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Supplement

GUIDELINES FOR PREVENTION OF HIV INFECTION IN ORGAN AND TISSUE TRANSPLANTATION

Health and Welfare Canada
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Canada

GUIDELINES FOR PREVENTION OF HIV INFECTION IN ORGAN AND TISSUE TRANSPLANTATION

INTRODUCTION

a) HIV Infection

Since the first cases of *Pneumocystis carinii* pneumonia (PCP) in 5 young homosexual men were reported in June of 1981, the disease now termed the acquired immunodeficiency syndrome (AIDS) has developed into an epidemic which is becoming the major public health problem of the late 20th century. Following the initial identification of homosexual men as a risk group, subsequent reports of AIDS in intravenous drug users, hemophiliacs, children of infected mothers, and heterosexual partners of individuals in other groups confirmed that AIDS was caused by a transmissible infectious agent with an epidemiologic pattern very similar to that of hepatitis B. Subsequently, a new human retrovirus, the human immunodeficiency virus (HIV), was identified as the cause of this devastating immunologic disease. The selective infection and subsequent destruction of the CD-4 "helper" lymphocytes by this virus appears to be the major contributor to the disintegration of the cell-mediated immune system in patients with AIDS. This deficiency in turn results in secondary infections and neoplasms difficult or impossible to treat effectively.

Reports of AIDS in hemophiliac patients were followed quickly by reports of the disease in individuals given blood transfusions for other reasons. This in turn pointed out the possibility of the development of AIDS in patients undergoing tissue and organ transplantation. Fortunately, the self-exclusion of blood donors at high risk for AIDS and the development of serologic tests to identify "footprints" of HIV in potential blood donors have led to screening programs that should prevent the transmission of HIV through blood or blood products. Such programs were introduced in the United States in March, 1985 and by the Canadian Red Cross in Canada in November, 1985.

Subsequent identification of HIV infection in patients undergoing transplantation of organs or tissues and in women participating in donor insemination programs has made it imperative to develop appropriate guidelines to eliminate the potential of HIV infection and AIDS in patients participating in such programs and to extend the screening programs associated with blood and blood-product donation to organ and tissue donation.

This issue was raised at a meeting of the National Advisory Committee on AIDS in March 1987, and a working group to develop guidelines for transplantation was subsequently established by the Federal Centre for AIDS in July, 1987.

The mandate of the Working Group on HIV Infection in Organ and Tissue Transplantation was to provide current information and recommendations for guidelines to ensure the least possible risk of transmitting HIV by transplantation of donated organs and tissues in Canada. Subsequently, with the agreement of the Canadian Fertility and Andrology Society, the scope of the Working Group was expanded to include examination and publication of guidelines for therapeutic donor insemination programs in Canada (Appendix I). The Working Group membership is listed in Appendix II.

b) Transplantation in Canada

Transplantation services available to Canadians are exemplary, and Canada has taken a leading role in the development of new human transplantation procedures and in the study of transplantation biology. In 1987 over 1000 transplants of perfused organs including kidney, heart, heart/lung, liver and pancreas were performed in Canada. Many Canadians with chronic organ failure, however, remain on transplant lists awaiting the availability of donated organs. A summary of the Canadian transplantation experience and current centres in Canada providing organ transplantation is given in Appendix III.

In addition to transplantation of perfused organs, almost 2000 corneal transplants were performed in 1987. Statistics for other non-perfused tissues such as bone and skin are not available except for bone marrow where 1984 figures show that 123 such transplants took place. Guidelines for bone marrow transplantation are those for blood and blood products and are not considered further in this document.

Data are not available for programs offering therapeutic donor insemination through fertility clinics or private offices, although this practice is an important component of infertility programs available in Canada. Embryo transfer and ova collection for *in vitro* fertilization (IVF) is offered only in specialized clinics. The Society of Obstetricians and Gynecologists of Canada is currently sponsoring an IVF registry which is collecting information on these pregnancies in Canada.

Human breast milk is collected and stored after freezing in several hospitals across Canada. The practices with regard to the screening of donors and the heat treatment of the milk before freezing differ in these banks.

Transplantation programs are administered at the provincial level with donor activities generally covered under variations of the Uniform Human Tissue Gift Act (as revised in 1971). This is a model act, developed by the Uniform Law Conference of Canada, which has been used by most of the provinces to prepare their own legislation. The text of this act is given in Appendix IV. Organ retrieval and transplantation programs are generally carried out consistent with the "Guidelines for Organ and Tissue Donation Services in Hospitals " and "Guidelines for Vital Organ Transplant Centres", published in 1986 by the Subcommittee on Institutional Programs, Health Services Directorate, Health Services and Promotion Branch, Department of National Health and Welfare.

c) Summary of HIV Infection and Transplantation

Reports of HIV infection and transplantation are provided in Appendix V and summarized here. It should be noted that no published reports of HIV infection acquired through transplantation or exacerbated by transplantation of either organs or tissues have been documented in Canada. In addition, it is important to distinguish between acquisition of HIV infection by transplantation and acquisition by blood or blood products received before, during or after transplantation. In the latter instance, immunosuppression by transplantation may accelerate the course of HIV infection. This experience is noted below and in Appendix V.

i) **HIV infection in kidney transplantation**[1-12]: Nineteen cases of HIV infection associated with renal transplantation have been reported. Of these cases, serologic studies suggested that 11 were related to previous or perioperative transfusion, 7 were associated with transplants obtained from high-risk donors, and 1 occurred in a homosexual male who received a kidney from a seronegative donor. Although follow-up was not reported on all patients, at least half expired of opportunistic infection or neoplasm following transplantation.

ii) **HIV infection in liver transplantation**[4,10,13]: Only one case related to liver transplantation has been documented, although 10 other patients were seropositive because of

transfusion prior to or during the transplantation procedure. The mortality related to HIV infection in liver transplantation, although poorly documented, has been approximately 50%.

iii) **HIV infection in heart, lung, and heart and lung transplantation**[10]: In the only documented case reported, the heart from the infected donor was transplanted but the recipient did not survive the operation.

iv) **HIV infection in corneal transplantation**[14-20]: Corneal tissue from HIV-infected donors has been transplanted into 4 recipients with no seroconversions.

v) **HIV infection and skin transplantation**[21]: One possible episode of the transfer of HIV through skin grafting has been reported from England.

vi) **HIV infection and bone transplantation**[22]: One case of HIV transmission resulting from a bone transplantation has been reported.

vii) **HIV infection in breast milk**[23-32]: A small number of cases of perinatal transmission of HIV have been reported following postnatal transfusion of the mother with acquisition of infection at that time.

viii) **HIV infection in bone marrow transplantation**[33-39]: Only one documented case of HIV infection by bone marrow transplantation (BMT) has been reported. All other cases in association with BMT appear to be related to transfusion of blood and blood products prior or concurrent with the transplantation procedure.

ix) **HIV infection and therapeutic donor insemination programs**[40-42]: Six cases of HIV infection transmitted by cryopreserved semen have been reported from Australia and Canada.

x) **HIV infection and other transplantation procedures**: There are no reports of HIV transmission through transplantations that occur less frequently, such as small bowel, adrenal, pancreas, and embryo transfer. One case of HIV infection has been reported in association with surrogate motherhood[43].

CURRENT PRACTICES FOR CONTROLLING TRANSMISSION OF HIV

a) Serologic Tests for HIV Infection

Several factors must be considered in examining appropriate screening tests for donors of transplanted organs and tissues. These include the sensitivity and specificity of the particular test utilized, the feasibility of performing the test within an appropriate time period between donation and transplantation, and the cost of the testing procedure.

Testing for the presence of HIV-1 antibody in serum has been greatly improved. Initial enzyme immunoassay (EIA) tests employed crude lysates of infected cells as the source of HIV antigen with subsequent identification of many "false" positives in populations at low risk of HIV infection. These reactions were primarily attributable to cross-reactions to cellular antigens from tissue cultures in which the virus was grown. Newer EIA tests are based on pure recombinant viral proteins and are as sensitive as earlier assays but have greater specificity. Currently approved EIA tests have had sensitivities of 96.5-97.8% and specificities from 99.6-100%. Because of the high sensitivities of these EIA screening tests, a number of false positive results are incurred. Individuals who are falsely reactive by EIA are not infected with HIV.

Interlot and interplate variations and "edge" and "centre" effects have been very low with these newer EIA kits compared to the earlier products. In a large prospective study of 51,000 tests performed by CDC, Atlanta, 434 were positive by single screening with 117 repeatedly positive by EIA. Of the repeat positives only 20 were confirmed as "true" positive tests indicating HIV infection by Western blot (WB) analysis. Thus, between 1 in 20 and 1 in 6 EIAs performed in a population at low risk for HIV infection would be "true" positives using WB as the "gold" standard in confirming HIV infections.

Immunofluorescence (IF) tests for HIV-1 have also been used for confirmatory purposes. However, more technical problems arise that may subvert the test results. The test is dependent on a quality supply of several materials including fixed HIV-1 infected cell cultures. These deteriorate more rapidly than WB or dot blot materials, and quality control problems are considerably greater with these reagents. The availability of pure HIV proteins from cloned HIV genes may reduce the cost of WB and dot blot confirmatory testing, suggesting that these tests may provide a more appropriate screening method for transplantation purposes than EIA and may allow transplantation of organs that would otherwise be discarded because of "false" positive EIA tests.

Currently available EIA tests for antibody to HIV provide the appropriate sensitivity and specificity for screening purposes. The screening of **recipients** for transplantation presents no time-related problems since the need for an organ or tissue transplant will have been determined sufficiently in advance to allow for screening by EIA with confirmation by IF or WB. On the other hand, time constraints may occur with **donor** screening. EIA procedures in most laboratories are "batched" to be run daily or once or twice weekly depending on demand. For transplantation purposes, surgeons require HIV status information for heart and liver donors within 4 hours of tissue removal. Currently available EIA tests can be performed within this time frame. Transplantations of kidneys as well as cornea and other non-perfused tissues do not require as rapid a turnaround for serologic tests. In practice, serologic testing should be available on a 24-hour basis for any transplantation procedure. Cost of the

test materials varies with EIA reagents and WB kits, but adds less than $40 to the overall costs per transplant. This is an insignificant amount in comparison to the overall cost of transplantation programs. Laboratories performing HIV serologic screening in support of transplant programs should attempt to determine the most sensitive and most specific serologic assays to provide information in the most rapid fashion and at minimal cost.

b) Summary of Previous Guidelines

Guidelines for donor screening in tissue and organ transplantation have been published previously in the United States. Recommendations for screening donated blood and plasma for antibody to HIV were the first to be published in 1985[44]. These guidelines suggested the use of a commercially available EIA for HIV antibody as an adjunct to donor self-exclusion in protecting the blood supply. Blood and plasma positive by EIA on initial testing would be discarded. Confidentiality and informed consent for such screening was emphasized.

These guidelines for blood products were subsequently extended to include "donors of organs, tissue and semen"[46]. Once again, donor self-exclusion was emphasized regardless of the antibody test results, and the same policies and serologic studies followed for blood donations were recommended. The statement was made that "it is recognized that the circumstance of organ procurement and the logistics of transportation may, in some instances, not permit the use of an HTLV III/LAV test. However, when feasible, such testing is prudent". These guidelines were updated in 1988[45,47] with the additional recommendation that donor screening occur **before** necessary transfusions are given and that cryopreservation be mandatory for tissue and semen for 6 months prior to use.

In Canada, while local programs have developed **ad hoc** approaches to HIV screening, no national or provincial guidelines on organ transplantation and donor and recipient screening have been produced to date.

Guidelines for screening of semen were published in the United States by the American Fertility Society[48] and updated in 1988[49]. In Canada, guidelines for therapeutic donor insemination programs have been published under the auspices of the Canadian Fertility and Andrology Society[50]. These guidelines emphasize careful donor screening and self-exclusion, if in known high-risk groups, in addition to the exclusive use of cryopreserved semen. Serologic screening for HIV is performed on the donor and the cryopreserved semen is quarantined for 6 months following the negative serologic test and only released after rescreening the donor to ensure continued seronegativity.

There are no known regulations or standards dealing with collection and storage of human breast milk; however, certain recommendations were published in 1985 by the Nutrition Committee of the Canadian Paediatric Society[51]. In addition, WHO has published guidelines on breast milk and HIV infection[52].

LEGAL AND ETHICAL CONSIDERATIONS

Because a positive HIV antibody screening test may identify an individual as belonging to a high - risk group, lead to discrimination and jeopardize employment, insurance, and other opportunities, recipient screening programs must take into consideration these consequences. Donor screening must take into account the possibility of the adverse psychological effect on surviving family members if the donor's HIV test is positive. Confidentiality of test results must be ensured and specific informed consent for HIV testing must be obtained from the donor, or in the case of cadaveric organ donations, from the person authorized by law to give consent as well as from the recipient.

Guidelines for HIV antibody testing have been published by the National Advisory Committee on AIDS(53). These guidelines generally describe the legal and ethical considerations for HIV screening of donors and recipients in organ and tissue transplantation. They also state that absolute confidentiality of results must be ensured for donor and recipient. However, where provincial law dictates nominal reporting of positive results, donors (or the person authorized by law to give consent) and recipients must be aware that such reporting will occur.

Cadaveric donors can obviously not provide consent for either transplantation or testing. In such cases, or where minor children are being considered as living donors, the person authorized by law to give consent would be informed about the testing procedure and give consent. The physician responsible for the donor's care should have access to the information, because it may be necessary to divulge positive serologic data to previous sexual contacts of the donor in order to provide appropriate counselling. The public health authorities in the province should be involved in this decision process, compliance with existing governing regulations must be made, and any existing guidelines should be honored.

While HIV antibody screening should be considered mandatory for the donor, the recipient has the right to refuse such testing. Whether lifesaving transplantation can be denied in this case is uncertain, but the recipient would have to be aware of the increased risk of severe immunodeficiency and death when a seropositive recipient is transplanted and must take immunosuppressive drug regimens. If alternative forms of treatment are available, these should always be used in circumstances of recipient refusal to undergo HIV antibody screening.

The Working Group recognizes the difficulties in obtaining informed consent for HIV antibody testing and in obtaining information about high-risk activity where intensive, personal questions need to be asked during personal bereavement. However, the protection of the recipient must be paramount even at the risk of "losing organs". Families of potential donors must have access to appropriate counselling if a potential donor is discovered to have a positive HIV test. Pre-test counselling will also have to be provided to ensure that families of potential donors are aware of the implications of the testing procedure.

GUIDELINES FOR HIV SCREENING IN TRANSPLANTATION PROGRAMS

The Working Group believes that certain measures are necessary at this time to prevent HIV infection in organ and tissue transplantation, and makes the following recommendations. Local statutes that may affect the implementation of these guidelines should be consulted.

1. Serologic screening for HIV antibodies should be required for persons volunteering for, or selected as donors of organs and tissues. These organs and tissues currently include kidneys, liver, heart, lung, pancreas, intestine, bone, bone marrow, skin, cornea, heart valves, ova, embryos, semen, and milk.

2. Screening of donors should only be undertaken with specific informed consent. Where specific informed consent for HIV antibody screening of the donor is not given, organs and tissues from this donor should not be used for transplantation. In the case of cadaveric organ donations, consent should be obtained from the person authorized by law to give consent.

3. HIV antibody screening of potential recipients of donated organs and tissues is strongly recommended, particularly when immunosuppressive regimens likely to exacerbate pre-existing HIV infection will be used. In the case of tranplantation of tissues not requiring subsequent immunosuppressive regimens, HIV antibody testing of the recipient would be unnecessary. If organ transplantation will be lifesaving and no alternative therapy exists, a positive screening test for HIV may not necessarily constitute grounds to deny transplantation. Where alternative forms of therapy are available, the presence of a positive screening test may be a factor in the decision to transplant but does not itself constitute grounds to deny a lifesaving procedure.

4. Where cryopreservation or other forms of preservation of organs or tissues is undertaken, only preserved tissues that have been quarantined for at least 6 months should be utilized. In this instance, living donors should undergo voluntary serologic testing at the time of donation and 6 months following the donation. Harvested tissues should be discarded if serologic test for HIV are positive at either the time of donation or 6 months following donation. In the instance of cryopreservation of heart valves, where repeat donor testing is not possible, the tissue must be quarantined until both EIA and WB test results are available.

5. Because of the small, but measurable possibility of transmissible HIV infection in a seronegative potential donor, organs and tissues from the following individuals should not be used in transplantation programs:

   a) Potential male donors who have had sexual activity with other men.

   b) Potential male or female donors with a history of parenteral drug abuse.

   c) Potential donors with a history of multiple blood transfusions prior to the institution of HIV antibody screening of blood (November 1985) or persons who received human coagulation products prior to 1988.

   d) Potential donors who are the sexual partners of individuals known to be HIV antibody positive or sexual partners of individuals in categories a) through c).

An additional factor to be considered in donor selection is the prevalence of HIV infection in a given population, particularly with reference to donors who have visited or resided in an endemic area. A decision regarding donor suitability because of previous residence in an endemic area requires detailed knowledge about other potential risk factors for HIV that may be present in these potential donors. Therefore, a determination of the donor suitability of potential donors in any category should be discussed with an expert in the epidemiology of HIV infection.

6. Under exceptional circumstances, where serologic testing cannot be performed and a history of risk factors for HIV infection cannot be obtained, transplantation of unscreened tissues and organs may be appropriate when lifesaving or emergency procedures are considered. Under these circumstances, the recipient or responsible guardian must be informed about the potential risk of HIV infection prior to the transplantation procedure.

7. In the case of therapeutic donor insemination (TDI), donors should be tested at donation, and the preserved semen used only after the donor is shown to be HIV antibody negative on retesting after a minimum of 6 months. Since it is not possible to evaluate the screening of donors in other countries, imported cryopreserved semen should not be used in TDI programs in Canada.

   The use of fresh semen is not recommended. However, when fresh semen is obtained from one partner or spouse for insemination in the other, both parties should be advised of the potential risk of HIV infection.

8. Any human breast milk collected for pooling and storage should be heat-treated (pasteurized) at a time and temperature combination sufficient to inactivate HIV. In addition, screening of all donors for HIV infection should be seriously considered.

9. Currently available donor cards do not provide information that would allow potential donors to discard them without a signature on the basis of high-risk activity for HIV infection. Modifications to these cards should be considered to include information on HIV risk activity similar to that provided by potential blood donors. The Working Group recommends that donor cards be modified by the responsible organizations to reflect these guidelines.

10. Consent forms for organ and tissue transplantation recipients should include a statement concerning the small risk of HIV infection for recipients even when screening programs are in place and operating properly. Patients undergoing TDI should also be informed about the small risk of HIV transmission with quarantined cryopreserved semen even when HIV antibody screening of the donor has been done.

11. Current stocks of preserved tissues to be used in transplantation such as those in semen, skin, bone and milk banks

should be discarded if they were collected after 1978 and where no serum specimens are available from the donors to confirm that the banked tissues are not contaminated with HIV. Alternatively, where possible, procedures to inactivate HIV, such as pasteurization of breast milk, should be undertaken.

12. Central registries for HIV infection associated with transplantation should be established under the auspices of the Canadian Transplantation Society. Reporting of transplantation- associated HIV infections to provincial and federal authorities should be mandatory so that ongoing evaluation of the effectiveness of these guidelines can be assessed.

THE FUTURE

Rapid serologic tests that directly detect the presence of HIV in transplantable organs will be available in the future. These tests would eliminate the need for quarantining preserved tissues and will ensure that tissues from donors who are incubating HIV infection prior to seroconversion will not be used in transplantation. An additional benefit of this biotechnical improvement would be the potential to use organs which are obtained from donors who have a "false positive" serologic screening test by current methods. These organs are currently discarded.

Medical, legal, and ethical considerations might also change if mandatory HIV testing of populations in Canada were to become more widespread in the face of the growing AIDS epidemic.

The Working Group recommends that federal and provincial authorities ensure that mandatory reporting of HIV transmission in organ and tissue transplantation be uniform across Canada. This means that federal and provincial authorities must ensure adequate surveillance of the effectiveness of the proposed guidelines. While regulations that ensure compliance by transplantation programs are not envisioned at this time, identification of "critical" incidents that reflect non-compliance may lead to regulatory action. Transplantation of perfused organs is more complex than tissue transplantation and the administrative infrastructure required to monitor activities in this area is already in place. The Working Group is particularly concerned that guidelines be uniformly applied in therapeutic donor insemination and other tissue transplantation activities which are not currently regulated activities. Tissue transplantation and donor insemination are more widely practised, even in the office setting, and Canadians must be assured that the same rigorous approach to HIV screening occurs in this setting as well as in perfused organ transplantation programs.

The growth of organ and tissue transplantation and the evolving medical, legal and ethical considerations associated with the AIDS pandemic mandate ongoing review of these guidelines.

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APPENDIX I

WORKING GROUP ON HIV INFECTION IN ORGAN AND TISSUE TRANSPLANTATION

Terms of Reference

1. To identify the main issues associated with HIV infection, organ donation, tissue transplantation and artificial insemination with donor sperm (therapeutic donor insemination - TDI).

2. To explore and assess existing guidelines and regulations relating to the issue in Canada.

3. To consult with appropriate interested parties regarding needs of donors and recipients.

4. To make recommendations regarding the development of guidelines for HIV infection, organ donation and tissue transplantation, with consideration to issues related to the international exchange of organs and tissues.

5. The Working Group will report to the Federal Centre for AIDS.

APPENDIX II

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APPENDIX III

CANADIAN VITAL ORGAN TRANSPLANT CENTRES

LOCATION	INSTITUTION	TYPE(S) OF TRANSPLANTATION
NOVA SCOTIA		
Halifax	Izaak Walton Killam Hospital	Kidney (Child)
	Victoria General Hospital	Kidney (Adult)
		Pancreas
		Liver (Adult)
		Heart
QUEBEC		
Montreal	Hôpital Maisonneuve-Rosemont	Kidney (Adult)
	Hôpital Notre-Dame	Liver (Adult)
		Heart
		Kidney (Adult)
		Kidney/Pancreas
	Hôpital Sainte-Justine	Kidney (Child)
		Liver (Child)
	Hôpital Saint-Luc	Liver (Adult)
	Institut de cardiologie de Montréal	Heart
	Montreal Children's Hospital	Liver
	Montreal General Hospital	Kidney (Adult)
	Royal Victoria Hospital	Heart
		Heart/Lung
		Kidney (Adult)
		Lung
Quebec City	Hôtel-Dieu de Québec	Kidney (Adult)
Sherbrooke	Centre hospitalier universitaire de Sherbrooke	Kidney (Adult)
ONTARIO		
Hamilton	St. Joseph's Hospital	Kidney (Adult)
Kingston	Kingston General Hospital	Kidney (Adult)
London	University Hospital	Heart
		Heart/Lung
		Kidney (Adult)
		Liver (Adult & Child)
		Pancreas
Ottawa	Children's Hospital of Eastern Ontario	Kidney (Child)
	Ottawa Civic/Ottawa Cardiac Institute	Heart
		Kidney (Adult)
	Ottawa General Hospital	Kidney (Adult)
Toronto	Hospital for Sick Children	Kidney (Child)
		Liver (Child)
	St. Michael's Hospital	Kidney (Adult)
	Toronto General	Kidney (Adult)
		Heart
		Heart/Lung
		Liver (Adult)
		Lung (Single & Double)
	Toronto Western Hospital	Heart
		Kidney (Adult)

LOCATION	INSTITUTION	TYPE(S) OF TRANSPLANTATION
MANITOBA		
Winnipeg	Health Sciences Centre	Kidney (Adult & Child)
SASKATCHEWAN		
Saskatoon	University Hospital	Kidney (Adult & Child)
ALBERTA		
Calgary	Foothills Hospital	Kidney (Adult & Child)
Edmonton	University of Alberta Hospital	Heart Heart/Lung Kidney (Adult & Child)
BRITISH COLUMBIA		
Vancouver	St. Paul's Hospital Vancouver General* B.C. Children's Hospital	Kidney (Adult) Kidney (Adult) Heart Kidney (Child)

* Plans to start lung, heart/lung and liver programs in 1989

CANADIAN HOSPITALS PERFORMING BONE MARROW TRANSPLANTS

ALBERTA		
	Cross Cancer Institute	Edmonton, Alberta
	Tom Baker Cancer Institute Foothills Hospital	Calgary, Alberta
BRITISH COLUMBIA		
	Vancouver General Hospital	Vancouver, British Columbia
ONTARIO		
	McMaster University Medical Centre	Hamilton, Ontario
	Ottawa General Hospital	Ottawa, Ontario
	Hospital for Sick Children	Toronto, Ontario
	Princess Margaret Hospital	Toronto, Ontario
QUEBEC		
	Hôpital Maisonneuve – Rosemont	Montreal, Quebec
	Montreal Children's Hospital	Montreal, Quebec
	Royal Victoria Hospital	Montreal, Quebec

APPENDIX IV

HUMAN TISSUE GIFT ACT

(Revised 1971)

Interpretation

1. In this Act,

a) "consent" means a consent given under this Act;

b) "physician" means a person (to be adopted to refer to licensing or registration under provincial Medical Act);

c) "tissue" includes an organ, but does not include any skin, bone, blood, blood constituent or other tissue that is replaceable by natural processes of repair;

d) "transplant" as a noun means the removal of tissue from a human body, whether living or dead, and its implantation in a living human body, and in its other forms it has corresponding meanings;

e) "writing for the purposes of Part II includes a will and any other testamentary instrument whether or not probate has been applied for or granted and whether or not the will or other testamentary instrument is valid.

PART I - *INTER VIVOS* GIFTS FOR TRANSPLANTS

Transplants under Act are lawful

2. A transplant from one living human body to another living human body may be done in accordance with this Act, but not otherwise.

Consent for transplant

3. (1) Any person who has attained the age of majority, is mentally competent to consent, and is able to make a free and informed decision may in a writing signed by him consent to the removal forthwith from his body of the tissue specified in the consent and its implantation in the body of another living person.

Consent for person under age, etc.

(2) Notwithstanding subsection 1, a consent given thereunder by a person who has not attained the age of majority, was not mentally competent to consent, or was not able to make a free and informed decision is valid for the purposes of this Act if the person who acted upon it had no reason to believe that the person who gave it had not attained the age of majority, was not mentally competent to consent, and was not able to make a free and informed decision, as the case may be.

Consent is full authority to proceed

(3) A consent given under this section is full authority for any physician

a) to make any examination necessary to assure medical acceptability of the tissue specified therein; and

b) to remove forthwith such tissue from the body of the person who gave the consent.

Stale consent void

(4) If for any reason the tissue specified in the consent is not removed in the circumstances to which the consent relates, the consent is void.

PART II - *POST MORTEM* GIFTS FOR TRANSPLANTS AND OTHER USES

Consent by person for use of his body after death

4. (1) Any person who has attained the age of majority may consent

a) in a writing signed by him at any time; or

b) orally in the presence of at least two witnesses during his last illness,

that his body or the part or parts thereof specified in the consent be used after his death for therapeutic purposes, medical education or scientific research.

Where donor under age

(2) Notwithstanding subsection 1, a consent given, by a person who had not attained the age of majority is valid for the purposes of this Act if the person who acted upon it had no reason to believe that the person who gave it had not attained the age of majority.

Consent is full authority, exception

(3) Upon the death of a person who has given a consent under this section, the consent is binding and is full authority for the use of the body or the removal and use of the specified part or parts for the purpose specified, except that no person shall act upon a consent given under this section if he has reason to believe that it was subsequently withdrawn.

Consent by spouse, etc., for use of body after death

5. (1) Where a person of any age who has not given a consent under section 4 dies, or in the opinion of a physician is incapable of giving a consent by reason of injury or disease and his death is imminent,

a) his spouse of any age; or

b) if none or if his spouse is not readily available, any one of his children who has attained the age of majority; or

c) if none or if none is readily available, either of his parents; or

d) if none or if neither is readily available, any one of his brothers or sisters who has attained the age of majority; or

e) if none or if none is readily available, ano other of his next of kin who has attained the age of majority; or

f) if none or if none is readily available, the person lawfully in possession of the body other than, where he died in hospital, the administrative head of the hospital,

may consent,

g) in a writing signed by the spouse, relative or other person; or

h) orally by the spouse, relative or other person in the presence of at least two witnesses; or

i) by the telegraphic, recorded telephonic, or other recorded message of the spouse, relative or other person,

to the body or the part or parts thereof specified in the consent being used after death for therapeutic purposes, medical education or scientific research.

Prohibition

(2) No person shall give a consent under this section if he has reason to believe that the person who died or whose death is imminent would have objected thereto.

Consent is full authority, exceptions

(3) Upon the death of a person in respect of whom a consent was given under this section the consent is binding and is, subject to section 6, full authority for the use of the body or for the removal and use of the specified part or parts for the purpose specified except that no person shall act on a consent given under this section if he has actual knowledge of an objection thereto by the person in respect of whom the consent was given or by a person of the same or closer relationship to the person in respect of whom the consent was given than the person who gave the consent.

Person lawfully in possession of body, exceptions

(4) In subsection 1, "person lawfully in possession of the body" does not include

a) the supervising coroner or a coroner in possession of the body for the purposes of The Coroners Act (to be adapted to provincial requirements);

b) the Public Trustee in possession of the body for the purpose of its burial under The Crown Administration of Estates Act (to be adapted to refer to provincial provisions for administration of estates by the Crown);

c) an embalmer or funeral director in possession of the body for the purpose of burial, cremation or other disposition; or

d) the superintendent of a crematorium in possession of the body for the purpose of its cremation.

Coroner's direction

6. Where in the opinion of a physician, the death of a person is imminent by reason of injury or disease and the physician has reason to believe that section ..... of The Coroners Act (to be adapted to refer to provincial provisions making the death a coroner's case) may apply when death does occur and a consent under this Part has been obtained for a post-mortem transplant of tissue from the body, a coroner having jurisdiction, notwithstanding that death has not yet occurred, may give such directions as he thinks proper respecting the removal of such tissue after the death of the person, and every such direction has the same force and effect as if it had been made after death under section ..... of The Coroners Act (to be adapted to refer to provincial provision empowering coroner to permit interference with body after death).

Determination of death

7. (1) For the purposes of a post-mortem transplant, the fact of death shall be determined by at least two physicians in accordance with accepted medical practice.

Prohibition

(2) No physician who has had any association with the proposed recipient that might influence his judgment shall take any part in the determination of the fact of death of the donor.

Idem

(3) No physician who took any part in the determination of the fact of death of the donor shall participate in any way in the transplant procedures.

Exception

(4) Nothing in this section in any way affects a physician in in the removal of eyes for cornea transplants.

Where specified use fails

8. Where a gift under this Part cannot for any reason be used for any of the purposes specified in the consent, the subject matter of the gift and the body to which it belongs shall be dealt with and disposed of as if no consent had been given.

PART III - GENERAL

Civil liability

9. No action or other proceeding for damages lies against any person for any act done in good faith and without negligence in the exercise or intended exercise of any authority conferred by this Act.

Sale, etc. of tissue prohibited

10. No person shall buy, sell or otherwise deal in, directly or indirectly, for a valuable consideration, any tissue for a transplant, or any body or part or parts thereof other than blood or a blood constituent, for therapeutic purposes, medical education or scientific research, and any such dealing is invalid as being contrary to public policy.

Disclosure of information

11. (1) Except where legally required, no person shall disclose or give to any other person any information or document whereby the identity of any person

a) who has given or refused to give a consent;

b) with respect to whom a consent has been given; or

c) into whose body tissue has been, is being or may be transplanted,

may become known publicly.

Exception

(2) Where the information or document disclosed or given pertains only to the person who disclosed or gave the information or document, subsection 1 does not apply.

Lawful dealings not affected, exception

12. Any dealing with a body or part or parts thereof that was lawful before this Act came into force shall, except as provided in this Act, continue to be lawful.

Offence

13. Every person who knowingly contravenes any provision of this Act is guilty of an offence and on summary conviction is liable to a fine of not more than $1,000 or to imprisonment for a term of not more than six months, or to both.

Application of The Coroners Act

14. Except as provided in section 6, nothing in this Act affects the operation of The Coroners Act (to be adapted to provincial requirements).

REPORTS OF HIV INFECTION AND TRANSPLANTATION

a) HIV Infection and Kidney Transplantation

For perfused organs, kidney transplantation from cadaveric or living related donors is the most commonly performed transplantation procedure in Canada, with over 800 carried out in 1987. These transplants were performed in 7 provinces led by Ontario, British Columbia and Quebec. There have been no reports to date of AIDS or HIV infection in patients receiving kidney transplants in Canada. However, several reports of transmission of HIV during transplantation in other countries have been published.

Prompt et al[1] in Brazil described immunologic abnormalities (not AIDS) and a strongly positive EIA test to HIV in a 42-year-old man who had received a cadaveric kidney from a hemophiliac donor in February, 1984. The other kidney was transplanted into a 52-year-old man who subsequently developed miliary tuberculosis and also had a positive EIA test. Both patients did not possess HIV antibodies prior to transplantation and had not received any blood transfusions before or after transplantation.

Another patient was transplanted in January 1983 at Hammersmith Hospital, London, and subsequently developed severe herpes simplex virus (HSV) infection, PCP and cytomegalovirus (CMV) retinitis[2]. This patient, however, had a positive EIA for HIV prior to transplantation and had received blood transfusions in the Los Angeles area in 1981. The patient who received the other donated kidney was seronegative, suggesting that the source of infection may have been the blood transfusions rather than the transplant. However, the severity of the opportunistic infections suffered by this individual did suggest that the immunosuppressive regimen associated with the transplant may have exacerbated a previously asymptomatic HIV infection contributing to severe immune deficiency.

Kumar et al[3] reported AIDS in a 38-year-old woman who received a living related donor transplantation from a human leucocyte antigen (HLA) identical brother in 1982. This patient developed PCP, disseminated histoplasmosis, and Kaposi's sarcoma. Stored serum samples from the recipient before transplantation were negative for HIV by EIA and WB. Transfusions associated with the transplantation were negative for HIV. P24 antibody to HIV appeared 10 days after transplantation and P42 antibody, 42 days later. The brother was homosexual and had antibody to HIV before this donor nephrectomy. The immunosuppression regimen (prednisone) may have contributed to the rapid development of the opportunistic infections 8 months after transplantation.

Shaffer et al[4] studied 151 transplant recipients in Boston, 110 of whom had received renal allografts. Four of these 110 patients had repeatedly reactive EIAs and 2 had positive WB tests. No seroconversions occurred but the 2 patients with HIV infection died with overwhelming sepsis complicated by perirectal HIV infection. The cadaveric grafts were from seronegative donors suggesting transfusion-related infection in these patients.

Kerman et al[5] studied 572 renal transplantations associated with 436 donors performed between June 1977 and March 1985 in Texas. Pre-transplantation, 5 of the recipients had positive EIAs, none confirmed by WB, and all attributed to cross-reacting antibody to the HT-9 cell line in which the antigen was produced. Post-transplantation, 20/381 cadaveric kidney recipients had positive EIAs and negative WBs. Of patients undergoing a living related donor transplantation, 4/167 had postive EIAs and 2 of these were confirmed positive by WB. One cadaveric donor was EIA and WB positive, but none of the living related donor sera were reactive. The first patient also probably acquired infection from blood transfusions associated with a complicated postoperative course (both he and the donor were seronegative pre-transplantation). The second patient also probably acquired infection through blood transfusion postoperatively. Another patient who received the second kidney from the cadaveric donor had not seroconverted at 36 months and was alive and well.

Another study, reported from one of the epicentres of the AIDS epidemic, San Francisco, examined 2550 consecutive renal transplants performed between 8 January 1964 and 15 January 1986[7]. Three of the recipients developed AIDS. The first case was a 39-year-old male homosexual who developed PCP, Kaposi's sarcoma and staphylococcal septicemia several months after transplantation in January 1984. EIAs for HIV were persistently negative. No WB analyses were performed. The donor was a 19- year-old male accident victim with no unusual medical or social history.

The second patient was a 43-year-old heterosexual female who received her first transplant in May 1980. She had received a pre-transplant transfusion in 1980 from a donor later found to be EIA positive. Seroconversion to HIV, therefore, occurred prior to a second transplantation in May 1982, suggesting that this was a transfusion-related case. The patient was first noted to be HIV seropositive after the second transplant.

The third case was a 27-year-old heterosexual male who received a living related transplant in December 1981 from his sister who did not have an unusual medical or social history. The patient received multiple transfusions before and after transplantation. He was found to be EIA positive in June 1986 and expired a month later with appendicitis and peritonitis. His course had been complicated by a non-A, non-B hepatitis, oral candidiasis and PCP. These studies in a population with a high rate of "false" positive EIA tests suffer from the absence of confirmatory serologic testing.

In West Berlin, in another study, 4 of 666 patients who had received transplants had positive HIV serology by EIA and WB[8]. These 4 patients had received kidneys from 3 donors who had a history of intravenous drug (IV) abuse. Three of the 4 patients were asymptomatic 2 years after transplantation despite continued immunsuppressive therapy with cyclosporin A. One patient has generalized lymphadenopathy. Although it is not stated, these cases were probably the same cases reported by L'Age-Stehr et al[6].

Another case of renal transplantation associated with HIV infection is of particular interest[9, 10]. A 30-year-old cadaveric donor had received 56 units of blood and blood components during an attempted resuscitation; an HIV antibody test by EIA was negative post-transfusion. Two days following these transfusions, the heart, liver and kidneys were obtained for transplantation. One blood sample accompanying the donated organs was both EIA and WB positive for HIV. Unfortunately, the organs had already been transplanted before this information was available. The donor's sera were re-examined and a specimen obtained at admission prior to transfusion was highly reactive, suggesting that the multiple transfusions had transiently diluted his serum

fusion was highly reactive, suggesting that the multiple transfusions had transiently diluted his serum resulting in a false-negative HIV antibody test. The kidney recipient seroconverted at 10 weeks in association with a brief febrile episode which occurred 8 days following transplantation. Of note is that other patients who have received transplants from HIV-positive donors have developed fevers, splenomegaly, and leukopenia attributed to acute HIV infection.

More recently, Malekzadeh et al[11] reported the first pediatric AIDS case associated with renal transplantation. An 11-year-old boy developed invasive Kaposi's sarcoma 5 years after transplantation. An HIV antibody test was positive by EIA and WB. However, he had received multiple pre-operative transfusions and the recipient of the other kidney was HIV negative and well.

Carbone et al[12] reported 2 cases of AIDS in renal transplantation. A 24-year-old female with systemic lupus erythematosis received a kidney from an HLA identical homosexual brother. Multiple opportunistic infections developed 10 months after the procedure, with death at 3 years from CMV, *Mycobacterium avium-intracellulare* and *Aspergillus* infection. She had received no transfusions and the brother was HIV positive. The second case was a 23-year-old female who received a second cadaveric renal allograft following the failure of a first. Three years later CNS toxoplasmosis as well as other opportunistic infections developed and HIV tests (EIA and WB) were retrospectively positive 3 months after the second transplant. She did receive blood during the procedure and the donor status remained unknown. Of note, is that between transplantation and death she delivered a healthy HIV antibody-negative infant following caesarian section.

b) HIV Infection and Liver Transplantation

One hundred liver transplants, 20 in children and 80 in adults, were performed in Canada in 1987. The provinces performing these transplantations were Ontario (87), Quebec (10), and Nova Scotia (3). No reports of HIV infection in liver transplant recipients have been received in Canada. Shaffer, in addition to studying renal transplantation, examined the Boston experience with 41 liver transplants in 1987[4]. Two of these 41 patients were EIA positive in 1987 and WB negative and pre-transplantation. A third patient was EIA negative and WB positive prior to transplantation, and a fourth had a seroconversion to HIV (both EIA and WB positive) post-transplantation due to a blood transfusion from a seropositive donor. This study, therefore, suggests that neither case of HIV infection was associated with the liver transplant itself. The third patient had episodes of rejection as well as oral HSV infection and CMV hepatitis. He died of overwhelming sepsis the year following transplantation. The patient who seroconverted had a complicated early course prior to receiving the contaminated transfusion. Post-transfusion the only complication to date of HIV infection has been idiopathic thrombocytopenic purpura requiring splenectomy. Both HIV infected patients had received immunosuppressive therapy with cyclosporin A and prednisone.

Nine other patients undergoing liver transplantation have been reported to be HIV positive at the time of transplantation but without symptoms attributable to HIV infection[13]. These patients had multiple septic complications although 4 were alive and well at the time of the report. In the cases associated with organs from a North Carolina donor[9], the liver was transplanted into a previously seronegative man with biliary duct sclerosis who had no other risk factors for HIV infection. Seroconversion to HIV occurred at 4 weeks without symptoms, although fever and malaise did develop 4 months later with moderate rejection of the transplant.

c) HIV Infection and Heart, Lung, and Heart and Lung Transplantation

In 1987, 150 heart, lung or heart/lung transplants were carried out in Canada. Heart and heart/lung transplants were performed in Ontario, Quebec and Alberta; lung transplants were performed in Ontario only. No reports of HIV infection in recipients of these organs have been reported in Canada. Similarly, there have been no reports from other countries of HIV infection associated with these transplantations. In the North Carolina case(9), the heart from the infected donor was transplanted but the recipient did not survive the operation.

d) HIV Infection and Tissue Transplantation

Tissue transplantation is more commonly performed throughout the world than organ transplantation which is more technically difficult and requires a greater utilization of health care resources. Data on tissue transplants are not readily available in Canada except for corneal grafts.

i) HIV infection and corneal transplantation

In Canada, corneal transplants were performed on 1,956 patients in 1987. Hospitals in all Canadian provinces carried out this procedure. No reports of AIDS in corneal transplant recipients have been documented. HIV has, however, been found in tears, aqueous humor, conjunctival epithelium, and corneal tissue of individuals known to be HIV positive[14-17]. While the use of corneal tissue from HIV-infected donors has been documented, no transmission of HIV has occurred. Schwartz[18] reported on 4 recipients of corneal tissue from 2 seropositive donors, one a 55-year-old alcoholic transient with no known HIV risk factors and the other, a 38-year-old IV drug abuser. Three years after transplantation, in December 1983, 2 patients showed no clinical evidence of HIV infection, 1 had negative serologic tests, the other refused testing. The second set of transplants were performed in January 1984 and 3 years following transplantation both patients had normal immunologic studies and negative serologic tests for HIV antibody. It is of interest that hepatitis B, with the same patterns of transmission as HIV, but far more infectious, has not been transmitted during corneal transplantation. This is in contrast to other infections such as rabies[19] and Creutzfeld-Jakob disease (CJD)[20] where transmission through corneal transplantation has clearly occurred. The neurotropic attributes of HIV, rabies virus and the CJD agent, as opposed to hepatitis B, suggests that the rich innervation of ocular tissues may play some role in enhancing transmission of these agents in comparison to hepatitis B.

ii) HIV infection and skin transplantation

No data are available on the extent of skin grafting and the availability of skin banks in the Canadian health care system. Allograft skin is often used as a dressing to reduce the risk of infection in burns, and to improve subsequent epithelialization with the recipient's own skin. With skin used as a dressing, the potential for HIV transmission does exist. Clarke has documented this potential when a skin donor was found to have antibody to HIV[21]. Thirty-nine skin donors in his group were tested. The skin was used from a positive donor prior to the serologic result being available. A "weakly positive antibody test was noticed in the recipient 37 days after exposure".

No other references to transmission of HIV infection by skin allograft have been reported. Clearly more information is needed

on skin banking procedures in Canada and patterns of donor selection and skin utilization.

iii) HIV infection and bone transplantation

No data are available about screening procedures or EIA testing for HIV in institutions supporting bone banks for use in transplantation. This highly specialized orthopedic procedure is not widely available but approximately 10 centres in Canada have established bone banks. One case of HIV infection from bone transplantation has been reported[22]. Four years after a bone allograft for progressive scoliosis, the patient developed PCP associated with HIV infection. Three weeks following the procedure, an illness had occurred consistent with a primary HIV infection. Progressive generalized lymphadenopathy had developed 2 years later. No other risk factors for HIV infection were present. The donor, a 52-year-old male who had an arthroplasty in November 1984, developed PCP associated with HIV infection in July 1986. He had previously used IV drugs but denied other risk factors. The donor's wife was also HIV seropositive.

iv) HIV infection and bone marrow transplantation

Although bone marrow is considered a tissue transplant, immunosuppressive regimens following allogeneic bone marrow transplantation (BMT) are necessary. No reports of BMT complicated by HIV infection have been reported in Canada. However, several reports from other countries have been published. Bierling et al[33] found 4 patients, in 50 studied after BMT, with antibody to LAV using IF. Two patients were alive and well at the time of the report. One patient had an illness consistent with AIDS, and another died of leukemic relapse. Donors were not traced but all patients had received multiple transfusions. Antin et al[34] reported a 19-year-old man who underwent allogeneic transplantation in April 1982 for leukemia. He had received platelets 6 months prior to transplantation from an HIV-positive donor. The patient died of presumed CNS toxoplasmosis 2 1/2 years following transplantation.

Vilmer et al[35] studied 125 donor-recipient pairs undergoing BMT in 1982. One donor from a high-risk group was HIV positive and the recipient died of CMV pneumonia 2 months following transplantation; serology to LAV was negative. Five other patients with leukemia or aplastic anemia who had received multiple transfusions were seropositive. The clinical histories were not reported although these cases may have been identified in a subsequent paper[38]. Spiers et al[36] reported another case who died from PCP 61 months after transplantation. The patient had received multiple transfusions in the past and was seropositive at death. The donor who was the patient's brother and "had not abused parenteral drugs for several years" was not tested. Atkinson reported 2 patients who received HLA identical bone marrow transplants from siblings for non-lymphocytic leukemia[37]. Both patients developed AIDS at 1 year and 18 months, respectively, following transplantation. One had received blood from a donor known to be HIV seropositive. Both patients died of severe opportunistic infection in the absence of graft vs. host disease.

Finally, Verdonck et al[39] reported a 22-year-old man who underwent a syngeneic bone marrow transplantation for acute lymphoblastic leukemia. He had received blood products from a high- risk donor at the time of BMT and had acute encephalopathy with immune thrombocytopenia 5 weeks later. He died of multiple opporunistic infections and dementia 56 months following BMT.

These reports suggest that blood and blood products are more likely to be the source of HIV infection than the marrow itself. It is not clear if the immunosuppression required after BMT accelerates the course of HIV disease.

v) HIV infection and breast milk

The rich cellular composition of human breast milk suggests that it could be classified as a tissue although it is obviously not used in transplantation. Thiry et al[23] have isolated HIV from cell-free breast milk of 3 infected mothers. Two of the 3 infants of these mothers had symptomatic HIV infection but transplacental or perinatal infection may have occurred. Ziegler[24], however, has reported 1 case of post-natal transmission of HIV from mother to child. The mother was seronegative at the time of delivery but was given an HIV-contaminated transfusion for postpartum bleeding. Subsequently, the virus was transmitted from mother to child, possibly through breast feeding. Recently, a number of case reports have been published suggesting that HIV infection in infants has occurred by breast milk transmission of the virus. In these cases, HIV-negative and/or low risk mothers were transfused postpartum with HIV-positive blood. However, the results of a study in Haiti, presented at the 4th International Conference on AIDS in Stockholm in 1988, failed to document such transmission indicating that there was a low risk of HIV infection through breast feeding[25-27].

The extent of HIV screening by milk banks, the use of pasteurization of human milk, and patterns of utilization of milk banks are not available. However, the possibility of closing human milk banks providing unpasteurized milk has been raised[28-31]. Donor screening programs must also be considered.

Informal surveys of human breast milk banking procedures in Canada show a wide variation in HIV screening and patterns of use. In the largest program in Canada, pasteurized milk is used in conjunction with HIV-antibody screening of donors. At last report, at least 1 centre was using unpasteurized breast milk from unscreened donors. One centre restricts milk obtained from mothers to their own infants.

e) HIV Infection and Therapeutic Donor Insemination Programs (TDI)

Because HIV infection is primarily transmitted through sexual activity, the possibility of transmitting HIV infection by artificial insemination has been raised. In 1985 Stewart et al reported on 4 Australian women treated with cryopreserved semen from a carrier of HIV[40]. All 4 women were found to have antibody to HIV by EIA and WB. One woman had progressive lymphadenopathy and 2 others who were asymptomatic had abnormal immunologic studies. The 3 children conceived following these inseminations were uninfected as determined by both serologic and immunologic analysis. In Canada, TDI is widely practiced using both fresh and frozen semen. Two instances of HIV infection (from 1 donor) have been reported in British Columbia[41]. Both recipients and 1 infant who was seronegative continue to be well. Semen has been the source of other sexually transmitted infections and this information has been recently reviewed[42].

The references cited in Appendix V can be found starting on page 6.