment, malgré des données internationales faisant foi de résultats cliniques positifs, les Canadiens atteints d’une maladie hépatique terminale infectés par le VIH n’étaient pas admissibles à une transplantation, sauf en Colombie-Britannique (C.-B.), où le programme de transplantations de BC Transplant les accepte en vue d’un aiguillage, d’une évaluation, de l’inscription sur la liste d’attente et de l’exécution d’une allogreffe du foie. L’évaluation de l’expérience de la C.-B. s’impose pour déterminer les enjeux entourant la transplantation hépatique chez les patients infectés par le VIH.

**MÉTHODOLOGIE :** Les chercheurs ont procédé à l’étude des dossiers des 28 patients infectés par le VIH qui ont été orientés vers BC Transplant pour subir une transplantation hépatique entre 2004 et 2013. Ils ont colligé les données sur l’état du VIH et de la maladie hépatique, l’évaluation initiale de la transplantation et les résultats cliniques.

**RÉSULTATS :** La plupart des patients étaient des habitants de la C.-B. qui avaient été évalués par l’équipe multidisciplinaire de la clinique de C.-B. La majorité présentant des charges virales indétectables du VIH, prenaient des antirétroviraux et étaient infectés par le virus de l’hépatite C (n=16). Les comorbidités les plus courantes étaient l’anxiété et les troubles des humeurs (n=4), ainsi que l’hémophilie (n=4). Parmi les patients admissibles à la transplantation, quatre ont subi une transplantation consécutive à une hépatite auto-immune (5,67 ans après la transplantation), à une stéatose hépatique non alcoolique (2,33 ans), à un virus de l’hépatite C (2,25 ans) et à une co-infection par l’hépatite B et le virus delta (transplantation récente). Un patient est décédé d’une insuffisance rénale aigüe alors qu’il était en attente de transplantation. Dix sont décédés pendant la pré-evaluation et dix n’étaient pas des candidats adéquats pour la transplantation. La principale raison de ne pas être un candidat adéquat était une maladie stable ne nécessitant pas de transplantation (n=4).

**CONCLUSIONS :** Jusqu’à présent, les soins interdisciplinaires et une sélection attentive des patients permettent d’obtenir des résultats positifs, y compris la présence au Canada du greffé hépatique infecté par le VIH ayant vécu le plus longtemps depuis sa transplantation.

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The life expectancy of an individual infected with HIV in the modern antiretroviral therapy (ART) era is approaching parity with the general population in North America, and HIV is becoming increasingly recognized as a chronic illness in developed countries. Concerns surrounding opportunistic infections due to immunocompromise and reduced survival have been attenuated (1). It was once believed that further immunosuppression of HIV-positive patients would further exacerbate opportunistic infection. However, it has been demonstrated that similar levels of immunosuppression are required for both HIV-infected and HIV-noninfected recipients to prevent graft rejection (2,3). In addition, the rates of surgical complications are similar to what has been observed in the non-HIV setting in carefully selected HIV-infected liver and kidney transplant recipients (4).

Nevertheless, the management of HIV-infected transplant recipients is complex because there are numerous pharmacokinetic interactions between certain antiretroviral agents and immunosuppressants...
The reasons for referral for transplantation were reviewed, in addition to the status of the patients and their clinical outcomes. The present study was approved by the University of British Columbia Clinical Research Ethics Board (Vancouver, BC).

The Liver Transplant Program’s policy with regard to placement of HIV-infected patients on the transplant waiting list after successful assessment include the following:

1. All candidates must meet the general criteria for transplantation that applies to all non-HIV-infected candidates (eg, no active infection, no active malignancy, abstinence from substance abuse, etc.).
2. Candidates should be on ART supervised by an HIV specialist.
3. Candidates must be free from opportunistic infection.
4. The HIV viral load should be undetectable.
5. Although there is no absolute threshold CD4 count, the minimum accepted CD4 count is approximately 150 cells/mm³.

Patients who did not meet these criteria were assessed on an individual basis.

RESULTS

Demographics
Since 2004, there have been 28 HIV-infected patients referred for liver transplant assessment. The majority (23 of 28 [82%]) of these patients were men and most were assessed as outpatients of the pre-assessment clinic, with a small minority referred to the transplant program as inpatients (including hospital to hospital transfer for assessment). The mean age of these patients was 47 years and the mean follow-up time was 4.1 months (Table 1). The majority of these patients were BC residents; some were from other provinces and one was from the United States.

All patients had chronic liver disease and there were no patients with acute liver failure assessed. One patient in an out-of-province hospital was referred on an urgent basis to the Liver Transplant Program with acute drug hepatotoxicity secondary to highly active ART (HAART) medications. The Program accepted the patient in transfer for the purposes of expedited transplant assessment but the patient died en route to BC. There have been no other referrals of HIV-infected patients with acute liver failure. The majority of assessed patients were infected with HCV. Five patients were infected with HBV and seven patients had nonviral causes of liver failure. Of the non-liver and non-HIV-related medical comorbidities, the majority of these patients also had hemophilia, anxiety and depression (Table 2).

Five patients were activated for transplantation and four were transplanted. One patient had autoimmune hepatitis, one had nonalcoholic hepatosteatosis, one had hepatitis C, one had HBV and hepatitis delta virus coinfection, and one died waiting (Table 3). One listed patient died from acute renal failure before transplantation. This patient was from out of province and referred to our centre specifically because of HIV infection. The most common reason for transplant unsuitability was stable liver disease not requiring transplantation (n=4). The patients had undetectable HIV viral loads and were on HAART at the time of transplantation. Currently, three patients with HCV are being assessed to determine whether they are suitable transplant candidates.

Description of transplant recipients
Patient 1 was transplanted at 59 years of age for autoimmune hepatitis. This patient is now six years, four months post-transplant. This patient’s HIV infection is well controlled on abacavir, lamivudine and nelfinavir. His immunosuppression induction consisted of low-dose tacrolimus starting at 1 mg twice a day.
The patient is nine months post-transplant. The immediate post-transplant complications included postoperative bleeding, acute renal dysfunction and delayed surgical biliary anastomosis. Pretransplant, the patient has not experienced any rejection episodes; however, he has experienced decreasing ALT and aspartate aminotransferase (AST) levels, with an increased serum bilirubin level but no other evidence of decompensation. At two years, three months post-transplant, the patient is stable as an outpatient. His hepatitis B surface antigen and hepatitis D nucleic acid tests have remained negative (Table 3).


tacrolimus (ie, 0.5 mg every third day), mycophenolate mofetil and tapered corticosteroids because pharmacokinetic interactions with the HAART medications occurred. This patient sustained acute renal injury while on tacrolimus; however, renal function has recovered and his graft is now receiving mycophenolate mofetil monotherapy. This patient has not experienced any rejection episodes; however, he has required regular endoscopic retrograde cholangiopancreatography to manage and drain biliary sludge due to recurrent biliary anastomotic stricture. As a result, he has a persistent increase in hepatobiliary liver biochemistry (ie, alkaline phosphatase, gammaglutamyltransferase). A recent liver biopsy was unremarkable (Table 3).

Patient 2 was transplanted at 55 years of age for nonalcoholic steatohepatitis (NASH). This patient is three years post-transplant. This patient’s HIV is controlled with abacavir/lamivudine (Kivexa, ViiV Healthcare, Canada) and raltegravir, and because there were no drug interactions, the standard induction tacrolimus, mycophenolate mofetil and tapered corticosteroid dosing was used. This patient also has not experienced any graft rejection, but developed persistent increases in his serum alanine aminotransferase (ALT) level, which was previously normal (ie, ALT 120 U/L to 150 U/L). This was initially attributed to recurrent NASH at one year, four months post-transplant. He was subsequently discovered to have acquired acute HCV genotype 1b infection that is now chronic. Recent elastography (Fibroscan, Echosens, France) revealed only mild fibrosis (ie, Metavir score F1, where F4 is cirrhosis).

Patient 3 was transplanted at 49 years of age for HCV coinfection and is two years, six months post-transplant. This patient’s HIV infection is controlled with Kivexa and raltegravir, and also received standard induction dosing with tacrolimus, mycophenolate mofetil and tapered corticosteroids. At three months post-transplant, it was demonstrated biochemically and with a liver biopsy that there was evidence of graft hepatitis and Metavir stage 2 fibrosis (ie, F2). Two years later, this patient has experienced decreasing ALT and aspartate aminotransferase (AST) levels, with an increased serum bilirubin level but no other evidence of decompensation. At two years, three months post-transplant, the patient suddenly developed ascites indicative of cirrhotic decompensation. The patient’s ascites is being managed with diuretics with the hope that he will be suitable for a non-interferon-based antiviral regimen in the future (Table 3).

The final transplanted patient is 50 years of age and has HBV and hepatitis delta virus coinfection, and hepatocellular carcinoma. This patient is nine months post-transplant. The immediate post-transplant complications included postoperative bleeding, acute renal dysfunction and delayed surgical biliary anastomosis. Posttransplant, the patient’s HIV antiviral agents included tenofovir DF/emtricitabine and raltegravir. His HBV viral load was undetectable and locoregional therapy of his hepatocellular carcinoma included transarterial chemoembolization. Post-transplant, he has received hepatitis immunoglobulin in addition to tenofovir. Despite a prolonged hospitalization for convalescence and physical rehabilitation, the patient is stable as an outpatient. His hepatitis B surface antigen and hepatitis D nucleic acid tests have remained negative (Table 3).

Overall, the post-transplant quality of life in these transplant recipients has been excellent, although the recipient with pretransplant HCV infection has developed ascites more than two years post-transplant.

DISCUSSION

Nearly a decade after the establishment of an HIV liver transplant program in BC, we demonstrated that successful transplantation in HIV-infected and HIV-HCV coinfected patients is possible. The success of these candidates is due to a multidisciplinary team that includes a transplant surgical team, transplant medicine team, HIV specialty team and psychosocial support. These patients were selected for transplantation based on their failing liver disease. There is absolutely no bias against the HIV-infected individual; in fact, we have been their advocates. In the first year of the program, and in the time leading up to the establishment of the program, there was uncertainty as to what subgroup of HIV-infected patients would be suitable for transplantation. Within a short time, however, the attitude of the liver transplant program became one of advocacy. With the realization that patients outside of BC did not have any option for transplantation within Canada, it was decided that no referred patient with HIV would be declined without assessment, both inside BC and outside of the province.

Information about death during preassessment is often not accurate because if a patient dies during the preassessment, the liver transplant program is not informed immediately by the community physicians and hospitals. In general, death during the assessment is often a reflection of an untimely late referral because the patient should have been referred earlier, or is a reflection of a patient’s nonadherence to clinic appointments; however, it is not the aim of the present article to criticize the referring physician or the patient.

We note that our three long-term transplant recipients are the longest-surviving HIV-infected transplant recipients in Canada and were the second, third and fourth HIV-infected patients to receive liver transplants in this country. To date, three HIV-monoinfected recipients have experienced rejection-free survival. The HIV-HCV coinfected patient has experienced graft hepatitis from HCV

### TABLE 2

| Background profiles of all patients referred to clinic (n=28) | Non-HIV or liver-related medical comorbidities |
|------------------------------------------------------------|------------------------------------------------|
| Liver disease and etiology | Anxiety/depression (n=4) |
| Chronic hepatitis B (n=5) | | |
| Chronic hepatitis C (n=16) | Hemophilia (n=4) |
| Other causes (n=7) | Hypertension (n=2) |
| Cirrhosis secondary to ART | Epilepsy (n=2) |
| Autoimmune | Gout (n=2) |
| Chronic active hepatitis | Endocarditis (n=2) |
| Cryptogenic cirrhosis | Benign prostatic hypertrophy (n=2) |
| Alcoholic cirrhosis | | |
| Liver failure NYD | | |
| Nonalcoholic steatohepatitis | | |
| Sclerosing cholangitis | | |

### TABLE 3

| Outcomes of patients referred and assessed in clinic (n=23) | n |
|----------------------------------------------------------|---|
| Deemed unsuitable | 8 |
| Patient recovered | 1 |
| Medical reasons | 1 |
| Lack of symptoms | 1 |
| Insufficient CD4 count | 3 |
| Lost to follow-up | 2 |
| Died in preassessment stage | 10 |
| Liver failure | 5 |
| Multisystem organ failure | 2 |
| Pneumonia | 1 |
| Infection | 1 |
| Unknown cause | 1 |
| Declined transplant | 1 |
| Activated for transplant | 5 |
| Transplanted* | 4 |
| Autoimmune hepatitis | 1 |
| Nonalcoholic hepatoserositis | 1 |
| Hepatitis C | 1 |
| Hepatitis B and D, and hepatocellular carcinoma | 1 |
| Died waiting | 1 |

*No graft loss or patient death to date (follow-up = 8 months to >4 years)
reasmultinomaximumvemodynamic].

Therefore, we do not see any reason to restrict the liver transplant process to only HIV-infected individuals without HCV coinfection. We note that our HIV-HBC-HCV tri-infected patient is very stable nine months post-transplant with appropriate anti-HBV prophylaxis. It should be noted that before 1996, HBV was a contraindication in Canada for transplant; currently, however, HBV is considered to be a prime indication for transplantation.

In the time period leading up to the decision to offer liver transplantation to HIV-infected patients, there was a great deal of concern, both within and outside of the transplant program, of the risk to operating room personnel from viral transmission of HIV during an occupational injury such as a needlestick accident. Viral transmission during surgery poses a major concern among health care providers. The risk for transmission of HIV is 0.3% (95% CI 0.2% to 0.5%) and is lower than the risk for transmission of HCV (1.8%; range 0% to 7%) (14,15). In the setting of HIV, as in all health care practices, universal precautions should be practiced routinely; after the first liver transplant surgery was performed using standard precautions, the concerns regarding intraoperative viral transmission dissipated as the very minimal threat of inadvertent viral transmission became apparent.

CONCLUSION
The life-span of an HIV-infected individual receiving HAART is now near that of their noninfected counterparts (15). HIV is recognized as a chronic disease controlled with HAART (16). The demand for liver transplantation as definitive and curative for ESLD will only increase. Despite increasing in public awareness, developing living-related-donor programs and exploring other potential donors, there continues to be an organ shortage. Until better treatments for ESLD are developed and implemented, both in the HIV patient population and the non-HIV patient population, the demand for liver transplant for definitive management of ESLD will only increase. Although our single-centre experience in Canada is noteworthy, we acknowledge that any single-centre experience is limited and we are hopeful that a Canadian national database will be established as transplantation of HIV-infected patients becomes more common.

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