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TRANSPLANTATION

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TRANSPLANTATION IN HIV+ PATIENTS[1,2]

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Twenty-five whole-organ recipients treated from 1981 through September 1988 were HIV carriers. Eleven were infected before transplantation, although this was not known until later in 8 recipients. The other 14 were infected perioperatively. Ten of the 25 recipients were infants or children. The organs transplanted were the liver (n = 15), and the heart or kidney (n = 5, each). After a mean follow-up of 2.75 years (range, 0.7–6.6 years), 13 recipients are alive. Survival is 7/15, 2/5, and 4/5 of the liver, heart, and kidney recipients, respectively. The best results were in the pediatric group (70% survival) in which only 1 of 10 patients died of AIDS. In contrast, AIDS caused the death of 5 of 15 adult recipients and was the leading cause of death. Transplantation plus immunosuppression appeared to shorten the AIDS-free time in HIV+ patients as compared to nontransplant hemophiliac and transfusion control groups. Accrual of HIV+ transplant recipients has slowed markedly since the systematic screening of donors, recipients, and blood products was begun in 1985.

Human immunodeficiency virus has been a subject of concern in transplantation (*1, 2*) since the infection became a known clinical entity. It was anticipated that transplant patients would be at high risk of HIV infection because of their exposure to blood, blood components, and other sources of HIV infection. However, the extent of the problem was not known until demographic studies were performed by Dummer et al. (*3*) who examined the stored and current sera of 1043 patients treated with organ transplantation at the University of Pittsburgh from 1981 to 1986. They found that 1.7% of the recipients were either HIV+ at the time of transplantation or seroconverted soon after. Pediatric patients had an unusually high risk (2.3%). Similar disquieting statistics have been reported from single centers (*4, 5*) and from multiinstitutional collaborations (*6–8*).

Although this was not the intention, a clinical experiment was created by the presence of this pool of HIV+ transplant recipients, many of whom now have lived for years under posttransplant immunosuppression. The records of these patients were studied with particular emphasis to their clinical course, long-term survival, and current status.

MATERIALS AND METHODS

Transplantation patients. Of 3023 transplant recipients treated at the University of Pittsburgh between January 1, 1981 and September 5, 1988, 25 were found to be HIV+ and are included in this report. Eighteen of these patients were found to be positive in a look-back epidemiologic study performed at our center (*3*). The other 7 have been diagnosed since this study was completed. Two of the 17 male patients had a history of sexual contact with other men.

Two groups of HIV+ transplant recipients were identified: those who were HIV+ at the time of transplantation (prevalent group) and those who seroconverted to HIV after transplantation (seroconverter group). HIV+ patients were those whose sera were positive for antibody to HIV-1 by enzyme immunoassay (LAV-EIA; Genetic Systems, Seattle, WA) and confirmed by Western blot (Immunoblot; Biorad, Richmond, CA). The serologic findings in all HIV+ patients have been confirmed with multiple testing. Universal HIV testing of all blood and tissue donors has been implemented in Pittsburgh since March 1985. Screening for HIV of recipients as a condition for candidacy has been routine since the summer of 1985.

Patients were defined as having AIDS if they met the Centers for Disease Control[8] (CDC)* criteria for AIDS (*9*). All AIDS defining complications were attributed to HIV alone even though these same infections occur frequently after transplantation without AIDS (*10*).

All patients received CsA and prednisone as maintenance immunosuppression. Polyclonal antilymphocyte globulin (Stanford ALG) was used for heart recipients. Monoclonal OKT3 was used for kidney and liver recipients after November 1984 (*11*). Azathioprine was given to 13 of the 25 patients. Bactrim and Acyclovir prophylaxis has been used since mid-1987, but only 2 new HIV+ patients were accrued subsequently.

Information regarding the type of immunosuppressive therapy received, the incidence and type of rejection, other complications, long-term survival and current condition, graft function, social status, and general health was also collected. Graft failure in the case of kidney recipients was defined by the need to return to dialysis. In the case of liver and heart transplant recipients, all surviving patients had normal graft function, obviating the need for further categorization of transplant results.

Control groups. Two HIV+ control groups of age-matched nonimmunosuppressed patients with known seroconversion dates were obtained. The first control group consisted of 28 hemophiliac patients cared for (*12*) at the Hemophilia Center of Western Pennsylvania.[9] The second consisted of 42 patients collected at the CDC who were known to have been accidentally infected by a blood transfusion (*13*).

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* Abbreviation: CDC, Centers for Disease Control.

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We also compared the survival of our HIV+ transplant recipients to that of 1303 consecutive liver recipients treated between January 1, 1980 and September 5, 1988 (*14*).

Statistical methods. Seroconversion dates for the transfusion and transplantation HIV seroconverter groups were taken as the day of transfusion or transplantation. Seroconversion dates for the hemophiliac group were estimated as the midpoint between last negative and first positive serum samples. All follow-ups were to March 1, 1989. Patients who did not develop AIDS but died, contributed AIDS-free time until their death. Similarly, patients who eventually developed lethal AIDS complications contributed variable amounts of AIDS-free time before the onset of these complications.

Statistical analysis utilized BMDP Statistical Software to generate Kaplan-Meier product-time estimations for both survival and AIDS-free time. The Breslow generalized Wilcoxon test was used for inferences of statistical significance.

RESULTS

Of the 25 HIV+ transplant recipients, 11 were prevalent, and 14 were seroconverters. Seventeen were male, and 8 were female. Three patients underwent transplantation despite their known HIV+ status. Their treatment reflected an institutional policy of not allowing HIV+ status as a sole factor to rule out organ-transplant candidacy.

Survival

Of the 25 patients, 13 (52%) are alive (Tables 1 and 2). Survival is the same in males (53%) as in females (50%).

Survival by organ. Seven (47%) of the 15 liver recipients are alive as well as 4 (80%) of 5 kidney recipients, and 2 (40%) of 5 heart recipients. Mean follow-up in the liver survivors is 4.5± 2.1 SD years (range, ⅔–6.5). Mean follow-up in the kidney survivors is 3.4±2.2 SD years (range, 1.0–5.0). The 2 heart recipients have lived for 6.6 and 2.2 years. Because the majority of the HIV+ transplant patients were liver transplant recipients, the survival of the HIV patients was compared to the overall liver transplant (n = 1303) survival in our CsA experience of 1980–1988 (Fig. 1). Survival was practically identical at 1 year. Subsequent survival at 2, 4, and 5 years was lower in the HIV+ group although it never reached statistical significance. Five-year survival was 63% in the reference population compared to 53% in the HIV+ group.

Prevalent HIV+ versus seroconverters. The survival was not different in the seroconverter and prevalent transplantation groups (Fig. 2) at any point up to and including 5 years after transplantation ($P = 0.69$).

The 11 patients who were HIV+ at the time of transplantation (7 livers, 3 kidneys, 1 heart) are listed individually in Table 1. Six (54%) of these patients are alive after a mean 3.3±2.3 (SD) years (range, 0.7–5.7). All 5 of the deaths were of liver recipients, and 3 of them were AIDS related (Table 1).

Seven (50%) of the 14 patients who seroconverted to HIV+ after transplantation are alive (Table 2) after 4.8±1.8 (SD) years (range, 2.1–6.6) including 5 of 8 liver recipients, 1 of 2 kidney recipients, and 1 of 4 heart recipients. One of the surviving liver recipients received a graft from an HIV+ donor and seroconverted between 30 and 80 days after transplantation (*15*). This patient is alive 2.6 years after transplantation. Ten months ago, he developed a rectal carcinoma that was considered a complication of his preexisting ulcerative colitis. He was treated with total protocolectomy and is well. Of the 7 deaths, 3 were AIDS related with 1 example each among the liver, kidney, and heart recipients (Table 2).

Pediatric versus adult. The 10 children had a mean age of 7.8±6.2 (SD) years at the time of liver (n = 7), kidney (n = 2), and heart transplantation (n = 1). Seven (70%) are alive after 4.7±1.8 (SD) years (range, 2.1–6.5). Three pediatric liver recipients died, 1 at 5 months from a ruptured hepatic-artery aneurysm, another at 9 months from a preexisting nervous system disorder. The third death at 3.5 years from a systemic CMV infection was attributed to AIDS. One of the pediatric renal recipients was returned to dialysis when the kidney was rejected after 8 months, but the patient is otherwise well (Table 1).

The results were worse in the adults, mean age of 43.1±9.2 (SD) years of whom only 6 (40%) are alive 3.5±2.4 SD years after transplantation (range, 0.7–6.6). The mortality was organ related: with 1 (25%) death after 4 kidney transplantations, 3 (75%) of 4 after heart transplantation, and 5 (63%) of 8 after liver transplantation. Five of these deaths were from AIDS (Tables 1 and 2).

Correlations of rejection and immunosuppression. Treatment was started with CsA and prednisone in 12 patients of whom 5 are still alive. Rejection was diagnosed in 8 of them. Azathioprine was also used from the outset in the other 13, and 8

TABLE 1. Transplant recipients who were HIV+ before transplantation

Patient	Organ[a]	Age (years)	Current status	Survival time[b]	No. transplants	Cause of death
1a	H	15	Alive	26 months	1	—
2a	L	48	Alive	8 months	1	—
3a	K	29	Alive	5 years	1	—
4a	K[c]	16	Alive	5 years, 5 months	1	—
5a	K	64	Alive	1 year	1	—
6a	L	15	Dead	3 years, 6 months	1	CMV
7a	L	48	Dead	4 months	1	PCP[d]
8a	L	0.5	Dead	9 months	2	Preexisting CNS disease[e]
9a	L	32	Dead	18 months	1	Immunoblastic sarcoma
10a	L	42	Dead	6 months	2	Colchichine toxicity
11a	L	3	Alive	5 years, 8 months	3	—

[a] Abbreviations: L, liver; H, heart; K, kidney.
[b] Time from first transplant.
[c] Currently on dialysis, kidney graft lost to acute rejection 8 months after transplant.
[d] PCP: *Pneumocystis carinii.*
[e] CNS: central nervous system.

TABLE 2. Transplant recipients who seroconverted after transplantation

Patient	Organ	Age (years)	Current status	Survival time[a]	No. transplants	Cause of death[b]
1b	K	38	Dead	5 months	1	Generalized TB
2b	K	13	Alive	25 months	2	—
3b	L	46	Dead	4 months	2	HAT
4b	L	5	Alive	6 years, 6 months	1	—
5b	L	44	Dead	5 years, 1 month	1	Pneumonitis of unknown cause
6b	L	5	Alive	5 years, 4 months	1	—
7b	L	3	Alive	5 years, 8 months	3	—
8b	L	2	Dead	5 months	2	HA aneurysm
9b	L	32	Alive	5 years, 2 months	1	—
10b	H	42	Dead	15 months	1	PCP + List + TOX
11b	H	53	Dead	4 months	1	Heart failure
12b	H	34	Alive	6 years, 7 months	1	—
13b	H	47	Dead	5 months	1	Heart failure
14b[c]	L	47	Alive	2 years, 7 months		—

[a] Time from first transplant.

[b] Abbreviations: TB, tuberculosis; HAT, hepatic artery thrombosis; HA, hepatic artery; PCP, *Pneumocystis carinii*; List, listeria monocytogenes meningitis; TOX, *Toxoplasma gondii*.

[c] Received a liver allograft from an HIV$^+$ donor and seroconverted after transplantation (*15*, see text).

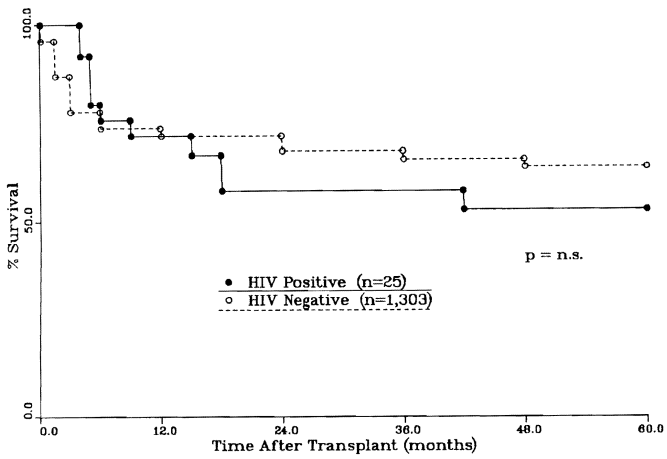

FIGURE 1. Kaplan-Meier survival estimates comparing HIV$^-$ liver transplant recipients to HIV$^+$ transplant recipients.

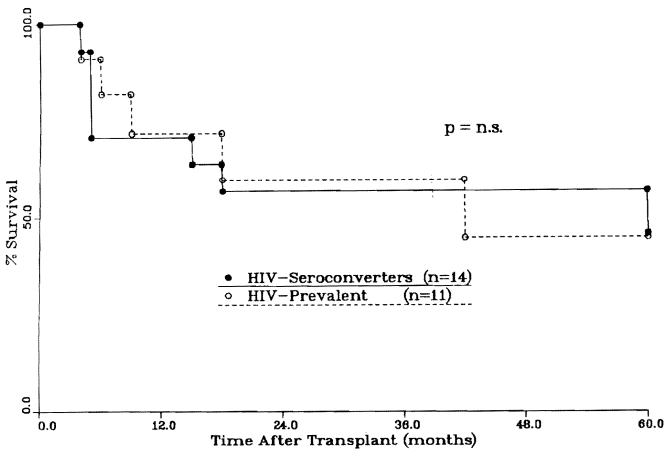

FIGURE 2. Kaplan-Meier survival estimates for HIV$^+$ transplant recipients, Pittsburgh, PA.

survived. Rejection was diagnosed in 9 of these recipients. Of the 17 patients who developed rejection in the foregoing 2 groups, 10 (59%) died. Six (55%) of 11 patients given OKT3 or ALG died. Only 2 (25%) of 8 who did not develop rejection have died.

Six liver recipients underwent retransplantation: 4 for hepatic artery thrombosis, 1 for uncontrollable acute rejection, and 1 for chronic rejection. Two of these patients are still alive and well 5.7 years later. One renal recipient is well 1.8 years after a second transplant.

AIDS-related morbidity and mortality. Six (24%) of the 25 HIV$^+$ transplant recipients (1 heart, 1 kidney, 4 livers) died of AIDS after 5 months to more than 5 years (Tables 1 and 2). Cause of death included *Pneumocystis Carinii* pneumonia (2 cases), in 1 case coexisting with *Listeria monocytogenes* and *Toxoplasma gondii* meningitis, generalized tuberculosis (1 case), systemic cytomegalovirus (1 case), pneumonitis of unknown etiology (1 case), and immunoblastic sarcoma (1 case).

One heart (patient 1a, Table 1) and 2 liver recipients (patients 4b and 9b, Table 2) have been living with AIDS for 8, 21, and 6 months, respectively. Two have interstitial pneumonitis, and the other has oral and esophageal candidiasis and recurrent CMV infections. Posttransplantation follow-ups are 2.2, 6.5, and 5.2 years. Patient 4b has had immunosuppression stopped for 18 months. Patients 1a and 9b have had immunosuppression drastically reduced. All 3 patients have normal graft function.

The AIDS-free time after transplantation was not significantly different in the prevalent versus the HIV seroconverters (Fig. 3). For this reason, the 2 transplant subgroups were combined for comparison with the 2 nontransplant control groups (Fig. 4).

The AIDS-free times of the transplant recipients were poorer than in the blood-transfusion and hemophiliac control groups in that the transplant patients had more-frequent early development of AIDS. Four of 25 transplant recipients developed AIDS within the first 15 months, compared to 0 and 1 example in the 2 control groups ($P = 0.04$, Fisher's exact test). However, beyond 15 months, the slope of the curves was similar in all 3

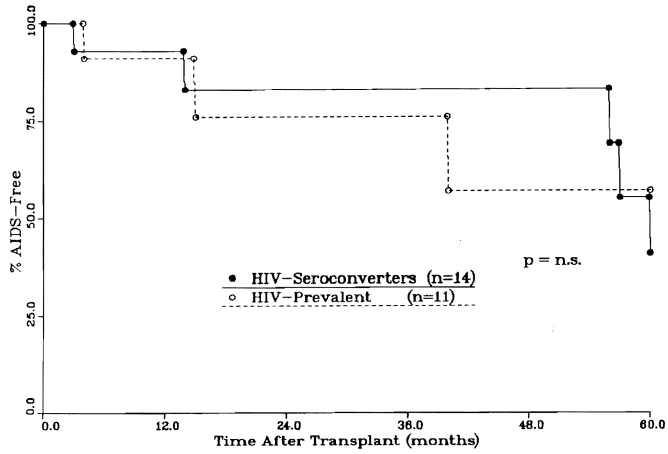

FIGURE 3. Kaplan-Meier estimates for the proportion of HIV+ transplant recipients who remain AIDS free.

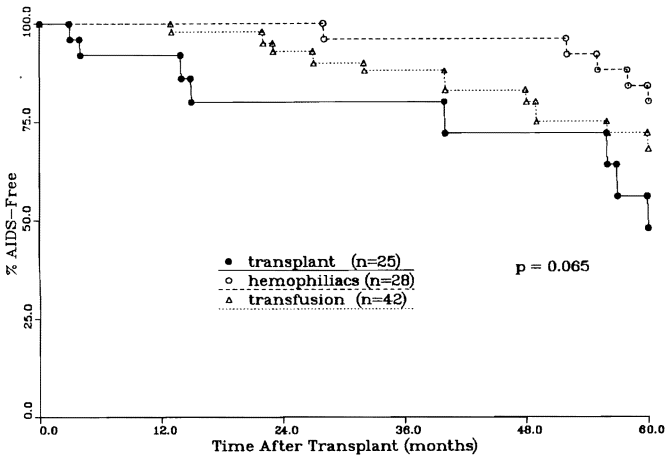

FIGURE 4. Kaplan-Meier estimates for the proportion remaining AIDS free comparing HIV+ transplant recipients to hemophiliacs and transfusion recipients.

groups, and for the 5-year period approached statistical significance ($P = 0.065$).

Rehabilitation after transplantation. Nine of the 13 surviving patients are working full time or at school. Three more live at home but are not able to work. One of the surviving patients is currently hospitalized with recurrent hepatitis B.

DISCUSSION

Candidates for transplantation of any of the vital organs apparently have a higher rate of HIV+ serology than the general population (*3–8*). Patients with vital organ failure are exposed to the virus in blood components, transplanted tissues, unsterile needles, and HIV+ patients who are concentrated in hospitals and clinics (*3, 15–18*). Whether or not the HIV+ patients with organ failure should be excluded from transplant candidacy if their positive HIV status is known remains a debatable issue, mainly due to the paucity of scientific data about subsequent survival.

When screening tests for this disease became generally available in the spring of 1985, HIV infections in kidney recipients were described almost immediately (*1, 2*). These reports emphasized the consequent morbidity and high mortality rates (*7*). However, the single institutional series of Dummer et al. (*3*) and multicenter studies (*6*) have shown that early AIDS and death may not be the inevitable or even the usual outcome after transplantation under immunosuppression.

Almost certainly, the presence of HIV antibodies would have precluded candidacy if the diagnosis in the cases cited above from the literature and most of those reported herein had been made in advance. In retrospect, the majority have benefited from transplantation, although the follow-up is limited to a few years. Children have been particularly hardy in that only 1 in 10 has died of what was defined as an AIDS-related complication, namely a cytomegalovirus infection 3½ years postoperatively. The results in adults were worse in that AIDS was the most important cause of mortality. The risk was greatest with the more-complex liver and heart transplantations, and least with the kidney.

With these findings, it was not surprising that the 5-year survival rate after transplantation of HIV+ recipients was 11% lower than in the HIV− liver patients. The difference was not statistically significant because of the small HIV+ sample, but there was evidence that the immunosuppression due to HIV+ status and immunosuppression for transplantation could be more dangerous than either factor alone during the first postoperative year. During this time, manifestations of AIDS in organ recipients (all organs) developed at an accelerated rate compared to HIV+ patients in the 2 control groups. After 15 months, this extra risk was no longer apparent.

As risk factors with high predictive value for subsequent AIDS are delineated (*19–25*), we should be able to better define which of the HIV+ transplant candidates have a reasonable prospect of benefitting from transplantation. It already is obvious that transplantation is medically contraindicated in patients who have AIDS or signs and symptoms of impending AIDS.

How to apply this information in future case selection may depend more on philosophic persuasions than scientific ones since no form of treatment can provide perpetual life. In HIV+ patients who have no evidence of AIDS, transplantation can prolong meaningful life in the majority of patients but less reliably and less safely than in HIV− recipients. It is self-evident that the same statement could be made about virtually every other major medical or surgical therapy available today. Such therapies are not withheld from HIV+ patients because of a predictably lower efficiency or because of high cost (*26–28*). The rationing of transplantation services to exclude asymptomatic HIV+ patients from candidacy for such reasons or even because of a potential shortage of organs would be a departure from past practices that will have to be carefully considered and decided upon by each individual center.

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