

## Barriers preventing liver transplantation in Canadians with HIV infection – Perceptions of HIV specialists

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Liver transplantation is a life-saving procedure with demonstrated utility. There are accumulating data indicating that this procedure is helpful in HIV-infected patients as well. Liver transplantation is currently largely unavailable to those living with HIV in Canada. Understanding the obstacles to this procedure is the first step to increasing access. Between August 2005 and November 2005, HIV physicians, one from each Canadian HIV Trials Network site, were asked to complete a quantitative questionnaire on adult liver transplant access and need. Forty-six per cent (16 of 35) of sites responded. A median 20% of the nearly 12,700 HIV patients followed at these sites had concurrent liver disease (20% caused by hepatitis C virus, 5% caused by hepatitis B virus and 5% were alcohol-related). On average, two patients per site were thought to be appropriate candidates for liver transplant evaluation. Eighty per cent of respondents anticipated increased need for liver transplantation over the next five years. Organ supply was universally identified as the chief obstacle to transplantation in patients with HIV. Other key issues included risk of hepatitis C virus reinfection and transplant surgical team willingness. Based on these data, it is believed that these issues should be the focus of efforts designed to increase access to transplantation in Canadians with end-stage liver disease and concurrent HIV.

**Key Words:** Alcohol; HBV; HCV; HIV; Liver; Transplantation

Liver transplantation is a life-saving procedure with demonstrated utility (1-3). Advances in immunosuppressants and in the dosing of these medications have reduced the frequency of organ rejection (4,5). In the case of hepatitis B virus (HBV)-indicated transplantation, post-transplant morbidity and mortality have been reduced through the use of oral antiviral therapy (6). Antiviral treatment for hepatitis C virus (HCV) is available; however, because of drug toxicity and poor efficacy, HCV-induced post-transplant injury remains a serious complication compromising successful outcomes (7-10). Initiatives to increase cadaveric organ donation (eg, the Government of Ontario's Trillium Gift of Life Network) and programs evaluating living liver donation partially address insufficient organ supply to meet an ever increasing demand

### Obstacles à la transplantation du foie chez les porteurs du VIH, au Canada : perception des spécialistes du traitement de l'infection à VIH

La transplantation du foie est une intervention salvatrice qui a déjà fait ses preuves, et de plus en plus de données montrent que l'intervention est également utile chez les personnes porteuses du VIH. Celles-ci n'ont pratiquement pas accès à la transplantation du foie à l'heure actuelle, au Canada, et une meilleure compréhension des obstacles est la première étape à franchir pour en faciliter l'accès. Entre août 2005 et novembre 2005, on a demandé à des spécialistes du traitement de l'infection à VIH, soit à un médecin dans chacun des centres du Réseau canadien pour les essais VIH, de remplir un questionnaire quantitatif sur les besoins en matière de greffes du foie chez l'adulte et sur l'accès à l'opération. Quarante-six pour cent (16 sur 35) des centres ont répondu. Une médiane de 20 % des patients porteurs du VIH (presque 12 700), suivis dans ces centres étaient atteints d'une autre maladie du foie (20 % : hépatite C; 5 % : hépatite B; 5 % : maladie liée à l'alcool). Deux patients par centre, en moyenne, étaient considérés comme bons candidats à une évaluation en vue d'une transplantation du foie. Quarante-vingts pour cent des répondants prévoyaient une augmentation de la demande de greffes hépatiques au cours des cinq prochaines années. Le principal obstacle à la transplantation du foie chez les personnes porteuses du VIH, indiqué par tous les répondants, était le manque d'organes. Parmi les autres grands problèmes relevés figuraient le risque de réinfection par le virus de l'hépatite C et le manque de volonté de l'équipe chirurgicale. Aussi croyons-nous que ces obstacles devraient faire l'objet d'efforts visant à accroître l'accès à la transplantation du foie chez les porteurs du VIH, rendus à la phase terminale de la maladie du foie, au Canada.

(11-13). Nevertheless, insufficient organ supply remains a major obstacle to obtaining liver transplantation in Canada (14).

Since the introduction of combination antiretroviral therapy, the effectiveness of liver transplantation in HIV patients has been demonstrated (2,3,15-17). Despite this, liver transplantation is currently largely unavailable to Canadians living with HIV. There are opportunities for HIV-HCV coinfecting patients to be referred to transplant centres based in the United States, but only a handful of Canadian HIV patients have received transplants by this route. The aim of the present survey was to better understand why access to this procedure does not meet the perceived need in HIV-infected patients. To address the question of need, Canadian HIV physicians were asked to estimate the current burden of liver

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**TABLE 1**  
**Baseline characteristics of survey population**

Measure	Result
Responding CTN sites (n=35), n (%)	16 (46)
Responding sites by region, n (%)	
Pacific (n=5)	2 (40)
Prairies (n=4)	4 (100)
Ontario (n=12)	6 (50)
Quebec (n=11)	2 (18)
Atlantic (n=3)	2 (67)
Academic sites responding (n=24), n (%)	10 (42)
Community sites responding (n=11), n (%)	6 (55)
Total number of patients at responding sites	12,659
Median number of patients per site (range)	650 (130–2500)
Median number of patients per site with any liver disease (range)	181 (24–400)
Median per cent of patients per site with any liver disease (range)	20 (10–46)
Hepatology consultation readily available (n=16), n (%)	15 (94)
Site specialist with expertise in HIV-related liver disease, (n=16), n (%)	12 (75)

CTN Canadian HIV Trials Network

disease within their clinic population. Furthermore, they were asked to identify key obstacles precluding routine liver transplantation in Canadian HIV-infected patients.

## METHODS

The Canadian HIV Trials Network (CTN) is a research organization comprised of academic and community clinics across Canada. Between August 2005 and November 2005, HIV physicians, one from each CTN site who provided care for HIV-seropositive adults, were asked to complete a quantitative questionnaire pertaining to the burden of liver disease and liver transplant need at their specific clinic. Information on the number of HIV patients treated, the HIV physicians' clinical expertise in HIV-related liver disease and their access to hepatology consultation was captured. Expertise in HIV-related liver disease refers to experience and competence in the management of commonly observed liver problems seen in the clinical setting, including antiretroviral liver toxicity and viral hepatitis infection. Information on the total number of patients, patients with cirrhosis and need for assessment at a transplant centre was captured specific to HCV, HBV and excessive alcohol use (ie, greater than 50 g of alcohol daily). An assessment of transplantation consultation appropriateness was made by the HIV physician. For example, among HIV physicians, it is standard practice that those with active substance abuse, unstable psychiatric health or poor HIV control should not be considered for referral. An estimate of the anticipated need for organ transplantation in patients with HIV over the next five years was requested. Information on the data source (ie, computerized database, chart review and best estimate) and quality of the provided information were solicited. HIV physicians were asked to identify what they believed were obstacles to liver transplantation in Canadians with HIV infection. A Likert scale ranging from 0 to 5 (0 denoting no barrier to liver transplantation and 5 representing a major barrier to liver transplantation) was used. A list of options was generated by the authors (Drs Cooper, Lalonde and Gill) after consultation with each other and experts in the field. Space to write in additional obstacles not included on the list was provided.

**TABLE 2**  
**Liver disease, cirrhosis and transplant need in HIV-seropositive patients**

Measure (per site)	Hepatitis C virus	Hepatitis B virus	Excess alcohol use
Number of patients	121 (18–350)	37 (7–102)	50 (0–375)
Per cent of patients	20 (5–49)	5 (0–5)	5 (0–63)
Number of patients with cirrhosis	9 (0–35)	3 (0–5)	9 (0–35)
Per cent of patients with cirrhosis	7 (0–35)	8 (0–20)	20 (0–50)
Patients warranting transplant consideration	2 (0–7)	1 (0–2)	1 (0–7)
Patient appropriate to request consultation with transplant centre	1 (1–10)	1 (0–3)	0 (0–1)

Data presented as median (range)

A descriptive analysis was conducted with medians and ranges reported. Analysis was conducted using SPSS version 12.0 (SPSS Inc, USA).

## RESULTS

Sixteen of 35 (46%) sites responded (Table 1). Responses were obtained from clinics in each of the five Canadian HIV treatment network regions (Pacific, Prairies, Ontario, Quebec and Atlantic). Data from clinics following a total of 12,659 HIV patients were collected. A median of 650 patients (range 130 to 2500 patients) were followed per clinic site. HIV physicians from 10 of 24 (42%) university-based clinics and six of 11 (55%) community-based sites replied to the survey. Fifteen of the 16 responding sites indicated that hepatology consultation was available at their site if required. Twelve of the 16 sites reported that there was an HIV physician within their clinic who possessed special interest and expertise in HIV-related liver disease.

Overall, a median of 20% of patients (range 10% to 46%) followed at these sites had concurrent liver disease (Table 2). Twenty per cent (range 5% to 49%) were identified as HCV-infected. Five per cent (range 0% to 5%) were identified as being HBV coinfecting. Five per cent (range 0% to 63%) of HIV-infected patients were noted to have concurrent alcohol-related liver disease defined as greater than 50 g of alcohol per day. These groups were not mutually exclusive.

In patients with HIV-HCV coinfection, a median 7% (range 0% to 35%) were cirrhotic. In the judgement of the responding CTN physicians, 15% of these HCV-infected cirrhotic patients were currently in need of liver transplant assessment. In absolute numbers, this represents a median of two patients per site. Approximately one-half of these patients were thought to be appropriate candidates for referral to a transplant clinic according to the well-known criteria for transplant eligibility (eg, no substance use, stable psychiatric health and stable HIV disease).

Eight per cent (range 0% to 20%) of patients with HIV-HBV coinfection were reported to be cirrhotic. The need for transplant assessment requirement ranged broadly from 0% to 50%. In absolute terms, approximately one HIV-HBV coinfecting patient per survey site was currently in need of transplant evaluation. Approximately one-half of these patients were thought to be appropriate for transplant assessment.

Of those with alcohol-related liver disease, approximately 20% were reported to be cirrhotic. In absolute terms, approximately one patient per responding site was in need of transplant evaluation. Seven of eight respondents, providing data specifically on alcohol-related liver disease and transplant eligibility, did not consider patients consuming excess alcohol as appropriate candidates for transplantation. This is consistent with current liver transplantation guidelines (18).

HIV-physicians were asked to identify key obstacles to liver transplantation for Canadians living with HIV (Table 3). Organ supply was identified as the chief limitation to liver transplantation in those living with HIV. This was followed by concerns related to the willingness of the transplant surgical team to perform this procedure in those living with HIV and risk of HCV reinfection of the liver graft. Use and abuse of illicit drugs and alcohol were considered limitations. Interactions between HIV antiretroviral drugs and immunosuppressants used to prevent post-transplant rejection procedure was listed as a moderate obstacle. Despite the current level of concern in those with HIV, the potential for metabolic complications of combined antiretroviral treatment and transplant medications was not considered to be a major limitation to transplantation. Patient willingness to pursue this treatment option was also not considered to be a key limitation. Of interest, despite the theoretical risk of immune suppression-related post-transplant malignancy (ie, lymphoma, human papilloma virus-related malignancy and Kaposi sarcoma), this was not documented as a major limitation.

Eighty per cent of responding sites foresaw an increased need for liver transplantation in HIV-infected patients over the next five years. No respondent predicted a diminished need within his or her clinic population. In contrast, 66% of sites anticipated no change in the need for other organs within the next five years. Specifically, 77% of sites anticipated no increased need for kidney transplantation.

## DISCUSSION

Despite therapies for HBV and HCV, viral liver disease remains a significant cause of death in those living with HIV (19). In the period following the introduction of combination antiretroviral therapy, liver transplantation has been demonstrated to be a life-saving option for at least a portion of those living with HIV (2,3,15-17). Accumulating data suggest that well-selected HIV-HBV and HIV-HCV transplanted patients can achieve survival rates at three years and beyond that are comparable with those from patients without HIV infection receiving transplants (2,3,17). This body of work demonstrates that antiretroviral therapy continues to suppress HIV viremia during the post-transplant period and that opportunistic infections are rare despite the use of powerful immunosuppressants necessary to prevent organ rejection.

Our survey suggested that there is a heavy burden of liver disease in Canadians living with HIV, and HIV physicians expect the rates to increase. At any one time, most CTN sites follow several patients who are in need of transplant assessment. This represents a significant need given that there are over 30 centres, affiliated with the CTN, providing care for large numbers of HIV-infected adult patients. We estimated the current number of patients, both in need of and appropriate for liver transplant assessment by a transplant specialist, to be approximately 3.9 per 1000 HIV-infected individuals (20). Our survey indicated that most CTN clinics had experience in

**TABLE 3**  
HIV physician perceptions of limitations to liver transplantation in those living with HIV, measured using the Likert scale\*

Limitation	Mean	Median				
		1	2	3	4	5
Organ supply	4.5					×
Transplant surgical team willingness	3.7					×
Risk of hepatitis C virus reinfection	3.7					×
Illicit substance use and abuse	3.1				×	
Drug interactions	3.0				×	
Graft survival	2.6				×	
Lack of expertise for post-transplant follow-up	2.6				×	
Patient survival	2.5				×	
Metabolic complications of HIV and transplant medications	2.2				×	
Patient willingness	2.1				×	
Post-transplant malignancy risk	1.9				×	

\*Likert scale 0 denoting no barrier to liver transplantation, to 5 representing a major barrier to liver transplantation

the management of HIV-related liver disease and readily available consultation with a hepatologist when required. This information suggested that most HIV-infected patients would have access to the level of expertise required to safely and competently manage a liver transplant patient on antiretroviral therapy. In support of this impression, expertise in postliver transplant patient management was not identified in the present survey to be a major obstacle to this procedure in patients living with HIV.

In patients without HIV infection (11), organ supply was universally identified as the chief obstacle to the widespread availability of liver transplantation. The current frequency of cadaveric liver donation in Canada is 11.52 per million population (L Trpeski, personal communication). This falls well short of current requirements (14). There are examples, some controversial, in which proactive efforts to increase organ donation has met with success (11). Living liver donation continues to be evaluated and perfected as an option (21,22). There is limited experience with this procedure in patients with HIV infection (23).

HCV reinfection was identified as a major barrier to liver transplantation in those with HIV infection. In 5% to 10% of HIV-seronegative patients transplanted for HCV-related end-stage liver disease, an aggressive and destructive HCV-induced fibrosing cholestatic hepatitis occurs, eventually leading to liver failure (7,8,17,24). The frequency of this may be higher in those with HIV coinfection (17). Strategies using post-transplant HCV antiviral therapy at the first sign of acute HCV disease may prevent this adverse outcome (10). Assessment of this therapeutic approach in transplanted HIV-HCV coinfecting patients is needed.

Surgical team willingness continues to be perceived by HIV physicians as a key obstacle to liver transplantation in HIV-infected patients. This concern may have some basis given the results of a recent survey of transplant surgeon willingness to provide organs to HIV-infected patients (25). In that study, most surgeons believed that HCV patients were appropriate transplant candidates. In contrast, only one-third of surgeons were willing to transplant HIV-infected patients, even though they believed that the post-transplant survival

rates of HIV-infected and HCV-infected patients were similar. Risk of HIV infection to the surgical team during the procedure is an often-raised and legitimate concern. It is important to remember that most HIV-infected transplant recipients are on combination antiretroviral therapy with undetectable viral loads, thereby greatly diminishing the risk to near zero. Furthermore, many other surgical procedures are routinely conducted within this population despite this concern.

There are several limitations in the present work that are acknowledged. Although eight of 16 sites used clinical databases to provide quantitative values, most sites relied at least in part on estimates. This issue is most relevant to excess alcohol use. For these reasons, our data on alcoholic liver disease in patients with HIV should be interpreted with caution. Low response from the CTN Quebec region was noted. However, the two responding sites that followed 2687 patients represented approximately 15% of the estimated 18,000 patients living with HIV in Quebec (26). Because there is an estimated 56,000 Canadians living with HIV, our overall data are based on results from clinics following approximately

25% of all Canadians with HIV. Based on this proportion of representation, we are satisfied that our findings reflect all regions in Canada. Finally, the present work was a survey of HIV-treating physician opinions and practices (eg, the need for transplantation and timing of referral for transplant assessment). The results do not necessarily reflect the perspectives and practices of liver transplant specialists, transplant surgeons or patients living with HIV.

In the present survey, HIV physicians identified a large and possibly increasing need for liver organ transplantation in Canadians living with HIV. These HIV care providers believe that the chief obstacle to transplantation in this population is organ supply, which was universally identified among survey responders. Other key issues include the risk of HCV reinfection during the post-transplant period and transplant surgical team willingness to routinely perform this procedure. Based on the present survey, we recommend that the focus of efforts designed to increase access to liver transplantation in Canadians with end-stage liver disease and concurrent HIV should concentrate on these issues.

## REFERENCES

- Belle SH, Porayko MK, Hoofnagle JH, Lake JR, Zetterman RK. Changes in quality of life after liver transplantation among adults. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Liver Transplantation Database (LDT). *Liver Transpl Surg* 1997;3:93-104.
- Stock PG, Roland ME, Carlson L, et al. Kidney and liver transplantation in human immunodeficiency virus-infected patients: A pilot safety and efficacy study. *Transplantation* 2003;76:370-5.
- Ragni MV, Belle SH, Im K, et al. Survival of human immunodeficiency virus-infected liver transplant recipients. *J Infect Dis* 2003;188:1412-20.
- Furukawa H, Todo S. Evolution of immunosuppression in liver transplantation: Contribution of cyclosporine. *Transplant Proc* 2004;36:274S-84S.
- Moser MA. Options for induction immunosuppression in liver transplant recipients. 2002;62:995-1011.
- Lok AS. Prevention of recurrent hepatitis B post-liver transplantation. *Liver Transpl* 2002;8:S67-73.
- Berenguer M. Natural history of recurrent hepatitis C. *Liver Transpl* 2002;8:S14-8.
- Testa G, Crippin JS, Netto GJ, et al. Liver transplantation for hepatitis C: Recurrence and disease progression in 300 patients. *Liver Transpl* 2000;6:553-61.
- Tolan DJ, Davies MH, Millson CE. Fibrosing cholestatic hepatitis after liver transplantation in a patient with hepatitis C and HIV infection. *N Engl J Med* 2001;345:1781.
- Samuel D, Bizollon T, Feray C, et al. Interferon-alpha 2b plus ribavirin in patients with chronic hepatitis C after liver transplantation: A randomized study. *Gastroenterology* 2003;124:642-50.
- Steinbrook R. Public solicitation of organ donors. *N Engl J Med* 2005;353:441-4.
- Gridelli B, Remuzzi G. Strategies for making more organs available for transplantation. *N Engl J Med* 2000;343:404-10.
- Keeffe EB. Liver transplantation: Current status and novel approaches to liver replacement. *Gastroenterology* 2001;120:749-62.
- McAlister VC, Badovinac K, Fenton SS, Greig PD. Transplantation in Canada: Review of the last decade from the Canadian Organ Replacement Register. *Clin Transpl* 2003;101-8.
- Prachalias AA, Pozniak A, Taylor C, et al. Liver transplantation in adults coinfecting with HIV. *Transplantation* 2001;72:1684-8.
- Neff GW, Bonham A, Tzakis AG, et al. Orthotopic liver transplantation in patients with human immunodeficiency virus and end-stage liver disease. *Liver Transpl* 2003;9:239-47.
- Norris S, Taylor C, Muiesan P, et al. Outcomes of liver transplantation in HIV-infected individuals: The impact of HCV and HBV infection. *Liver Transpl* 2004;10:1271-8.
- Consensus conference: Indications for Liver Transplantation, January 19 and 20, 2005, Lyon-Palais Des Congres: Text of recommendations (long version). *Liver Transpl* 2006;12:998-1011.
- Bica I, McGovern B, Dhar R, et al. Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. *Clin Infect Dis* 2001;32:492-7.
- National HIV Prevalence and Incidence Estimates for 2002 – HIV/AIDS Epi Update. Ottawa: Centre for Infectious Disease Prevention and Control. Public Health Agency of Canada, 2005.
- Oliveros FH, Santamaria ML, Gamez M, et al. Comparative study between living and cadaveric donors in pediatric liver transplantation. *Transplant Proc* 2005;37:3936-8.
- Elola-Olaso AM, Gonzalez EM, Diaz JC, et al. Short- and long-term outcomes after living donor liver transplantation. *Transplant Proc* 2005;37:3884-6.
- Sugawara Y, Ohkubo T, Makuuchi M, et al. Living-donor liver transplantation in an HIV-positive patient with hemophilia. *Transplantation* 2002;74:1655-6.
- Rodriguez-Luna H, Douglas DD. Natural history of hepatitis C following liver transplantation. *Curr Opin Infect Dis* 2004;17:363-71.
- Halpern SD, Asch DA, Shaked A, Stock PG, Blumberg E. Determinants of transplant surgeons' willingness to provide organs to patients infected with HBV, HCV or HIV. *Am J Transplant* 2005;5:1319-25.
- Allard R, Turmel B, Venne S, et al. Portrait des infections transmissibles sexuellement et par le sang (ITSS), De L'Hépatite C, De L'Infection Par Le VIH et du sida au Québec. Collection Analyses et Surveillance. Québec: Ministère de la Santé et Services sociaux Québec, 2004.