HIV and Solid Organ Transplantation

A review of the literature with recommendations for action

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OACHA Working Group on HIV and Transplantation

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The issue

Since the late 1980s, infection with the human immunodeficiency virus (HIV) has been accepted as an absolute contraindication for solid organ transplantation in Canada and all other industrialized countries. As a result, HIV-positive individuals are excluded from receiving a standard treatment for end-stage organ failure. This restriction was instituted long before effective antiretroviral therapy became available and even before the approval of many of the drugs currently used to treat AIDS-related opportunistic infections. At that time, HIV infection led to life-threatening complications from AIDS and rapid progression to death.

The demand for transplantation is high and increases each year while donor organs remain scarce. Thus, potential survival is a major consideration in organ allocation. Recipient-candidates must be ill enough to desperately need a new organ, but not so ill that they might not survive the surgery and the first few crucial months after transplantation. Fifteen years ago, the prognosis for people living with HIV/AIDS was so dismal they were deemed unlikely to survive the surgery or the first few post-operative months.

Moreover, successful transplantation depends on the regular use of immune-suppressive drugs in order to prevent the body from rejecting the new organ. Giving such treatment to patients whose immune systems had already been severely damaged by HIV seemed likely to cause even faster progression to AIDS and death.

However, by the mid-1990s, progress in HIV medicine led to the development of new drugs and treatment modalities for many of the AIDS-defining illnesses. Ironically, prior to the HIV pandemic, the opportunistic infections and cancers associated with AIDS had been seen only rarely, in specific populations, including people who had received organ transplants.

The most significant break-through in the medical management of HIV/AIDS has been the development of Highly Active Antiretroviral Therapy (HAART). A combination of at least three potent antiretroviral drugs, HAART has demonstrated conclusive benefit in significantly improved survival and health-related quality of life. Since it became widely available in Canada in 1997, HAART has been so effective that many researchers and treating physicians consider HIV infection to be a chronic, manageable condition.

Increasingly, HIV-associated nephropathy, co-infection with hepatitis viruses, and liver damage and coronary artery disease secondary to antiretroviral therapy are contributing to the morbidity and mortality of people whose HIV is controlled with effective treatment. Currently they are denied access to organ transplantation - a standard treatment for irreversible end-stage organ disease - solely on the basis of their HIV infection and assumptions about the lack of benefit they might derive from the procedure.
Although the restriction against offering organ transplantation to HIV-positive individuals is not based in law in Canada or in the USA, the international transplant community seems to have arrived at a consensus to restrict access to HIV-positive persons. This despite the bylaws of the United Network for Organ Sharing (UNOS), the national organ allocation and distribution agency in the USA, which have stated since 1994 that "a potential candidate for organ transplantation whose test for HIV-Ab is positive but who is in an asymptomatic state should not necessarily be excluded from candidacy for organ transplantation." In Canada, the criteria for selecting transplant candidates are established by individual transplant centres and may vary from province to province, or from one provincial site to another. Only one provincial transplant group, the British Columbia Transplant Society Liver Transplant Program, has publicly declared itself willing to accept HIV-positive persons as candidates for liver transplant. (Living+ magazine, BCPWA Society, 2003).

Given the improved prognosis for people living with HIV, and the increasing burden of end-stage organ disease, it is time to review the progress made in the past 20 years in both HIV and transplant medicine and to lift the outdated restriction against offering solid organ transplantation to HIV-positive people.
Background: solid organ transplantation

Medical issues:

Solid organ transplantation is a relatively new field of medicine. The first successful kidney transplant was performed in 1954 when a man donated a kidney to his identical twin. The first successful liver transplant occurred in 1967, with the patient surviving 400 days. In December 1967, the first human-to-human heart transplant was performed - - a procedure that inspired 100 attempted heart transplants the following year. In its first two decades, progress in solid organ transplantation was hampered by poor patient survival. In the early series of heart transplants, only 20% of patients survived one year. Between 1967 and 1983, about 30% of liver transplant recipients survived the first year. (Ashok 2000). Despite the professional and public interest these procedures created, the poor survival rate ensured that organ transplantation remained an experimental procedure until the early 1980s.

Organ transplantation procedures were stymied by rejection; the immune system's response to the presence of foreign material in the body. The immune system can distinguish between "self" and "foreign" by reacting to proteins on the surfaces of cells or against substances that it recognizes as foreign or "not-self." The presence of foreign tissue in the body triggers an immune response that can result in graft rejection when antibodies are formed against the foreign proteins on the transplanted organ. Unless it is controlled, the rejection response will damage or destroy the new organ. In the case of the first kidney transplant, because the donor and recipient were identical twins, the grafted kidney was not identified as foreign tissue. This perfect match demonstrated that organ transplantation was possible, if graft rejection could be controlled.

Until the early 1980s, corticosteroids and azathioprine were the only drugs available to suppress the immune system and help reduce the incidence of rejection. However, these drugs leave the recipient vulnerable to wide range of infections and cancers. These conditions are related to immune suppression; they would not ordinarily cause disease in a person with a healthy, fully-functioning immune response.

Over the past twenty years, organ transplantation has evolved from an experimental form of salvage therapy to the standard treatment for end-stage organ failure. Refinements in organ preservation techniques, improvements in the rapid detection of acute and chronic organ rejection, new diagnostic tools, the development of a range of medications to prevent and treat infections, and a better understanding of the risk factors that affect patient outcome have all contributed to the improved prognosis of transplant recipients.

The most significant improvement has been in the introduction of new immunosuppressive agents and regimens to control rejection. The history of transplantation medicine may be divided in three eras denoting the introduction and use of new immunosuppressive agents: the Early Era: 1954-1983 with only azathioprine and prednisone; the Cyclosporine Era 1983-1990 with the arrival of cyclosporine and the monoclonal antibody OKT3; and the Modern Era: from 1991 onward with the arrival of the drugs tacrolimus, mycophenolate, and sirolimus.
The introduction of cyclosporine renewed medical interest in organ transplantation. The efficacy of cyclosporine was clearly demonstrated by the increased numbers of transplants. In the twenty years between 1954 and 1973, about 10,000 kidney transplants were performed in the USA. In contrast, 9,000 kidneys were transplanted in 1986 alone. Canadian developments in transplantation science and medicine have contributed to the global capacity, with several pioneering surgeries performed for the first time ever. The world's first lung transplant took place in Toronto in 1983, the first double-lung transplant followed in 1986, and in 1988 the world's first liver-bowel transplant was performed in London, Ontario.

**Risk and benefits of transplantation**

While organ transplantation can be a life-saving procedure, considerable morbidity is still associated with the procedure. Up to 80% of transplanted patients will develop, on average, one or two serious infections in the first year of transplantation. By category, these infections are 50%-60% bacterial, 20%-40% viral and 5%-15% fungal. Most bacterial infections, *Candida* infections and reactivation of herpes simplex virus infection occur within the first month. Cytomegalovirus reactivation and aspergillosis usually occur at weeks four through ten. Epstein Barr virus and varicella-zoster viral infections occur around months four through six. *Pneumocystis carinii* pneumonia and toxoplasmosis infections also occur within the first six months post-transplant. Recurrent hepatitis B or C, cryptococcal pneumonia and meningitis may appear during the fourth through sixth months following transplantation.

In the longer term, transplant patients are at risk for a variety of conditions related to the chronic use of immunosuppressive drugs. These conditions can include: osteoporosis and arthritis; hypertension; renal insufficiency; hyperglycemia; hyperlipidemia; bone marrow suppression; hyperuricemia/gout; chronic headache; GI distress (ulcer disease, chronic diarrhea); encephalopathy/neurotoxicity (central pontine myelinolysis, chronic fatigue); chronic pain; and cancers. (Kunder 2000)

Despite the potential risks, health-related quality of life is clearly improved in almost all transplant recipients. Researchers from the University of Western Ontario surveyed 203 patients who had received a new liver between 1982 and 1992, and found that 57% had returned to work. Of the 43% who were unemployed, only 18% felt they were not well enough to work. Among the other reasons cited for not working were early retirement (8%), return to school (3%), family reasons (3%), could not find work (3%), and chose not to work (3%). (Adams 1995) More recently, researchers at Baylor University in Texas questioned 344 patients about changes in their quality of life after liver transplantation. In eight of the nine categories studied, scores improved after transplant and continued to increase to the tenth year. Employment was low (38%) in the first year after surgery, but improved in the second year and continued to increase in the long-term (64% at 5 years, 52% at 10 years). (Chinnakotla 2003)
Supply and Demand

The remarkable achievements in transplant medicine have led to the current worldwide situation where demand far exceeds supply. As in most developed countries, the transplant experience in Canada has been enormously successful but it is limited by the shortage of donor organs. As a result, transplant waiting lists have grown in numbers and the time spent waiting for a new organ has increased, to several years in the case of kidney transplants. As the tables below show, organ transplantation has increased substantially, but the demand for these procedures has more than doubled in a decade.

Number of Transplants, Cadaveric Donor Transplants, Living Donor Transplants and Patients on the Transplant Waiting List, Canada, 1992-2000

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Waiting List</td>
<td>2076</td>
<td>2150</td>
<td>2159</td>
<td>2592</td>
<td>2829</td>
<td>2874</td>
<td>3229</td>
<td>3514</td>
<td>3800</td>
</tr>
<tr>
<td>All Transplants</td>
<td>1149</td>
<td>1422</td>
<td>1456</td>
<td>1524</td>
<td>1535</td>
<td>1565</td>
<td>1577</td>
<td>1664</td>
<td>1820</td>
</tr>
<tr>
<td>Cadaveric Donor Transplants</td>
<td>1000</td>
<td>1243</td>
<td>1246</td>
<td>1300</td>
<td>1270</td>
<td>1280</td>
<td>1209</td>
<td>1275</td>
<td>1411</td>
</tr>
<tr>
<td>Living Donor Transplants</td>
<td>149</td>
<td>179</td>
<td>210</td>
<td>224</td>
<td>265</td>
<td>285</td>
<td>368</td>
<td>389</td>
<td>409</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th></th>
<th>Patients waiting in Ontario, 2003</th>
<th>Transplants performed in Ontario, 2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>41</td>
<td>28</td>
</tr>
<tr>
<td>Kidney</td>
<td>1335</td>
<td>145 (71 cadaveric, 64 living donor)</td>
</tr>
<tr>
<td>Liver</td>
<td>315</td>
<td>73 (62 cadaveric, 11 living donor)</td>
</tr>
<tr>
<td>Lung</td>
<td>30</td>
<td>24</td>
</tr>
<tr>
<td>Heart/Lung</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Kidney/Pancreas</td>
<td>40</td>
<td>11</td>
</tr>
<tr>
<td>Pancreas</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>TOTAL</td>
<td>1768</td>
<td>274</td>
</tr>
</tbody>
</table>

Organ Donation and Allocation

Over the past ten years or more, federal, provincial, and territorial governments have been examining organ transplantation issues in Canada. Much of the discussion has centred around the means of expanding Canada's organ donor pool. Various initiatives to enhance organ donation and transplantation are being studied at the federal level, including the possibility of creating a formalized, national system to identify and match donors with recipients. Although Canada is the only developed country without a national agency to coordinate organ donation, at the provincial and regional levels there are well-established programmes with effective, if informal, systems for organ sharing.

Ontario's first centralized agency, the Multiple Organ Retrieval and Exchange (MORE), was established in 1988 to coordinate the retrieval and distribution of organs province-wide. In December 2000, the provincial government created the Trillium Gift of Life Network, which has assumed the role of Ontario's central organ and tissue donation agency. As outlined by the Trillium Gift of Life Network Act, the Network's mandate includes: advising the Minister of Health and Long-Term Care on matters relating to the donation of organs and tissue; planning, promoting, coordinating and supporting activities relating to the donation of organs and tissue for transplant; planning, promoting, coordinating and supporting activities relating to education or research in connection with the donation of organs and tissue.

The Network is charged with the task of significantly increasing organ and tissue donation across the province and improving related processes and functions. A major step towards achieving these goals has been the separation of staff who request organ donation from the clinical staff who had worked to save the patient's life. In Ontario hospitals with neurosurgery and trauma centres, the Gift of Life Network provides trained donor coordinators, not associated with any transplant programs, to approach surviving relatives regarding organ donation. The donor coordinator program will be expanded to include hospitals without specific trauma centres.

The Gift of Life Network is not involved in determining which patients are wait-listed for transplant. That decision is made by the individual transplant program. However, as soon as potential candidates begin their assessment for transplantation, they are registered on the Network's computer system, linking solid organ transplant centres in Ottawa, Kingston, Toronto, Hamilton, and London. The name and medical information about each potential recipient is entered at the regional site and updated as required. Once patients are accepted as suitable candidates for transplantation, they are entered onto the waiting list and become eligible for allocation. Information on donor organs is also entered into the database and the automatic allocation system identifies a list of the best potential recipients (based on blood type, illness of patient, time on waiting list, size of the organ, etc).

The algorithms used to allocate donor organs are reviewed yearly and updated when appropriate. Organ allocation is based on provincially agreed-upon algorithms that include considerations about blood type, tissue typing and cross-matching, medical priority, length of time on waiting list and donor/recipient size comparisons. Within each province, donor coordinators maintain
lists of high priority patients from out-of-province. Ontario's system has been expanded to incorporate registration of those out-of-province and international patients who require consideration for organ allocation.

**Organ donors**

In Ontario, potential organ donors over the age of 16 can sign an organ donor card or register with OHIP's donor registry. There is no maximum age limit for organ donation; the overall condition of the donor's organs is the deciding factor. Health cards are updated to indicate that the card carrier is a potential donor. However, the potential donor's family can over-ride the donor's wishes in every province and territory, except British Columbia.

Before being considered a potential organ donor, a patient must be declared brain dead. Only 2-3% of all deaths are the result of brain death. Brain death is determined by two physicians, neither associated with the transplant team and independent of each other, following the guidelines set out by the Canadian Congress of Neurological Services in 1983 and updated by the Canadian Neurocritical Care Group in 1999. The potential donor is artificially maintained on a ventilator until the organs can be transplanted.

To increase the opportunities for transplantation, some criteria for organ donors have been relaxed. Years ago, organs from female donors may not have been accepted, and donors over the age of 35 would not have been accepted, and donors over the age of 35 would not have been accepted; today, the oldest organ donor on record in Canada was over 90 years old. Indeed, by 1995 the National Consensus Conference on the Safety of Organs and Tissues acknowledged that the only absolute contraindication for donor organs is cancer in the specific organ; all other contraindications, such as hepatitis B or C, HIV, or HTLV infection, are relative contraindications (Health Canada, 1995). Although such virally infected organs would not ordinarily be transplanted, Health Canada sanctions "exceptional releases." For example, a liver from an HBV-antibody-positive donor may become available. If there is a potential recipient in liver failure unlikely to live more than 48 hours, the Gift of Life Network will inform the medical director of the transplant program. The transplant surgeon and transplant team are informed, the risks and benefits are discussed within the team and with the patient and the family to ensure informed consent is given.

New surgical techniques such as living donation, split liver transplants, and "domino" transplants have helped to expand the donor pool. Living organ donation allows a healthy, living donor to give an organ - usually a kidney or part of the liver - to a transplant candidate. A healthy individual can live a full life with only one kidney; within months of removing about half the liver, the remaining organ regenerates to full size. For split-liver transplants, one whole organ is divided into two pieces so two recipients can benefit from one cadaveric donor. The smaller piece of the liver (about 25 per cent) is used for a child and the remaining 75 per cent is used for an adult. The results of this technique have shown similar graft and patient survival rates when compared with whole liver transplantation. "Domino" transplants are rarely performed procedures in which a transplant recipient is also an organ donor. For example, a patient with cystic fibrosis in need of a lung transplant may receive a combined heart-lung transplant in order
to have both organs develop together. This patient's healthy heart is then transplanted into another recipient. The liver of a patient with familial amyloid neuropathy (FAP) produces a protein that accumulates in organs and tissues, eventually affecting the autonomic nervous system. A donor liver is found for the FAP patient whose own liver is transplanted into another recipient.

**Transplant candidates**

The ideal transplant candidate has severe disease in the target organ, but is otherwise healthy. Unfortunately, such patients are extremely rare: end-stage organ disease almost invariably has a detrimental effect on other organs and systems. Co-existing medical conditions must be thoroughly investigated in order to understand their effect on the outcome of surgery. The transplant team must consult specialists in other fields in order to assess candidates accurately and to provide appropriate follow-up care. Transplant medicine and surgery are highly specialized fields but their success depends on a multidisciplinary approach to patient care.

Candidates for organ transplantation must be referred by their primary care physician or specialist to a transplant centre where they undergo assessment. As soon as the assessment begins, patients are registered with the Gift of Life Network which allows for data entry of information as the assessment proceeds. The criteria for accepting candidates and assigning a rank on the waiting list are determined by the individual transplant centres. When patients are accepted as suitable transplant candidates, they are entered onto the waiting list and become eligible for organ allocation.

Despite the constant and chronic shortage of donor organs, transplantation is offered to a increasingly wide range of patient-candidates. Surgical innovations, refinements in transplant medicine, and a better understanding of the risk factors affecting patient prognosis have allowed the criteria for transplant candidates to be broadened. Until recently, hepatitis B infection and primary liver cancer were seen as absolute contraindications for liver transplantation by the directors of Canadian liver transplant centres (Mullen 1996). Moreover, transplantation is offered to people who have more post-transplant complications and reduced survival, such as those with acute organ failure, diabetes or hepatitis C; older patients (over 50 years); or patients of African or Asian heritage.
Transplant Outcomes

As the tables below clearly demonstrate, transplantation medicine has advanced exponentially beyond the pre-1983 "Experimental Era," when only about 20% of heart transplant recipients and 30% of liver recipients survived one year.

**Transplant patient survival rates in Canada 1991-2000**

<table>
<thead>
<tr>
<th>Organ</th>
<th>1 year</th>
<th>3 years</th>
<th>5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cadaveric kidney</td>
<td>95.1</td>
<td>91.2</td>
<td>86.2</td>
</tr>
<tr>
<td>Living kidney</td>
<td>98.2</td>
<td>96.7</td>
<td>93.7</td>
</tr>
<tr>
<td>Liver</td>
<td>84.7</td>
<td>79.1</td>
<td>75.1</td>
</tr>
<tr>
<td>Heart</td>
<td>83.9</td>
<td>75.1</td>
<td>74.7</td>
</tr>
</tbody>
</table>


**Transplant patient survival rates in USA 1995-2000.**

<table>
<thead>
<tr>
<th>Organ</th>
<th>1 year</th>
<th>3 years</th>
<th>5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cadaveric kidney</td>
<td>94.0%</td>
<td>88.4%</td>
<td>79.0%</td>
</tr>
<tr>
<td>Living kidney</td>
<td>97.7%</td>
<td>94.7%</td>
<td>89.7%</td>
</tr>
<tr>
<td>Cadaveric liver</td>
<td>86.4%</td>
<td>79.5%</td>
<td>72.4%</td>
</tr>
<tr>
<td>Living liver</td>
<td>85.2%</td>
<td>80.2%</td>
<td>85.6%</td>
</tr>
<tr>
<td>Heart</td>
<td>85.1%</td>
<td>78.6%</td>
<td>69.8%</td>
</tr>
</tbody>
</table>

Background: HIV and organ transplantation pre-HAART (1980 - 1995)

Most of the published medical experience with HIV and organ transplantation came from patients with unrecognized infection prior to surgery or those who were infected perioperatively, either through the new organ or contaminated blood products, during the 1980s.

It is difficult to evaluate the clinical progress and outcomes of these patients from the literature. The reports are retrospective studies or case reports with a complex mix of patients at different stages in their HIV infection. A limited attempt was made to create an international registry to collect both retrospective and prospective information on the effects of HIV on transplantation (Rubin 1987). The registry was able to identify 18 cases and, in 1988, the information was reported to the US National Institute of Health-National Kidney Foundation Task Force on AIDS (Glassock 1990).

Some of these early reports indicate that HIV-infected transplant recipients fared worse than HIV-negative recipients, while others seem to show equivalent survival rates. In other reports, the HIV-infected recipients progressed to AIDS more quickly than the general HIV-positive population. Paediatric patients generally had better results than adults, an observation consistent with transplant outcomes in the HIV-negative population.

During this period, there were reports of HIV-infected transplant recipients surviving at least 5 years with normal graft function and successful management of HIV-related complications. Three heart transplant recipients, 12 kidney recipients, and 11 liver recipients survived at least 5 years after their surgery. Two HIV-positive patients - one with unrecognized HIV infection prior to surgery, one infected perioperatively - who received liver transplants at the University of Pittsburgh are alive and well more than fifteen years after their surgery.

None of the patients described in these reports received effective treatment for their HIV infection. Most of them received their transplants before any single anti-HIV drug was available; indeed, most became infected before highly sensitive and accurate HIV tests became available. The first anti-HIV drug, AZT (Retrovir), received marketing approval in the USA only in 1987. Used as a single agent, its benefit lasts only a few months before drug resistance develops. Few of these early HIV-infected transplant recipient were given AZT; those who did receive it may not have tolerated the competing toxicities between this drug and their immune suppressing medications.

The immunosuppressive regimen following transplantation may have had an effect on the outcome of these patients. Cyclosporine - the drug that revolutionized transplantation - only became generally available in 1983. Not all the patients described in these early studies received cyclosporine, and their reliance on older, more primitive immune suppressants may have contributed to both graft failure and infectious complications leading to death. Although it seems counter-intuitive to give an immune suppressant like cyclosporine to patients with the immune deficiency caused by HIV, there are at least a dozen published laboratory and clinical reports, with varying results, describing the use of cyclosporine in HIV/AIDS. Indeed, in 1985 an overly-
enthusiastic team of French researchers proclaimed cyclosporine as the cure for AIDS. In practical terms, one study noted that patients who received cyclosporine for immune suppression following transplantation progressed to AIDS at the same rate as HIV-positive people without transplants or exogenous immune suppression. Patients who received immune suppressants other than cyclosporine progressed to AIDS at a much higher frequency than non-transplanted HIV-positive persons (90% versus 31% at 5 years). (Erice 1991). More recently, mycophenolate (CellCept), one of the newer immunosuppressive agents, has been evaluated in several studies as part of a HAART combination, particularly as adjunct to abacavir (Ziagen).

Furthermore, in the 1980s, there were few effective drugs available to treat the infections resulting from immune suppression caused either by post-transplant medications or by HIV/AIDS. In some of these early reports, deaths from infections following transplantation in HIV-positive recipients may have been attributed solely to HIV infection, even though the same infections may occur after transplantation in HIV-negative patients (Tzakis 1990). Such assumptions have likely contributed to the general impression, within the transplant community, that organ transplantation does not benefit HIV-positive individuals and may indeed cause irrevocable harm.

Our review of the medical literature revealed 126 cases of organ transplantation in HIV-positive individuals prior to the arrival of effective anti-HIV treatment in 1997. Amongst this group of 126 transplant recipients, 54 deaths were reported: 27 were deemed to be AIDS-related and another 27 were due to other causes. Due to the varying types of reports it is impossible to assess accurately the effect of immune suppression on HIV progression and it is difficult to systematically compare the outcomes in these patients with those of HIV-negative transplant recipients. However, it seems that 112 of the 126 (88%) survived one year and 67 (53%) survived 5 years or more. These outcomes do not seem very different from those of HIV-negative transplant recipients in the early to mid-1980s. Prior to the arrival of cyclosporine, survival rates for transplant recipients were poor - - for example, only about 30% of liver transplant recipients survived one year. One report describing a clinical trial of cyclosporine noted that this new drug increased the one-year survival for heart and kidney transplants to 70 - 80% and 60 - 65% for liver transplants. (Cohen 1984)

It seems significant that none of the authors of these early reports called for the exclusion of HIV-positive patients from transplant programs. On the contrary, several reports concluded that HIV infection, per se, should not be a contraindication for transplantation (Rubin 1987, Dummer 1989, Tzakis 1990, Jacobson 1991). Rather, they emphasized the need to screen HIV-positive transplant candidates carefully. They recognized that patients with full-blown AIDS would not make good transplant candidates, but asymptomatic HIV-positive patients should be considered.
### Table 1. Summary of Pre-HAART (1980 - 1995) Solid Organ Transplantation & HIV

<table>
<thead>
<tr>
<th>Source</th>
<th>Organ</th>
<th>No. of Patients</th>
<th>Patient survival</th>
<th>Deaths due to HIV/AIDS</th>
<th>Deaths due to other causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calabrese F et al. 1998 (Italy)</td>
<td>Heart</td>
<td>1</td>
<td>6.5 years</td>
<td>1: AIDS &amp; severe chronic rejection</td>
<td></td>
</tr>
<tr>
<td>Anthuber M et al. 1991 (Germany)</td>
<td>Heart</td>
<td>1</td>
<td>5.5+ years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erice A et al. 1991 (USA)</td>
<td>Heart</td>
<td>1</td>
<td>72+ months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tzakis et al. 1990 (USA)</td>
<td>Heart</td>
<td>5</td>
<td>2/5 alive at 2.2 and 6.6 years</td>
<td>1: AIDS</td>
<td>2: cardiac failure</td>
</tr>
<tr>
<td>Erice et al. 1991</td>
<td>Pancreas</td>
<td>1</td>
<td>168 days</td>
<td></td>
<td>1: graft failure; multi-organ failure</td>
</tr>
<tr>
<td>Swanson SJ et al. 2002 (USA)</td>
<td>Kidney</td>
<td>32</td>
<td>1 yr = 97% HIV+, 95% HIV-</td>
<td>8: other causes</td>
<td></td>
</tr>
<tr>
<td>Kahn D et al. 2001 (South Africa)</td>
<td>Kidney</td>
<td>18</td>
<td>1 yr = 50%, 5 yrs = 44%</td>
<td>8: AIDS</td>
<td></td>
</tr>
<tr>
<td>Purgus R et al. 1998 (France)</td>
<td>Kidney</td>
<td>1</td>
<td>13.5+ years (Long-term HIV non-progressor)</td>
<td>8: AIDS</td>
<td></td>
</tr>
<tr>
<td>Ahuja TS et al. 1997 (USA)</td>
<td>Kidney</td>
<td>1</td>
<td>109 months</td>
<td>1: death from sepsis</td>
<td></td>
</tr>
<tr>
<td>Keay S et al. 1993 (USA)</td>
<td>Kidney</td>
<td>4</td>
<td>1 death at 30 mo; 2 deaths at 3 years; 1 death at 8.5 years</td>
<td>3: AIDS (PCP)</td>
<td>1: renal failure</td>
</tr>
<tr>
<td>Source</td>
<td>Organ</td>
<td>No. of Patients</td>
<td>Patient survival</td>
<td>Deaths due to HIV/AIDS</td>
<td>Deaths due to other causes</td>
</tr>
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<td>---------------------------------------------</td>
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<td>----------------------------------------</td>
</tr>
<tr>
<td>Schelling et al. 1993 (USA)</td>
<td>Kidney</td>
<td>1</td>
<td>12 years post transplant; 4 years post HIV-diagnosis</td>
<td></td>
<td>1: death from sepsis</td>
</tr>
<tr>
<td>Schwarz et al. 1993 (Germany)</td>
<td>Kidney</td>
<td>4</td>
<td>2 alive, AIDS-free at 8+ yrs; 2 deaths at 66 and 74 months</td>
<td></td>
<td>2: 1 endocarditis, 1 cerebral haemorrhage</td>
</tr>
<tr>
<td>Erice et al. 1991 (USA)</td>
<td>Kidney</td>
<td>3</td>
<td>2 alive at 67 &amp; 79 months; 1 death at 78 months</td>
<td>1: AIDS (PCP)</td>
<td></td>
</tr>
<tr>
<td>Gootenberg et al. 1991 (USA)</td>
<td>Kidney</td>
<td>1</td>
<td>5 years</td>
<td>1: AIDS (disseminated MAC)</td>
<td></td>
</tr>
<tr>
<td>Tzakis 1990 (USA)</td>
<td>Kidney</td>
<td>5</td>
<td>4/5 alive at mean of 3.4 yrs</td>
<td>1: AIDS (disseminated TB)</td>
<td></td>
</tr>
<tr>
<td>Briner V et al. 1989 (Germany)</td>
<td>Kidney</td>
<td>1</td>
<td>slightly less than 5 years</td>
<td>1: pulmonary embolism</td>
<td></td>
</tr>
<tr>
<td>Poli F et al. 1989 (Italy)</td>
<td>Kidney</td>
<td>8</td>
<td>5/8 alive at 4 to 5+ years</td>
<td>2: AIDS (1 at 5 years, 1 at 2 years)</td>
<td>1: cerebral haemorrhage</td>
</tr>
<tr>
<td>Bowen et al. 1988 (USA)</td>
<td>Kidney</td>
<td>1</td>
<td>15+ months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kumar et al. 1987 (USA)</td>
<td>Kidney</td>
<td>1</td>
<td>308+ days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L Age-Stehr et al. 1985 (Germany)</td>
<td>Kidney</td>
<td>5</td>
<td>5/5 alive at 12 - 23 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prompt C et al. 1985 (Brazil)</td>
<td>Kidney</td>
<td>2</td>
<td>25 and 32 months</td>
<td>1: AIDS (miliary TB)</td>
<td>1: sepsis</td>
</tr>
<tr>
<td>Hanley JP et al. 1996 (UK)</td>
<td>Liver</td>
<td>1</td>
<td>13+ months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Source</td>
<td>Organ</td>
<td>No. of Patients</td>
<td>Patient survival</td>
<td>Deaths due to HIV/AIDS</td>
<td>Deaths due to other causes</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-------</td>
<td>-----------------</td>
<td>------------------</td>
<td>------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>McCarthy M et al. 1996 (UK)</td>
<td>Liver</td>
<td>1</td>
<td>6+ months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bouscarat F et al. 1994 (France)</td>
<td>Liver</td>
<td>11</td>
<td>4 alive at 81, 94, 100, and 102 months</td>
<td>3: AIDS: at 2, 5, 35 months</td>
<td>4: 2 rejech at 29, 55 mo; 1 HCV recurred; 1 superinfec'n hepatitis delta</td>
</tr>
<tr>
<td>Jacobson SK et al. 1991 (UK)</td>
<td>Liver</td>
<td>1</td>
<td>8+ years (AIDS-free)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tzakis et al. 1990 (USA)</td>
<td>Liver</td>
<td>15</td>
<td>7/15 (47%) alive at 4.5 yrs; 1 yr survival identical to non-HIV; 5 yrs HIV+ = 53%, HIV- = 63%</td>
<td>4 AIDS: CMV; PCP; immunoblastic sarcoma; pneumonitis of unknown cause</td>
<td>4: hepatic artery thrombosis; hepatic artery aneurysm; colchicine toxicity; pre-existing CNS disease</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>126</td>
<td></td>
<td>27 AIDS deaths</td>
<td>27 deaths from other causes</td>
</tr>
</tbody>
</table>
HIV and organ transplants post-HAART (1997- today )

Background

By the early 1990s, an array of new drugs allowed physicians to treat many AIDS-related illnesses. Despite the availability of several anti-HIV drugs, however, none was able to control the virus itself for more than a few months. Even a combination of two antiretrovirals is ineffective after a year or so, as the highly mutable virus quickly became resistant to the drugs. Thus, people with AIDS could receive effective treatment for specific illnesses, but their overall health continued to decline as HIV multiplied uncontrollably within their bodies.

The prognosis for HIV-positive individuals changed in July, 1996, with the announcement of a startling break-through in HIV treatment. Researchers at the International AIDS Conference held that year in Vancouver reported that the use of a three-drug combination of anti-HIV drugs could reduce the amount of virus in blood to undetectable levels for more than a year. Furthermore, as viral replication was controlled, the health of the study patients improved: their immune systems started to recover, they gained weight, felt more energetic, and chronic conditions (such as persistent Candida or herpes simplex infections) resolved.

The triple-drug combination was dubbed Highly Active Antiretroviral Therapy (HAART) and it became widely available in Canada in 1997. In the years since its arrival, HAART has demonstrated conclusive benefit in significantly improved survival and health-related quality of life. HAART is so effective that many researchers and treating physicians now consider HIV infection a chronic, manageable condition.

Increasingly, HIV-associated nephropathy, co-infection with hepatitis viruses, and liver damage and coronary artery disease secondary to antiretroviral therapy are contributing to the morbidity and mortality of people whose HIV is controlled with effective treatment. HIV-associated nephropathy (HIVAN) is a form of kidney disease that can progress within months to kidney failure. In the USA, it is estimated that 10% of patients infected with HIV will develop HIVAN and progress to end-stage renal disease (ESRD), requiring dialysis or transplantation. HIV-positive individuals who are co-infected with hepatitis B or C viruses experience a more rapid development of serious liver damage, and end-stage disease may occur within 20 years of infection. As of December, 1999, an estimated 11,194 Canadians, of whom 25% live in Ontario, were co-infected with HIV and Hepatitis C. A small but significant number of these co-infected individuals are hemophiliacs, infected through contaminated blood products in the early 1980s, who are now experiencing liver failure. Finally, the drugs that so effectively control HIV have potentially dangerous metabolic side effects that can cause serious liver damage or coronary artery disease.

Growing numbers of HIV-positive persons are developing end-stage organ disease and are dying from organ failure rather than from AIDS-related conditions. The number of HIV-positive Canadians who could potentially benefit from a transplant is unknown; furthermore, transplantation, a standard treatment for organ failure, is denied HIV-positive individuals.
Transplant trials

Following a series of reports describing organ transplantation in half a dozen HIV-positive patients in the early post-HAART era (Fung 2000, Schvarcz 2000, Schliefer 2000), two multi-centre "proof of principle" studies of kidney and liver transplantation in HIV-positive persons have been undertaken in the USA, and a proposed study is under review for several sites in Canada. The results of these studies, along with data from European transplant centres, should help to answer the following concerns around the safety and efficacy of the procedures:

1) what effect do organ transplantation and post-transplant immune suppression have on HIV disease progression and markers of immune function and activity?

2) what effect does HIV infection have on graft function and survival?

3) what are the pharmacokinetic drug interactions between HAART and immunosuppressive agents?

The entry criteria for the American studies are fairly conservative, selecting candidates who meet the criteria for transplantation and who are least likely to be harmed by the procedure (i.e., patients with relatively preserved CD4+ T cell counts, complete viral suppression, and no history of opportunistic infections). This cautious approach is necessitated in part by the reluctance of third-party medical insurance to cover the costs associated with transplantation. Despite legal challenges, HMOs and other third-party payers insist the that organ transplants in HIV-positive persons are experimental procedures and therefore are not covered. The universal health care coverage available in Canada and Europe should allow transplant centres to proceed to treat a broader population, including patients whose end-stage organ failure does not permit them to take antiretroviral medication or those who had an opportunistic infection years earlier.

Given the scarcity of donor organs, the designers of the US study considered using marginal or high-risk organs (i.e., from donors at increased risk of having pre-seroconversion HIV, HBV, or HCV infection). However, since the use of marginal organs might skew the results, they are not used by protocol, and study participants are evaluated and placed on waiting lists in the same way as other patients. Nonetheless, at some study sites, study participants have the option to accept high-risk organs to gain earlier access to transplantation. (Roland 2003)

Preliminary results

The preliminary, short-term results from these post-HAART transplants are optimistic and thus far the answers to the three main questions posed by the studies are positive. One-year survival rates equal to those in the general transplant population. None of the small number of deaths reported have been attributed to HIV/AIDS. Our review of the published literature revealed 76 post-HAART transplants in HIV-positive individuals, of whom 65 (85%) survived at least one year. Of the 11 deaths in this group, five were from severe, recurrent hepatitis C; two from graft failure; one from a CNS disease of unknown origin; one from complications following gastric
surgery unrelated to the transplant; one from a pulmonary embolism; and one from non-compliance with medication.

The post-transplant infectious complications in HIV-positive patients appear to be similar to those seen in HIV-negative patients. A review of 14 patients transplanted at the University of Pittsburgh since 1997 found that 10 had developed major bacterial infections, eight had at least one instance of CMV viremia but only two had symptomatic disease, and one patient had a probable invasive fungal infection. None of the infections could be specifically attributed to underlying HIV infection. There were four deaths in this group, two of which were directly attributed to infection (bacterial peritonitis and disseminated zygomycosis). (Kwak 2003)

Post-transplant immune suppression including cyclosporine does not seem to have an adverse effect on the immune systems of HIV-positive transplant recipients, at least in the first year after surgery. Cell samples from nine recipients at the University of California at San Francisco were analysed before and at multiple time points after surgery. There were no changes seen in immune activation phenotypes, response to antigen stimulation, or in CD8+ T cell-mediated HIV suppression. Only a transient decrease in activated CD4+ T cells was observed. (Roland 2003)
### Table 2. Summary of Post-HAART (1997 - today) Solid Organ Transplantation & HIV

<table>
<thead>
<tr>
<th>Source</th>
<th>Organ</th>
<th>No. of Patients</th>
<th>Patient survival</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calabrese et al. 2003 (USA)</td>
<td>Heart</td>
<td>1</td>
<td>2+ years</td>
<td>patient had multiple AIDS diagnoses</td>
</tr>
<tr>
<td>Toso C et al. 2003 (Switz)</td>
<td>Kidney-pancreas</td>
<td>1</td>
<td>2+ years</td>
<td>Long-term HIV non-progressor remains off HAART x 2 yrs</td>
</tr>
<tr>
<td>Neff et al. 2003 (USA)</td>
<td>Liver</td>
<td>16</td>
<td>15/16 (90%) at 1 year</td>
<td>1 pt died on day 12; 2nd pt died day 570 due to non-compliance</td>
</tr>
<tr>
<td>Vennarecci et al. 2003 (Italy)</td>
<td>Liver</td>
<td>1</td>
<td>7+ months</td>
<td>patient remains off HAART</td>
</tr>
<tr>
<td>Vittecoq et al. 2003 (France)</td>
<td>Liver</td>
<td>7</td>
<td>6/7 alive at average 14 months</td>
<td>1 patient died at 3 months from severe recurrent HCV; 3 pts received a domino graft; 2 living-related donor; 1 cadaveric</td>
</tr>
<tr>
<td>Nowak et al. 2003 (Sweden)</td>
<td>Liver</td>
<td>4</td>
<td>3/4 alive at 9+, 14+, 36+ mos</td>
<td>1 patient died at 3 mo of CNS disease not considered rel'd to HIV</td>
</tr>
<tr>
<td>Halkic et al. 2002 (Switz)</td>
<td>Liver</td>
<td>1</td>
<td>7+ months</td>
<td>pre-op CD4 = 18, VL=350,000</td>
</tr>
<tr>
<td>Sugawara et al. 2002 (Japan)</td>
<td>Liver</td>
<td>1</td>
<td>18+ months</td>
<td>living donor</td>
</tr>
<tr>
<td>Gow PJ et al. 2001 (UK)</td>
<td>Liver</td>
<td>1</td>
<td>12+ months</td>
<td></td>
</tr>
<tr>
<td>Prachalasia AA et al. 2001 (UK),</td>
<td>Liver</td>
<td>5</td>
<td>2 pts with HBV alive at 4 &amp; 34 mo</td>
<td>all HCV pts died of recurrent HCV at 6, 15, 25 months; none on effective HAART</td>
</tr>
<tr>
<td>Source</td>
<td>Organ</td>
<td>No. of Patients</td>
<td>Patient survival</td>
<td>Notes</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------</td>
<td>----------------</td>
<td>------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Roland et al. 2002 (USA)</td>
<td>Liver</td>
<td>4</td>
<td>12+ months</td>
<td>1 HCV, 2 x HBV, 1 HAV; HCV pt re-transplanted, died at 64 wks recurrent HCV</td>
</tr>
<tr>
<td>Tolan DJM et al. 2001 (UK)</td>
<td>Liver</td>
<td>1</td>
<td>223 days</td>
<td>persistent cholestasis, pt refused 2nd transplant</td>
</tr>
<tr>
<td>Schleifer K et al. 2000 (Germany)</td>
<td>Liver</td>
<td>1</td>
<td>27+ months</td>
<td></td>
</tr>
<tr>
<td>Ragni M. et al. 1999 (USA)</td>
<td>Liver</td>
<td>1</td>
<td>18+ months</td>
<td></td>
</tr>
<tr>
<td>Kumar A et al. 2002 (USA)</td>
<td>Kidney</td>
<td>20</td>
<td>18+ months</td>
<td>3 deaths: 1 from pulmonary embolism on day 3; 1 from bleeding post-gastric surgery in month 3; 1 from severe, uncontrolled chest infection</td>
</tr>
<tr>
<td>Stock P et al. 2002 (USA)</td>
<td>Kidney</td>
<td>10</td>
<td>12+ months</td>
<td>4 living donors, 6 cadaveric; 4/6 kidneys from high risk donors</td>
</tr>
<tr>
<td>Kobryn A et al. 2002 South Africa</td>
<td>Kidney</td>
<td>1</td>
<td>235+ days</td>
<td>patient infected by living donor</td>
</tr>
</tbody>
</table>
Ethical issues

The current restriction against organ transplantation for HIV-positive patients is based on two *a priori* assumptions: a high morbidity and mortality rate in persons with HIV infection, and the immune suppression required to sustain a transplanted organ has an adverse effect on disease progression, possibly resulting in earlier death. Thus the harms of transplantation would outweigh the benefits, violating the ethical principle to do no harm. As well, scarce, much needed organs would be wasted.

These assumptions date from the first decade of the HIV/AIDS pandemic, before HIV infection became what many physicians and researchers now believe is a chronic manageable illness. Variations in reports and the low number of transplants in HIV-positive patients preclude a systematic comparison with the outcomes of HIV-negative transplant recipients. However, evidence of successful transplants indicates that assumptions supporting exclusion of HIV-positive patients from a potentially life-saving treatment are no longer valid and must be reconsidered in keeping with ethical principles of respect for human dignity, fairness, equal opportunity and justice.

This means that HIV-positive patients should be considered for transplant in the same way as other patients, on the basis of medical need and explicit, justifiable, clinical criteria. Discrimination based on potential for increased complications or lower survival rates has already been rejected in organ transplant patients with Hepatitis C and diabetes, as well as in women, older patients, and patients of Asian or African heritage, who also suffer greater complications.

Concern has been raised about potential harm to health care workers from puncture wounds or cuts during surgery. Infection of health care workers from HIV and other infectious disease is a serious issue. However, the prompt use of antiretroviral prophylaxis following injury reduces the risk of HIV-infection. As with the provision of all hospital services, there is a legal and ethical responsibility to reduce risk by ensuring universal precautions are followed and the safest possible practice for patients and providers.
Conclusion

In the past twenty years, enormous changes have been brought about in the areas of both organ transplantation and HIV/AIDS.

Prior to 1983, organ transplantation was largely an experimental form of salvage treatment for end-stage organ disease. Survival rates were dismal, with only about 30% of liver transplant recipients surviving one year after surgery. The development of new drugs to control rejection and infection, innovations in organ preservation and surgical techniques, and an improved understanding of patient risk factors affecting prognosis have led to the acceptance of transplantation as a standard treatment for organ failure. Advances in other areas of medicine has meant that patients with co-existing medical conditions or poor risk factors (such as hepatitis B or diabetes or older age) that would have previously made them ineligible for transplantation are now considered candidates for surgery. Today, organ transplantation is a standard means of extending meaningful life for thousands of people.

During the same period, HIV was isolated as the cause of the acquired immune deficiency syndrome, antibody tests to identify HIV infection were developed, a range of medications to treat AIDS-related illnesses became available, and at least 20 different drugs specifically designed to control HIV are marketed in Canada. The benefit of these advances is clearly seen in marked improvements in survival and health-related quality of life.

With the improved life expectancy of HIV-infected patients in the era of HAART, and the positive results of recent transplants, there is no ethical nor medical justification to withhold organs from patients whose HIV disease is well controlled. Given the potential of transplantation to extend life, the failure to offer organs to medically appropriate HIV-positive patients could violate their right to universal and reasonable access to comprehensive quality care, reduce trust between patients and providers, and effectively constitute patient abandonment.

Lifting the restriction on organ transplantation in HIV-positive patients will present many challenges to health-care professionals and community support agencies. The existing multidisciplinary transplants teams that already include transplant surgeons, nurses, and coordinators along with hepatologists, cardiologists, nephrologists, or respirologists will have to include HIV specialists and pharmacologists. Community support agencies addressing the needs of both HIV-positive and transplant patients must receive support for staff and volunteer education and training. The excellent short-term results of the post-HAART experience in transplantation and HIV will form the basis for continued success, as long as there is a dedicated effort to optimize and integrate clinical and community care.
Recommendations

1. The Minister of Health and Long-Term Care publicly endorse the principle that HIV-positive individuals, including persons co-infected with hepatitis B or C, who meet eligibility criteria and for whom there are effective antiretroviral options available for treatment following surgery, must be considered viable candidates for organ transplantation.

2. The Minister of Health and Long-Term Care promote awareness of the need to prevent end-stage organ disease in HIV-positive patients and support training to that end among primary care providers, specialist physicians, and community support agencies.

3. The Minister of Health and Long-Term Care promote awareness of the need for early diagnosis of those patients at risk for end-stage organ disease among primary care and specialist physicians treating HIV-positive patients.

4. The Minister of Health and Long-Term Care initiate and facilitate communication between researchers and practitioners working in the areas of HIV and transplantation. A small Working Group, comprised of appropriate experts, should be convened within 6 months of receipt of this report, to investigate the most suitable means of enhancing communication, whether through annual professional meetings (such as the Canadian Association for HIV Research, Canadian Association for Studies of the Liver, Canadian Transplant Society, etc) or continuing medical education opportunities.

5. The Minister of Health and Long-Term Care initiate and facilitate communication and education between groups supporting both HIV-positive and transplant patients. A small Working Group, comprised of appropriate representatives, should be convened within six months of receipt of this report, to investigate the most suitable means of enhancing communication, education, and support for HIV-positive transplant recipients, including reciprocal staff and volunteer training.

6. The Ontario HIV Treatment Network (OHTN) undertake a survey, of contributing physicians in order to ascertain the potential need among HIV-positive individuals for organ transplantation over the next five years.

7. The Ministry of Health and Long-Term Care provide funds to support a registry to track the short- and long-term outcomes of all HIV-positive patients assessed for organ transplantation in Ontario, including patients assessed by not listed, patients listed but not transplanted, and patients who do receive transplants. Furthermore, we recommend that the Minister of Health and Long-Term Care work with his or her counterparts at the federal, provincial, and territorial levels to establish such a national, Canadian registry.
**References**


Kuo PC. Reconsideration of HIV as a contraindication to transplantation. Transplantation 2001;71(11):1689.


Premier's Advisory Board on Organ and Tissue Donation. Recommendations to increase organ and tissue donation. Available at http://www.lhsc.on.ca/transplant/recomend.htm


Spital A. Should all human immunodeficiency virus-infected patients with end-stage renal disease be excluded from transplantation?: the views of US transplant centers. Transplantation 1998;65(9):1187-1191.


**Internet Resources**

British Columbia Transplant Society: [http://www.transplant.bc.ca/](http://www.transplant.bc.ca/)

Canadian Organ Replacement Register:  
http://secure.cihi.ca/cihiweb/dispPage.jsp?cw_page=reports_corrinsites_e


Health Canada’s National Organ and Tissue Donation Information site:  

Canadian Association of Transplantation: [http://www.transplant.ca/welcomee.htm](http://www.transplant.ca/welcomee.htm)

Trillium Gift of Life Network: [http://www.giftoflife.on.ca/flash.cfm](http://www.giftoflife.on.ca/flash.cfm)

Toronto General Hospital Multi-Organ Transplant Program:  

London Health Sciences Centre Multi-Organ Transplant Program:  
[http://www.lhsc.on.ca/transplant/index.htm](http://www.lhsc.on.ca/transplant/index.htm)


Scientific Registry of Transplant Recipients [http://www.ustransplant.org](http://www.ustransplant.org)

Thomas E Starzl Transplantation Institute [http://www.sti.upmc.edu](http://www.sti.upmc.edu)
