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INFECTION WITH HUMAN IMMUNODEFICIENCY VIRUS IN THE PITTSBURGH TRANSPLANT POPULATION¹:

A Study of 583 Donors and 1043 Recipients, 1981–1986

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Abstract

We performed a retrospective serologic survey of 583 organ donors and 1043 transplant recipients for antibodies to human immunodeficiency virus type 1 (HIV-1). Two (0.34%) of the 583 donors and 18 (1.7%) of the 1043 recipients had HIV-1 antibodies by enzyme immunoassay and by Western blot. Two of 5 seropositive recipients tested also had blood cultures positive for HIV-1. Seven (0.7%) of the 1043 transplant recipients had antibodies to HIV-1 before transplantation; 2 of these had hemophilia A, and 5 had previous transfusions. Eleven (1.3%) of 860 recipients followed for 45 days or more seroconverted to HIV-1 a mean of 96 days after transplantation. Likely sources of HIV-1 infection for 3 of these 11 recipients included a seropositive organ donor in 1 patient and high-risk blood donors in 2 patients. A definite source of HIV-1 infection was not found for the other 8 recipients, 3 of whom seroconverted to HIV-1 after institution of blood donor screening for HIV-1 antibodies. Seroconversion to HIV-1 was less common in kidney recipients than in liver, heart, or multiple-organ recipients ($P < 0.02$). Nine (50%) of the 18 HIV-1 seropositive transplant recipients died a mean of 6 months after transplant surgery, and 9 (50%) are still alive a mean of 43 months after transplantation. AIDS-like illnesses occurred in 3 of the dead and 1 of the living patients and included pneumocystis pneumonia (3 cases), miliary tuberculosis (1 case), and recurrent cytomegalovirus infection (1 case). These data suggest that the course of HIV-1 infection is not more severe in transplant recipients receiving cyclosporine than in other hosts and that, despite screening of blood and organ donors, a small number of transplant recipients will become infected with HIV-1.

The most important routes of transmission of the human immunodeficiency virus type 1 (HIV-1) are through sexual activity, transfusion of blood products, and transplacental passage of the virus from an infected mother to her child (1,2). It is clear that exposure of transplant recipients to blood and blood products places them at risk for HIV-1 infection. In addition, donated organs may also transmit HIV-1 infection as was recently reported by the Centers for Disease Control (CDC)* for a patient who received a liver transplant in Pittsburgh (3).

The pharmacologic immunosuppression used in transplant recipients predisposes them to many of the same opportunistic infections and tumors that afflict patients with the acquired immunodeficiency syndrome (4–6). Also, altered in vitro in dices of immune function similar

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* Abbreviations: CDC, Centers for Disease Control; RATG, rabbit antithymocyte globulin.

to those seen in patients with HIV-1 infection may be seen in allograft recipients (7,8). Thus, the clinical diagnosis of AIDS may be difficult in the transplant setting.

In order to establish the extent of infection and disease from HIV-1 in the transplant population and to assess the risk of acquiring infection from donated organs and donated blood, it is necessary to study a sizable population on whom adequate data are available. These data should include serum samples from donors, multiple serum samples from recipients both before and after transplantation, and clinical follow-up of adequate duration to determine whether any HIV-1-associated disease occurs in the population. This study of 583 organ donors and 1043 organ recipients was undertaken to meet these needs.

MATERIALS AND METHODS

All patients underwent transplantation either at Presbyterian University Hospital or Children's Hospital of Pittsburgh, except for 2, who received liver transplants at Baylor University Medical Center in Dallas, Texas, but who were later cared for in Pittsburgh. The transplant recipients were immunosuppressed primarily with cyclosporine and prednisone; the actual doses varied between transplant groups and over the time period studied. Before the introduction of cyclosporine monitoring, the cyclosporine dosage was generally tapered from an initial dose of 17.5 mg/kg at surgery in accordance with clinical criteria such as the presence of rejection or the development of nephrotoxicity (9). Since mid-1983 cyclosporine dosage has been determined by targeting the dosage required to maintain a blood level of about 800–1000 ng/ml (Sandoz, RIA). Most patients were also treated with daily doses of prednisone tapered to between 10 and 20 mg by 2–3 months after surgery. Some patients also received either rabbit antithymocyte globulin (RATG) or OKT3 mouse monoclonal antibodies either for prophylaxis or therapy of rejection.

Since 1981 a serum bank has been maintained on transplant recipients and donors for use in the clinical investigation of herpesvirus infections associated with transplantation. Sera or plasma collected between February 13, 1981 and April 30, 1986 and stored in this serum bank were tested. All available serum samples from adult donors and the last available serum or plasma sample from both adult and pediatric recipients who survived more than 75 days after transplantation were screened. These included sera from 583 adult donors and 1043 transplant recipients, representing 42% of the 1394 donors acquired by the local donor procurement office and 61 % of the 1701 recipients given organs during the time period studied. Sera were tested for antibody to HIV-1 by enzyme immunoassay using a commercial kit (LAV-EIA; Genetic Systems, Seattle, WA). Positive samples were retested in duplicate by EIA. Repeat positives by EIA were confirmed by the Western blot method (Immunoblot; Biorad, Richmond, CA) using a scoring system based on the presence and density of bands corresponding to the molecular weight of HIV-1 proteins, p18, p24, p32, gp41–43, p55, p65, gp120 (10,11). A negative band was assigned a score of 0, a weakly reactive band 1, a moderately reactive band 2, a strongly reactive band 3, and a very strongly reactive band 4. A summed score of ≥ 3 was defined as a positive immunoblot, a score of 2 as equivocal and a score of ≤ 1 as a negative immunoblot. Selected specimens were also tested by a Western blot procedure in a commercial laboratory (Biotech Research Laboratories, Rockville, MD). A transplant recipient was considered to have HIV-1 antibodies if the EIA and either of the Western blot tests were positive on a serum sample, and if these antibodies, once detected, were persistently found in subsequent serum samples. In addition to the sera screened, the following sera were also tested for HIV-1 antibodies: (1) multiple, including pretransplant, sera from recipients positive on EIA screening; and (2) the last available serum from any recipient who had received an organ from an EIA or Western blot positive donor or who had received an organ from a donor who had donated organs to another recipient who became HIV-1 positive after transplantation.

HIV-1 isolation was performed by a modification of the method of Levy (12,13). Briefly, 8×10^6 mononuclear lymphocytes from a patient were cocultivated in 10 ml of RPMI medium containing 20% fetal bovine serum and 10% interleukin 2 with 3×10^6 phytohemagglutinin-stimulated cells from a normal donor. Thereafter, 3×10^6 mitogen-stimulated normal cells were added to the culture twice a week for a period of 4 weeks. Culture fluids were harvested every 4 days and tested for the presence of HIV-1 by the antigen capture assay (Cellular Products; Buffalo, NY).

Demographic and clinical data were collected on the seropositive recipients and included age at transplantation, sex, type of organ transplant, number of transfusions during the admission for transplant surgery, the use of additional RATG or OKT3, survival, and the occurrence of infections or tumors. T-helper and T-suppressor cell counts or ratios were noted when available. Since many patients were dead at the time of the study and others no longer resided near Pittsburgh, membership in a high-risk group for HIV-1 infection could often only be evaluated from medical records. An "AIDS-like illness" in a transplant recipient was defined as any opportunistic infection or tumor that fulfilled the CDC criteria for AIDS with the exception of invasive candida infections, which are common in liver transplant recipients. Seropositive donors were evaluated for age, sex, mode of death, known membership in a high-risk group for HIV-1 infection, and the number of transfusions received before organ donation.

Proportions were analyzed by a two-tailed Fisher's exact test. A *P*-value of ≤ 0.05 was considered significant.

RESULTS

Population studied

Characteristics of the recipient population are shown in Table 1. Of the 1043 recipients, 868 (83%) were adults. Of the 175 pediatric recipients, 144 (82%) received liver transplants. Recipient sera included samples from 171 heart recipients, 292 liver recipients, 550 kidney recipients, and 30 multiple-organ recipients of whom the majority were heart-lung recipients. The duration of serologic follow-up ranged from 0 to 1775 days. However, 860 (82%) of the 1043 transplant recipients had greater than 45 days of serologic follow-up (mean = 352 days) and represented 51 % of the total transplant population during the study period.

An important issue in this study was the route of transmission of the virus. Testing of blood products for HIV-1 antibodies was introduced at our central blood bank on March 31, 1985. The sera collected and studied included sera from 640 organ recipients who underwent transplantation before 3/31/85 and sera from 403 organ recipients who underwent transplantation after 3/31/85. Ninety-three percent (592/640) of the patients who received organs before this date, but only 67% (268/403) of the patients who received organs after this date, had more than 45 days of follow-up ($P < 0.001$).

Pretransplant HIV-1 positive recipients

Seven (0.7%) of 1043 patients had positive EIA and Western blot tests for HIV-1 before transplantation (Table 2); all remained positive for HIV-1 antibodies after transplantation. Two of the 7 patients were hemophiliacs, and the other 5 were not recognized as belonging to any high-risk group but had received transfusions prior to nationwide blood screening, generally at other centers, before transplant surgery. None had an illness associated with HIV-1 infection at the time of transplantation.

The prevalence of pretransplant HIV-1 positivity in recipients less than 18 years of age, 2.3% (4/175), was significantly higher than in adults (0.3%, 3/868 $P < 0.05$). Two positive pediatric liver transplant recipients were less than 3 years of age (Table 2). Serum was not available

from the mother of patient 5, but serum obtained from the natural mother of patient 2 was negative for HIV-1 antibodies. Patient 5 was positive for HIV antibodies at 5½ months old when she was evaluated for transplantation. She had received numerous blood transfusions since birth. It was unlikely that her HIV-1 antibody positivity was due to passive transfer of maternal antibodies since the last serum available from her was still positive 5 months after transplantation and 10 months after birth.

Three of the 7 recipients who were HIV-1 positive prior to transplantation died at 4, 6, and 9 months after transplantation. Four others are living and well at 26, 38, 43, and 46 months after transplantation, although 1 (patient 3; Table 2) has lost his transplanted kidney and is not receiving immunosuppression. Of the 3 patients who died, only 1 (patient 7; Table 2) developed an AIDS-like illness. This was a previously reported 48-year-old hemophiliac who received a liver transplant for cirrhosis secondary to chronic active hepatitis (14). At the time of transplantation, he had a T-helper/T-suppression ratio of 0.3. Ten weeks after transplantation, he developed pneumocystis pneumonia that responded slowly to treatment with sulfamethoxazole/trimethoprim and then pentamidine. He subsequently developed renal failure, hepatic artery thrombosis, ascending cholangitis, candida pyelonephritis, and terminal pneumonia due to *Pseudomonas aeruginosa*. The other deaths were due to probable drug toxicity (patient 1) and pulmonary aspiration (patient 5).

Posttransplant HIV-1 positive recipients

Eleven transplant recipients who were initially seronegative for HIV-1 developed HIV-1 antibody after transplantation (Table 3). Seven had 1 or more subsequent sera positive for HIV-1 antibodies, and 4 were positive for HIV-1 antibodies only on the last available serum. The mean time $\pm$ SD of seroconversion after transplantation, computed as the 1st day a postoperative sample was positive by EIA and/or Western blot, was 96 ± 49 days after transplantation. Only the organ donor of patient 4 (Table 3) was positive for HIV-1 antibodies. The other 10 recipients had 15 separate organ donors, including 3 recipients with 2 donors and 1 recipient with 3 donors. Sera from 11 of these 15 donors were negative for antibodies by EIA; sera were not available from the other 4 donors. All seroconverters received blood transfusions at the time of transplantation, and most also received transfusions after transplantation but prior to seroconversion. Two patients (patients 5 and 6; Table 3) were discovered to have received blood from a high-risk donor by the local blood bank's "look-back" program. Three other recipients (patients 9, 10, and 11; Table 3), however, received organ transplants after local screening of blood products for HIV-1 antibodies went into effect. Sera from the organ donors of patients 10 and 11 were negative for HIV-1 antibodies. Donor serum was not available from patient 9 for her 1st transplantation at another center. She was later brought to Pittsburgh for evaluation and retransplantation. The first HIV-1 positive sample from her was taken 1 day *before* her retransplant surgery and showed antibodies against multiple HIV-1 antigens on Western blot. Patient 10 was a 2-year-old boy who received 206 blood units during his hospital admission for transplantation. He developed a positive EIA 87 days after transplantation and 15 days later both a positive EIA and Western blot (p24, p55, gp120). Patient 11 received several units of blood in another hospital in the year preceding transplantation. He then received 3 blood units at the time of transplantation and also 20 units between 4 and 5 months after transplantation. He developed a positive EIA to HIV-1 145 days after transplantation and had both a positive EIA and Western blot (p24, p55) 2 weeks later.

Rates of seroconversion possibly due to blood were calculated for patients who did not have a positive organ donor, who were not seropositive for HIV-1 before transplantation, and who had at least 45 days of follow-up. The overall rate of seroconversion was 10/852 or 1.2%. This included 3 (2.3%) of 129 children and 7 (1.0%) of 723 adults ($P=NS$). The seroconversion rates in the different transplant populations were 0.2% (1/436) for kidney recipients, 1.8%

(3/162) for heart recipients, and 2.6% (6/228) for liver recipients. The rate of seroconversion observed in kidney recipients (0.2%) is significantly less than the rate of seroconversion (2.2%, 9/416) in all other recipients ($P<0.02$) and is consistent with their exposure to fewer blood products at transplantation. However, the rate of seroconversion in patients who underwent transplantation before screening of blood donors for HIV-1 antibodies was 1.2% (7/585) and did not differ significantly from the rate of 1.1% (3/267) in patients who underwent transplantation after screening of blood donors.

Six of the 11 transplant recipients who seroconverted to HIV-1 died at 4, 4, 5, 5, 6, and 14 months after transplantation, and 5 are still living at 40, 42, 45, 51, and 56 months after transplantation. Three of the 11 patients have had illnesses possibly associated with HIV-1 infection, and they are described below.

A 42-year-old heart transplant recipient (patient 1; Table 3) did well after transplantation except that he developed moderate rejection that required treatment with steroids and ATG. He seroconverted to HIV-1 49 days after transplantation but did not become ill at that time. Eleven months after transplantation he developed chronic fatigue, and 2 months later he developed listeria meningitis and subsequently fatal pneumocystis pneumonia. Focal involvement of his heart with toxoplasmosis was also found at autopsy.

Patient 7 (Table 3), a 32-year-old liver recipient, had a brief febrile illness 2 weeks after surgery for which no cause was found. She became HIV-1 positive 47 days after transplantation but was clinically well until 3 years after her transplant surgery when she developed recurrent episodes of esophagitis due to herpes simplex virus and cytomegalovirus.

Patient 11 (Table 3) was a 38-year-old man who developed pneumocystis pneumonia 3 months after renal transplantation. One month later he returned to the hospital with new diffuse chest infiltrates initially thought to be due to recurrent pneumocystis infection but later diagnosed as miliary tuberculosis on open lung biopsy. It is interesting that his seroconversion to HIV-1 positivity at 145 days after transplantation postdated these 2 opportunistic infections. He died of sepsis 6 months after transplantation.

Four patients in this series died without evidence of illnesses associated with HIV-1 infection. Two (patients 4 and 8; Table 3) died of rejection shortly after heart transplantation. The other deaths were in liver recipients. A 47-year-old woman with primary biliary cirrhosis (patient 9; Table 3) developed rejection requiring OKT3 therapy after hepatic transplantation and also had stenosis of the hepatic artery with an associated bacterial liver abscess. She eventually required retransplantation, and she died 1 day later of technical complications of surgery. The other (patient 10; Table 3) was a 2-year-old boy with biliary atresia whose postoperative course was complicated by severe rejection, thrombosis of the hepatic artery with an associated biliary leak, disseminated candida infection, and respiratory distress syndrome. Postmortem 4 months after transplantation disclosed thrombosis of the hepatic artery, multiple bile-stained intraperitoneal abscesses, and pseudomonas pneumonia.

EIA-positive but Western-blot negative recipients

Five recipients not reported above each had only a single serum positive by EIA but negative by Western blot. Three patients died shortly after the date of the positive EIA sample, and 2 are still living, but follow-up sera are not available.

Patients with transient appearance of HIV-1 antibodies

Three patients who had positive Western blot tests are not listed in Tables 2 or 3 because later serum samples did not contain HIV-1 antibodies. In 1 case a likely explanation for the transient appearance of HIV-1 antibodies was found. This patient underwent liver transplantation for

chronic active hepatitis and cirrhosis secondary to hepatitis-B infection. A pretransplant serum sample was negative for HIV-1 antibodies. A serum sample taken 22 days after transplantation was positive for HIV-1 antibodies by EIA and Western blot on multiple lanes, but a subsequent sample, taken 318 days after transplantation, was negative. He had received massive quantities (300 001) of hepatitis-B immune globulin in the peritransplant period as part of an experimental protocol to protect his hepatic allograft against reinfection with hepatitis-B virus. The transient appearance of HIV-1 antibody was felt to be due to passive transfusions of antibody as has been previously described (15).

In the other 2 patients the source of the transient Western blot positivity was not apparent. A man who received a heart transplant was HIV-1 seronegative before transplantation. Serum samples taken 16 and 37 days after transplantation were positive for HIV-1 antibodies by EIA; the 37-day sample was also positive for antibodies to p24 and p55 on Western blot testing. Two subsequent samples obtained 135 and 275 days after transplantation were negative. The other patient was a 3-year-old boy who had a single serum taken 113 days after liver transplantation that was positive by Western blot (p18, p24, p55, p65) but negative for EIA. The serum was tested by Western blot because the EIA result was in the high negative range. A sample taken 28 days later was negative by both EIA and Western blot. The patient died of multiple bacterial infections 165 days after transplantation. Both patients had received organ transplants after institution of HIV-1 blood screening, and a review of their records did not reveal any plausible source of passively transfused antibodies.

Donors positive for HIV-1

Two (0.34%) of 583 donors were found to be positive for HIV-1 antibodies. One donor was a single 28-year-old man who died of head injuries from a motor vehicle accident; the other donor was a 32-year-old married man who committed suicide. Neither donor received blood products before organ harvesting, and neither was known to be a member of a high-risk group for HIV-1 infection. One patient in our cohort received a heart from the 1st donor and seroconverted to HIV-1 44 days after transplantation. This donor also donated kidneys to 2 recipients at another hospital, but information on their HIV-1 status is not available. Two patients received kidneys from the other donor; neither had HIV-1 antibodies detectable on their last available serum samples obtained 32 and 945 days after transplant surgery.

Western blot patterns and viral cultures

All 20 individuals (18 recipients and 2 donors) identified as HIV-1 positive by Western blot in this study had antibodies against at least 2 of the major proteins of HIV-1. One donor and 1 recipient (patient 11; Table 3) had antibodies only against p24 and p55 on a single serum sample. All other 18 individuals had antibodies against p24 and at least 2 other HIV-1 antigens, including gp41–43 and/or gp120, on 1 or more sera. HIV-1 viral cultures were performed on 5 of the surviving HIV-1 seropositive patients, and 2 were positive (patients 3 and 6; Table 3).

Clinical outcomes

Nine (50%) of the 18 patients who had HIV-1 infection either before or after transplantation (Tables 2 and 3) are still living a mean of 43 months after transplantation; 9 died a mean of 6 months after transplant surgery. Three of the dead and 1 of the living patients have had AIDS-like illnesses as described above.

Infections with herpesviruses, particularly cytomegalovirus, are primarily reported as complications of AIDS (16). Only 1 of the 18 patients reported here had a documented tissue invasive cytomegalovirus infection (patient 7, Table 3). Three others had febrile CMV syndromes in the early posttransplant period, which resolved. It is possible that some febrile syndromes were missed because of the retrospective nature of the study. No patient had a

disseminated herpes simplex or herpes zoster infection or a lymphoproliferative syndrome either related or unrelated to Epstein-Barr virus infection.

Seven of the 18 HIV-1 infected patients received either antithymocyte globulin or OKT3 for the treatment or prophylaxis of rejection, and 6 (86%) died during the follow-up period. By contrast, only 3 (27%) of 11 patients who did not get RATG or OKT3 died ($P=0.05$). Three (75%) of the 4 patients with AIDS-like illnesses received OKT3 or ATG compared with 4 (29%) of 14 patients without AIDS-like illnesses ($P=NS$).

The largest organ subgroup of HIV-1 seropositive patients in this series consists of 11 liver transplant recipients, of whom 6 (55%) are still alive a mean of 42 months (range, 26–51 months) after transplantation. The duration of HIV-1 infection is known for the 6 who were seroconverters and is equivalent to the interval of follow-up after transplantation. The duration of HIV-1 infection for the 5 patients who were seropositive for HIV-1 before transplantation is unknown but is at least as long as the follow-up after transplantation. It is clear from these data that the combination of HIV-1 infection and cyclosporine and prednisone immunosuppression is compatible with years of survival in a substantial subgroup of transplant recipients.

DISCUSSION

A number of studies report HIV-1 infection in smaller cohorts of transplant recipients and discuss the role of donor transmission (17–24). This present study represents the largest investigation of HIV-1 infection in kidney, liver, heart, and multiple organ transplant recipients and donors to date. It is apparent that transplanted organs may transmit HIV-1 infection much like transfused blood products. In a report from Berlin, West Germany, 5 kidney allograft recipients who received organs from 3 intravenous drug users seroconverted to HIV-1 shortly after transplantation (19). Although HIV-1 serologies were not available on the donors, the transmission of the virus infection for 4 recipients of 2 pairs of kidneys makes the organs a likely source. A few other cases of apparent transmission via the donor organ have been reported in recipients of kidneys from a hemophiliac and a male homosexual (18, 21). Recently, an organ donor whose test for HIV-1 antibodies became negative after multiple blood transfusions was found to transmit the infection to both a liver and a kidney recipient (3). The liver recipient received his transplant at this center after the conclusion of this study. In our survey of 583 donors, 2 (0.34%) were found to be positive for HIV-1 antibodies. This is quite similar to the 0.38% rate reported by Kerman in Houston kidney donors but much higher than the rate of 0.04% reported in blood donors (17,25). Although we documented 1 transmission of HIV-1 by a donated heart, lack of adequate follow-up and the small number of cases precluded a full evaluation of the risk of transmission of HIV-1 infection by organ donation. However, because donated organs may transmit HIV-1 infection, all organ donors should be tested for HIV-1 antibodies, and their organs not used for transplantation if the screening test is positive. Testing should ideally be initiated early in the donor assessment process and performed on a serum sample taken before blood transfusion (3).

There is some evidence that immunosuppressed persons may handle HIV-1 infection poorly. Anderson et al. studied 10 cancer patients who had received transfusions from a single HIV-1 positive donor. Nine of the 10 seroconverted, and 6 of these 9 developed ARC or AIDS-like illnesses a mean of 286 days after infusion of the contaminated blood products (26). Other cases of fatal disease consistent with AIDS have been described in HIV-1 infected transplant recipients (18,20,22,23). In male homosexual, drug-abuser, and hemophiliac populations, it has been found that 8–34 % of individuals develop AIDS in a 3-year interval after detection of a positive antibody test (27). Using a mathematical model, Liu has estimated a mean incubation period for transfusion-related AIDS of 4.5 years (28). Our experience suggests that

at least half of trans plant recipients with HIV-1 infection may survive in good health for 3–4 years after transplantation even with cyclosporine immunosuppression. The 11 liver transplant recipients, who formed the largest subgroup, had an overall survival of 55% with a mean of 3½ years of follow-up in surviving patients. This compares favorably with an actuarial survival of 64% 3 years and 62% at 4 years in all liver transplant recipients on cyclosporine at this center from 1980 to 1987.³

Four patients had illnesses that fulfilled the CDC criteria for AIDS. In 2 cases the only AIDS-like illness was pneumocystis pneumonia, a not-infrequent complication in organ transplant recipients without HIV-1 infection (29). Another patient developed pneumocystis pneumonia and miliary tuberculosis, but both illnesses occurred before seroconversion to HIV-1. Conversely, several patients in this series had invasive candidiasis or severe bacterial infections but were not judged to have an AIDS-like illness, as these infections are common in transplant recipients (9,30). Notably absent in the series are cases of Kaposi's sarcoma, cryptosporidiosis, and disseminated *Mycobacterium-avium-intracellulare* infection, which are rare in transplant recipients but common in patients with AIDS (31,32).

These data suggest that it is premature to make HIV-1 infection an absolute contraindication to life-saving transplant procedures such as heart or liver transplantation on the presumptive basis of a poor outcome. The data available on outcomes in HIV-1 infected kidney-transplant recipients are limited, but it may be advisable to defer renal transplantation (and other nonlifesaving types of transplantation) in HIV-1 infected individuals until more information related to the outcome is available. Even the performance of heart and liver transplantation in infected individuals should be undertaken only after careful evaluation. In particular, the presence of AIDS (and possibly AIDS-related complex) in a transplant candidate should be a contraindication to transplantation at the present time since it is a sign of established immunosuppression, and would likely entail a high risk of serious infection in the early posttransplant period.

An interesting finding in the study was the significantly poorer outcome in transplant recipients who had HIV-1 infection and received either ATG or OKT3 treatment for rejection. Although most of the deaths in the group who received these anti-T-cell globulins for rejection did not appear to be directly related to HIV-1 infection, this finding suggests that careful consideration be given before administering these treatments to transplant recipients with HIV-1 infection. The timing of HIV-1 seroconversion in the recipients infected after transplantation is similar to or slightly longer than the incubation period in well-studied cases of primary HIV-1 infection (18,33,34). This suggests that these infections were probably transmitted around the time of transplantation or shortly thereafter. Although the source of infection was apparent only for 2 patients who were hemophiliacs and 3 patients who either received organs from seropositive organ donors or blood from high-risk blood donors, it is likely that most if not all of the other patients acquired their infection from blood products. This is suggested by the significantly lower rate of HIV-1 infection in kidney recipients who receive smaller quantities of blood than do heart and liver recipients. Furthermore, none of the the seroconverters were known to belong to a high-risk group for HIV-1 infection.

Seven patients in the study had positive HIV-1 antibodies before transplantation. Although the hemophiliac patients were known to have HIV-1 antibodies before transplantation, the presence of the infection was not suspected in the other patients. The prevalence of HIV-1 seropositivity before transplantation was higher in patients who are less than 18 years of age than in adults. This finding might indicate a greater susceptibility of children to infection with

³Starzl TE, Iwatsuki S, Esquivel CO, et al. Experience in 1000 liver transplantations. Presented at the International Organ Transplant Forum honoring Thoma Starzl, Pittsburgh, PA, September 8–11, 1987.

HIV-1 but might also only be due to a greater exposure of patients with liver disease, who make up the majority of the pediatric population, to infected blood products. We could not document a significant reduction in HIV-1 seroconversions in patients who underwent transplantation after the institution of routine blood screening for HIV-1 antibodies. Three patients seroconverted after blood screening was instituted, and 2 of the 3 also had organ donors with negative HIV-1 antibody tests. The source of HIV-1 infection in these 3 patients is not known. In the 2-year-old child, however, a false negative blood test on 1 of his many blood donors seems most likely. Such false negative tests have been described (35), and although they are thought to be uncommon their actual frequency is unknown.

A major issue in this study is whether the positive serologic tests reported here indicate true HIV-1 infection. Transplant recipients are exposed to foreign antigens from organ donation, blood transfusion, and exogenous infections, any of which might result in the formation of crossreacting antibodies. The detection of 3 patients with transiently positive Western blot tests shows the difficulties inherent in studying such a population and suggests that caution should be exercised in interpreting isolated positive serologies for HIV-1 in transplant recipients. However, 14 of the 18 HIV-1 positive recipients had more than 1 positive Western blot result. Few false positive Western blots have been described except for those with an isolated p24 band or occasionally for those with isolated p24 and p55 bands (11,36). Since most of our Western blots were repeatedly positive at multiple bands, it is likely that they indicate true infection. Another indication that we are not dealing with false positives is the isolation of the virus from the blood of 2 of 5 samples from surviving patients.

It is possible that cyclosporine may have modified the course of these patients' HIV-1 infection in some way. One group of researchers has reported that cyclosporine prevents both the binding of HIV-1 to T cells and viral replication in T cells in vitro (37). These results need to be confirmed, but immunologic surveillance of infected patients who are receiving cyclosporine may provide insight into this possibility.

Current screening procedures for blood and organ donors should reduce the number of new HIV-1 infections in organ transplant recipients. Nonetheless, we detected 3 HIV-1 seroconversions that occurred despite screening of blood products, and thus it is likely that occasional HIV-1 infections will continue to occur after transplantation. Increasing numbers of HIV-1 infected patients are also likely to present as candidates for transplantation. Only systematic screening and follow-up of transplant candidates and recipients for HIV-1 infection will allow the careful prospective evaluation that is necessary to formulate rational decisions regarding their transplantability and long-term management.

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Table 1

Transplant recipients studied for HIV infection

Transplant type	Any follow-up		>45 Days follow-up	
	≥18 ^a	<18 ^a	≥18 ^a	<18 ^a
Heart	165	6	171	163
Renal	529	21	550	420
Liver	148	144	292	119
Mult. organ	26	4	30	25
Total	868	175	1043	727
				133
				860

^a Age of recipient (years).

Table 2

Transplant recipients who were positive for HIV antibodies before transplantation^a

Patient	Organ type	Age/sex	DOT	Risk factor	ATG/OKT3	F/U (months)	Vital status	AIDS-like illness ^b
1.	Liver	42/F	11/82	Trans	No	6	Dead	No
2.	Liver	3/F	7/83	Trans	No	46	Alive	No
3.	Renal	13/M	10/83	Trans	No	43	Alive	No
4.	Renal	29/F	3/84	Trans	No	38	Alive	No
5.	Liver	0.5/F	2/85	Trans	Yes	9	Dead	No
6.	Liver	15/M	3/85	Hemoph	No	26	Alive	No
7.	Liver	48/M	10/85	Hemoph	Yes	4	Dead	PCP

^aDOT: date of transplant (month/year); ATG: antithymocyte globulin; OKT3: OKT3 mouse monoclonal antibodies; F/U: follow-up; PCP: *Pneumocystis carinii* pneumonia; Trans: blood transfusions; Hemoph: hemophilia A.

^bThese patients had illnesses, with the exception of candida infections, that fulfilled the CDC criteria for the acquired immunodeficiency syndrome.

Table 3

Transplant recipients who seroconverted to HIV after transplantation^a

Patient	Age/sex	Organ type	DOT	Time of conversion ^b	Blood (units) ^c	ATG/OKT3	F/U (months)	Vital status	AIDS-like illness
1.	42/M	H	8/82	43–49	56	Yes	14	Dead	PCP, listeria, toxoplasmosis
2.	34/M	H	9/82	75–189	130	No	56	Alive	None
3.	43/F	L	2/83	55–90	143	No	51	Alive	None
4.	53/M	H	2/83	28–44	67	No	4	Dead	None
5.	5/M	L	8/83	14–103	16	Yes	45	Alive	None
6.	3/M	L	11/83	90–105	414	No	42	Alive	None
7.	32/F	L	1/84	19–47	72	No	40	Alive	Recurrent CMV
8.	45/M	H	2/84	24–46	34	No	5	Dead	None
9.	47/F	L	6/85	0–148	299	Yes	5	Dead	None
10.	2/M	L	9/85	74–87	206	Yes	4	Dead	None
11.	38/M	R	4/86	135–145	3	Yes	6	Dead	PCP/TB

^aH: heart; L: liver; R: renal; CMV: cytomegalovirus infection; TB: tuberculosis; for other abbreviations are Table 2.

^bDay after transplantation of last negative serology—day of first positive serology).

^cIncludes total units of red blood cells, fresh frozen plasma, platelets, and cryoprecipitate during admission for transplantation.