

HIV transmission by organ and tissue transplantation

Robert J. Simonds

Purpose: Published reports in English of HIV infection in organ and tissue recipients were reviewed to examine (1) the effect of donor screening, allograft type, and allograft processing on risk of HIV transmission by transplantation; (2) the antibody response to HIV infection in organ recipients taking antirejection therapy; and (3) survival following transplantation for HIV-infected organ recipients.

Data extraction: Date of transplant, timing of HIV infection in relation to transplant, type of allograft, type of antirejection therapy, duration of follow-up, time to death, and time to antigen and antibody appearance were recorded for each of 32 reports.

Results: HIV transmission associated with transplantation of kidney (n = 50), liver (n = 13), heart (n = 6), pancreas (n = 1), bone (n = 4), and skin (n = 1) has been reported. In all but 14 cases, transplantation occurred before routine donor screening for HIV antibody began. In addition, 24 cases of an organ transplant after the recipient became HIV-infected have been reported. Non-transmission of HIV from HIV-infected donors has also been reported in recipients of corneas (n = 9), bone (n = 26), other musculoskeletal tissue (n = 3), dura mater (n = 3), and kidneys (n = 2). Of 40 recipients with organ transplantation-associated infection who were tested for HIV antibody within 6 months of transplantation, 34 (85%) tested positive; only one recipient remained seronegative more than 6 months after transplantation. Estimated 1- and 5-year survival following transplantation for 61 HIV-infected kidney recipients was 90 and 50%, respectively.

Conclusions: With current screening practices, HIV transmission by transplantation is rare. The transmission risk appears lower for recipients of processed or avascular tissues. The antibody response to HIV infection in organ recipients taking immunosuppressive therapy is similar to that reported in other infected people.

AIDS 1993, 7 (suppl 2):S35-S38

Keywords: HIV infection, HIV transmission, organ transplantation, tissue transplantation, survival, HIV serodiagnosis, immunosuppression, immunosuppressive agents.

Introduction

Receipt of transplanted organs and tissues, although recognized early in the AIDS epidemic as a risk factor for HIV infection, has been implicated only infrequently in HIV transmission. This transmission mode is unique in that infection occurs in people who are exogenously immunosuppressed and frequently have other complicated medical conditions. This paper reviews published reports of HIV infection in organ and tissue recipients to address the effect of donor screening, allograft type, and allograft processing on HIV transmission risk to recipients; the

serologic response to HIV infection in organ recipients taking antirejection therapy; and survival following transplantation for HIV-infected organ recipients.

Patients and methods

Thirty-two reports of 94 cases of HIV infection in organ recipients were reviewed [1-32]. For each patient, the date of transplant, whether HIV infection was known to precede the transplant, the type

From the Division of HIV/AIDS, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia, USA.

Requests for reprints to: Dr R. J. Simonds, Centers for Disease Control and Prevention, 1600 Clifton Road, Mailstop E-45, Atlanta, GA 30333, USA.

of organ or tissue allograft received, the type of antirejection chemotherapy taken, the duration of follow-up or time to death, and the time to appearance of HIV p24 antigen and antibody in the serum of recipients were recorded. Three reports of five cases of HIV infection in tissue allograft (excluding semen, bone marrow and breast milk) recipients [29,33,34] and three reports of HIV infection-free recipients of organs or tissues from HIV-infected donors [3,8,27,29,35] were also reviewed. Analysis of time between transplantation and death was performed by the product-limit method using BMDP statistical software (Cork, Ireland). Time to death from any cause was considered uncensored; event times were censored at the time of the report if the recipient was reported to be alive. To compare survival following transplantation between HIV-infected recipients and other organ recipients, data on survival following transplantation from several large clinical series of organ transplant recipients were reviewed [36–38]; Student's t-test was used to compare the proportions of patients surviving 1 and 5 years after transplantation.

Results

HIV infection had been reported in 61 recipients of kidneys [1–6,8–22,26–32], 24 recipients of livers [3,7,23–25,28,29,31,32], eight recipients of hearts [3,4,23,29,31], one recipient of pancreas [4], four recipients of bone [29,33], and one recipient of skin [34] up to May 1993. In 24 (24%) cases (11 kidney, 11 liver, and two heart recipients), the recipient was already infected with HIV at the time of transplantation; in 75 (76%) cases (50 kidney, 13 liver, six heart, four bone, one pancreas, and one skin recipient), HIV transmission was thought to have occurred at the time of transplantation. In most of the latter cases the organ or tissue donor was determined to be already infected or at risk of HIV infection, although in some cases transmission by perioperative transfusion was suspected. Fifty-nine (63%) of the 94 infected organ recipients were treated with cyclosporine, alone or in combination with other anti-rejection medication; for the remaining recipients, antirejection chemotherapy other than cyclosporine was used ($n = 14$) or the type of antirejection therapy was not specified ($n = 21$).

The date of transplantation was reported for 67 of the 75 cases of transplantation-associated transmission; 53 (79%) occurred before antibody screening tests became available in March 1985. Of the remaining 14 cases, three were attributed to perioperative receipt of blood transfusions [3,19], one recipient was transplanted urgently with a liver before the result of the donor's positive antibody test was available [25], one received a kidney from a

living donor who seroconverted after having been screened 8 months before organ donation [22], two received organs from a donor whose serum tested falsely negative after hemodilution from transfusion of a large volume of blood [32,39], and seven received organs or tissues from a seronegative donor who was thought to have early HIV infection [29].

Lack of HIV transmission from HIV-infected donors has been reported in nine recipients of corneas [27,29,35], 25 recipients of bone processed by ethanol and lyophilization [29], one recipient of fresh-frozen bone whose marrow was removed during processing [29], three recipients of lyophilized tendons or fascia [29], three recipients of lyophilized and irradiated dura mater [29] and two recipients of kidneys [3,8]. One of the kidney recipients took cyclosporine; in the second report, the type of immunosuppression was not specified.

In 40 of the 70 cases of organ transplantation-associated transmission, the recipient was tested for HIV antibody at least once within 6 months of transplantation. Thirty-four (85%) of these recipients tested positive between 10 and 148 days after transplantation. The first positive antibody test for the remaining six recipients was between 7 and 21 months after transplantation, although none of these recipients tested negative later than 75 days after transplantation. In 15 other cases, the recipient was first tested more than 6 months after transplantation. In 14 of these cases, the recipient first tested positive 7–55 months after transplantation. In only one case, that of a liver recipient who seroconverted between 33 and 36 months after transplantation, did an infected recipient remain seronegative for more than 6 months [24].

Measurement of recipient serum p24 antigen was reported in 15 cases of HIV transmission to organ recipients [4,19,25,26,29,32]. In 14 recipients, the first appearance of antigen was between 3 and 84 days after transplantation; in the remaining recipient, no antigen was detected in a single specimen taken 30 days after transplantation [32].

One-year survival following transplantation was 90% (SEM, 4%) for the 61 infected kidney recipients and 55% (SEM, 10%) for the 24 infected liver recipients. These survival times compare with 1-year survival of 93% (SEM, 0.2%) for 29 273 kidney recipients and 74% (SEM, 0.5%) for 9810 liver recipients as reported by the United Network for Organ Sharing [36]. Five-year survival was 50% (SEM, 10%) for HIV-infected kidney recipients and 35% (SEM, 11%) for HIV-infected liver recipients. In comparison, 5-year survival was 85% for 989 kidney recipients in one series [37] and 63% for 787 liver recipients in another series [38].

One- and 5-year survival was 73 and 53%, respectively, for the 59 organ recipients who took cy-

cyclosporine, and 89 and 26% for the 14 recipients who did not.

Discussion

HIV transmission associated with transplantation has been reported only rarely. Although more than 100 000 organs and one million tissue allografts have been transplanted since 1980 in the United States alone, a review of English language reports found only 75 cases in which transplantation was implicated as the mode of transmission, either through the allograft or through perioperative transfusion. Although additional cases of transmission may have occurred that have not been published, a 1991 review of United States AIDS surveillance reports detected no further cases [29].

Three important features contribute to the risk of HIV transmission by transplantation, the effectiveness of donor screening for HIV infection, the type of allograft transplanted and allograft processing, if any, before transplantation. First, transmission to transplant recipients has become even more uncommon since routine donor screening for HIV antibody began in 1985. Since then, only one case of transmission from a screened organ or tissue donor thought to be truly seronegative at the time of transplantation has been reported [29]. Second, HIV transmission has been implicated only in transplantation of organs and highly vascular tissues (large bone, skin) whereas transmission by transplantation of the cornea, a relatively avascular tissue, has not been reported even though HIV has been isolated from corneal tissue [40]. These observations suggest that the risk of transmission may be related to the risk of exposure to infected blood through the transplanted allograft. Finally, lack of transmission from HIV-infected donors of other avascular tissues may be due in part to tissue processing, which can inactivate HIV, as reported following transplantation of tissue that has been irradiated, lyophilized or treated with ethanol, all processing methods that have been shown to inactivate HIV in plasma [41–43].

The timing of the appearance of HIV antibody in infected organ recipients taking immunosuppressive antirejection therapy is similar to that reported in other infected people [44]. This finding suggests that the serologic response to infection is not delayed in those who take immunosuppressive therapy.

Decreased survival among HIV-infected organ recipients compared with other organ recipients may reflect complex interactions between the mortality risks associated with HIV infection and underlying medical conditions, transplant surgery and immunosuppressive chemotherapy. Some reports have suggested that cyclosporine modulates the effects of

HIV infection [45,46]. Both slower progression to AIDS [47] and lower survival [48] have been reported in cyclosporine-treated transplant recipients. The findings of the present review on the effect of cyclosporine on survival are inconclusive. Other significant morbidity and mortality risks may preclude detection of the effect of cyclosporine therapy on the outcome of HIV-infected transplant recipients.

Some of these findings have implications for the prevention of HIV transmission through transplantation [49,50]. Since antibody screening does not preclude a small risk of transmission from donors with early HIV infection, screening of prospective donors for HIV risk factors is critical. The United States Public Health Service recommends that potential donors with HIV-related risk factors be excluded from donation regardless of antibody status. Additionally, the use of other screening tests that may be more sensitive in early infection, such as p24 antigen tests or polymerase chain reaction, may be considered, based on the test's positive predictive value in the donor population, its availability, its cost and the timeliness with which results can be made available. However, the usefulness of these tests in donor screening has not been determined. Second, further research is needed to determine the effectiveness of processing techniques in inactivating HIV while maintaining the functional integrity of the allograft. Finally, because HIV antibody appearance following infection is not delayed in organ recipients, recipient testing may be a feasible method of early identification of HIV transmission through transplantation, as recommended in the United States Public Health Service guidelines.

References

1. AL-SULAIMAN M, AL-KHADER AA, AL-HASANI MK, DHAR JM: Impact of HIV infection on dialysis and renal transplantation. *Transplant Proc* 1989, 21:1970–1971.
2. CARBONE LG, COHEN DJ, HARDY MA, BENVENISTY AI, SCULLY BE, APPEL GB: Determination of acquired immunodeficiency syndrome (AIDS) after renal transplantation. *Am J Kidney Dis* 1988, 11:387–392.
3. DUMMER JS, ERB S, BREINIG MK, ET AL.: Infection with human immunodeficiency virus in the Pittsburgh transplant population: a study of 583 donors and 1043 recipients, 1981–1986. *Transplantation* 1989, 47:134–140.
4. ERICE A, RHAME FS, HEUSSNER RC, DUNN DL, BALFOUR HH: Human immunodeficiency virus infection in patients with solid-organ transplants: report of five cases and review. *Rev Infect Dis* 1991, 13:537–547.
5. FEDUSKA NJ, PERKINS HA, MELZER J, ET AL.: Observations relating to the incidence of the acquired immune deficiency syndrome and other possibly associated conditions in a large population of renal transplant recipients. *Transplant Proc* 1987, 19:2161–2166.
6. HIESSE C, CHARPENTIER B, FRIES D, SIMONNEAU G, DELFRAISSY JF: Human immunodeficiency virus infection in transplant recipients [letter]. *Ann Intern Med* 1986, 105:301.
7. JACOBSON SK, CALNE RY, WREGHITT TG: Outcome of HIV infection in transplant patient on cyclosporin [letter]. *Lancet* 1991, 337:794.

8. KERMAN RH, FLECHNER SM, VAN BUREN CT, *ET AL.*: Investigation of human T-lymphotropic virus III serology in a renal transplant population. *Transplant Proc* 1987, 19:2172-2175.
9. KUMAR P, PEARSON JE, MARTIN DH, *ET AL.*: Transmission of human immunodeficiency virus by transplantation of a renal allograft, with development of the acquired immunodeficiency syndrome. *Ann Intern Med* 1987, 106:244-245.
10. L'AGE-STEHR J, SCHWARZ A, OFFERMANN G, *ET AL.*: HTLV-III infection in kidney transplant recipients [letter]. *Lancet* 1985, ii:1361-1362.
11. LANG P, BUISSON C, FOUCHER A, *ET AL.*: Unusual immune deficiency syndrome associated with LAV/HTLV III in a kidney transplant recipient. *Transplant Proc* 1986, 18:1400-1401.
12. MALEKZADEH MH, CHURCH JA, SIEGEL SE, MITCHELL WG, OPAS L, LIEBERMAN E: Human immunodeficiency virus-associated Kaposi's sarcoma in a pediatric renal transplant recipient. *Nephron* 1987, 42:62-65.
13. MARGREITER R, FUCHS D, HAUSEN A, *ET AL.*: HIV infection in renal allograft recipients [letter]. *Lancet* 1986, ii:398.
14. MILGROM M, ESQUENAZI V, FULLER L, ROTH D, KYRIAKIDES GK, MILLER J: Acquired immunodeficiency syndrome in a transplant patient. *Transplant Proc* 1985, 17:75-76.
15. NEUMAYER III, FASSBINDER W, KRESSE S, WAGNER K: Human T-lymphotropic virus III antibody screening in kidney transplant recipients and patients receiving maintenance hemodialysis. *Transplant Proc* 1987, 19:2169-2171.
16. NOVOA D, CARBALLO E, ROMERO R, ARCOCHA V, SANCHEZ-GUISANDE D: HIV infection and renal transplantation. *Nephron* 1989, 51:144-145.
17. O'CONNELL PJ, MAHONY JF, SHEIL AGR: AIDS after renal transplantation [letter]. *Med J Aust* 1985, 143:631.
18. OLIVEIRA DBG, WINEARLS CG, COHEN J, IND PW, WILLIAMS G: Severe immunosuppression in a renal transplant recipient with HTLV-III antibodies. *Transplantation* 1986, 1:260-262.
19. PEREZ G, ORTIZ-INTERIAN C, BOURGOIGNIE JJ, LEE H, DE MEDINA M, ALLAIN JP: HIV-1 and HTLV-1 infection in renal transplant recipients. *J Acquir Immune Defic Syndr* 1990, 3:35-40.
20. POLI F, SCALAMOGNA M, PIZZI C, MOZZI F, SIRCHIA G: HIV infection in cadaveric renal allograft recipients in the North Italy Transplant Program. *Transplantation* 1989, 47:724-725.
21. PROMPT CA, REIS MM, GRILLO FM, *ET AL.*: Transmission of AIDS virus at renal transplantation [letter]. *Lancet* 1985, ii:672.
22. QUARTO M, GERMINARIO C, FONTANA A, BARBUOI S: HIV transmission through kidney transplantation from a living related donor [letter]. *N Engl J Med* 1989, 320:1754.
23. RAGNI MV, BONTEMPO FA, LEWIS JH: Organ transplantation in HIV-positive patients with hemophilia [letter]. *N Engl J Med* 1990, 322:1886-1887.
24. RUBIN RH, TOLKOFF-RUBIN NE: The problem of human immunodeficiency virus (HIV) infection and transplantation. *Transpl Int* 1988, 1:36-42.
25. SAMUEL D, CASTAING D, ADAM R, *ET AL.*: Fatal acute HIV infection with aplastic anemia, transmitted by liver graft [letter]. *Lancet* 1988, i:1221-1222.
26. SCHIRM J, DRENTJH J, VAN DEN AKKER R, *ET AL.*: Rapid HIV seroconversion after kidney transplantation. *Serodiag Immunother Infec Dis* 1988, 2:91-93.
27. SCHWARZ A, HOFFMANN F, L'AGE-STEHR J, TEGZESS AM, OFFERMANN G: Human immunodeficiency virus transmission by organ donation: outcome in cornea and kidney recipients. *Transplantation* 1987, 44:21-24.
28. SHAFFER D, PEARL RH, JENKINS RL, *ET AL.*: HTLV-III/LAV infection in kidney and liver transplantation. *Transplant Proc* 1987, 19:2176-2178.
29. SIMONDS RJ, HOLMBERG SD, HURWITZ RL, *ET AL.*: Transmission of human immunodeficiency virus type 1 from a seronegative organ and tissue donor. *N Engl J Med* 1992, 326:726-732.
30. TEIXIDO J, ARGELAGUES E, CARALPS A, *ET AL.*: Anti-HTLV-III antibodies in dialyzed or transplanted patients in Spain [letter]. *Nephron* 1987, 46:325-326.
31. TZAKIS AG, COOPER MH, DUMMER JS, RAGNI M, WARD JW, STARZL TE: Transplantation in HIV+ patients. *Transplantation* 1990, 49:354-358.
32. WARD JW, SCHABLE C, DICKINSON GM, *ET AL.*: Acute human immunodeficiency virus infection: antigen detection and seroconversion in immunosuppressed patients. *Transplantation* 1989, 47:722-724.
33. CENTERS FOR DISEASE CONTROL: Transmission of HIV through bone transplantation: case report and public health recommendations. *MMWR* 1988, 37:597-599.
34. CLARKE JA: HIV transmission and skin grafts [letter]. *Lancet* 1987, i:983.
35. PEPOSE JS, MACRAE S, QUINN TC, WARD JW: Serologic markers after the transplantation of corneas from donors infected with human immunodeficiency virus. *Am J Ophthalmol* 1987, 103:798-801.
36. UNITED NETWORK FOR ORGAN SHARING: *OPTN 1991 Annual Report*. Richmond, Virginia: United Network for Organ Sharing; 1992.
37. NORMAN DJ, BENNETT WM, WEIZSTEON PJ, *ET AL.*: Outcome of renal transplantation at Oregon Health Sciences University: 1982 to 1990. In *Clinical Transplants 1991*. Edited by Terasaki PI, Cecka JM. Los Angeles: UCLA Tissue Typing Laboratory; 1991:153-158.
38. GORDON RD, FUNG J, TZAKIS AG, *ET AL.*: Liver transplantation at the University of Pittsburgh, 1984-1990. In *Clinical Transplants 1991*. Edited by Terasaki PI, Cecka JM. Los Angeles: UCLA Tissue Typing Laboratory; 1991:105-118.
39. CENTERS FOR DISEASE CONTROL: Human immunodeficiency virus infection transmitted from an organ donor screened for HIV antibody: North Carolina. *MMWR* 1987, 36:306-308.
40. SALAHUDDIN SZ, PALESTINE AG, HECK E, *ET AL.*: Isolation of the human T-cell leukemia/lymphotropic virus type III from the cornea. *Am J Ophthalmol* 1986, 101:149-152.
41. HILFENHAUS JW, GREGENSEN JP, MEHDI S, VOLK R: Inactivation of HIV-1 and HIV-2 by various manufacturing procedures for human plasma proteins. *Cancer Detect Prev* 1990, 14:369-375.
42. KITCHEN AD, MANN GF, HARRISON JF, ZUCKERMAN AJ: Effect of gamma irradiation on the human immunodeficiency virus and human coagulation proteins. *Vox Sang* 1989, 56:223-229.
43. WELLS MA, WITTEK AE, EPSTEIN JS, *ET AL.*: Inactivation and partition of human T-cell lymphotropic virus, type III, during ethanol fractionation of plasma. *Transfusion* 1986, 26:210-213.
44. HORSBURGH CR, OU CY, JASON J, *ET AL.*: Duration of human immunodeficiency virus infection before detection of antibody. *Lancet* 1989, ii:637-640.
45. KLATZMANN D, LAPORTE JP, ACHOUR A, *ET AL.*: Cyclosporine A treatment for human immunodeficiency virus-infected transplant recipients. *Transplant Proc* 1987, 19:1828.
46. ANDRIEU JM, EVEN P, VENET A, *ET AL.*: Effects of cyclosporin on T-cell subsets in human immunodeficiency virus disease. *Clin Immunol Immunopathol* 1988, 46:181-198.
47. SCHWARZ A, OFFERMANN G, KELLER F, *ET AL.*: The effect of cyclosporine on the progression of human immunodeficiency virus type 1 infection transmitted by transplantation: data on four cases and review of the literature. *Transplantation* 1993, 55:95-103.
48. LANG P, NIAUDET P, AND THE GROUPE COOPERATIF DE TRANSPLANTATION DE L'ILE DE FRANCE: Update and outcome of renal transplant patients with human immunodeficiency virus. *Transplant Proc* 1991, 23:1352-1353.
49. USPHS: Availability of draft USPHS guidelines for prevention of transmission of HIV through transplantation of human tissue and organs. *Fed Reg* 1993, 58:14402.
50. SIMONDS RJ, ROGERS MF: USPHS guidelines for prevention of transmission of HIV through transplantation of human tissues and organs. *J Transplant Coordination* in press.