



July 2002

Solid-Organ Transplantation in HIV-Infected Patients

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Recommended Citation

Halpern, S. D., Ubel, P. A., & Caplan, A. L. (2002). Solid-Organ Transplantation in HIV-Infected Patients. Retrieved from http://repository.upenn.edu/bioethics_papers/5

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Solid-Organ Transplantation in HIV-Infected Patients

Abstract

Before the introduction of highly active antiretroviral therapy in the mid-1990s, transplantation centers were understandably reluctant to provide scarce solid organs for patients infected with the human immunodeficiency virus (HIV). However, because treated patients can now expect to live substantially longer than before, many will have end-stage organ disease long before they have life-threatening conditions related to HIV infection. It is therefore time for the transplantation community to readdress the safety, efficacy, and propriety of transplanting scarce organs in HIV-positive patients who need them.

In this article, we provide ethical arguments for viewing transplantation in patients with HIV infection as analogous to transplantation in patients with other chronic illnesses. Accordingly, transplantation in HIV-positive patients should be initiated at major centers and should not be considered experimental. In addition, reimbursement for such procedures should be similar to that for transplantation in other patients, unless evidence accumulates that HIV-infected transplant recipients fare poorly.

Comments

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*Sounding Board***SOLID-ORGAN TRANSPLANTATION
IN HIV-INFECTED PATIENTS**

BEFORE the introduction of highly active antiretroviral therapy in the mid-1990s, transplantation centers were understandably reluctant to provide scarce solid organs for patients infected with the human immunodeficiency virus (HIV). However, because treated patients can now expect to live substantially longer than before,¹⁻³ many will have end-stage organ disease long before they have life-threatening conditions related to HIV infection.⁴ It is therefore time for the transplantation community to readdress the safety, efficacy, and propriety of transplanting scarce organs in HIV-positive patients who need them.

In this article, we provide ethical arguments for viewing transplantation in patients with HIV infection as analogous to transplantation in patients with other chronic illnesses. Accordingly, transplantation in HIV-positive patients should be initiated at major centers and should not be considered experimental. In addition, reimbursement for such procedures should be similar to that for transplantation in other patients, unless evidence accumulates that HIV-infected transplant recipients fare poorly.

CURRENT PRACTICES

Although the United Network for Organ Sharing states that asymptomatic HIV-positive patients “should not necessarily be excluded from candidacy for organ transplantation,”⁵ most centers are concerned that transplantation might harm HIV-positive patients and believe that scarce organs should not be allocated to patients with a poor prognosis.⁶ In a 1997 survey of directors of U.S. renal-transplantation centers, 88 percent of respondents indicated that they would not consider transplanting an organ in a patient with “asymptomatic HIV-infection who is otherwise a good candidate for transplantation.”⁶ An earlier survey of Canadian transplantation centers revealed similar views.⁷ Only a small proportion of U.S. transplantation centers have agreed to participate in a proposed multicenter study of transplantation in HIV-positive patients. There is evidence that most patients and nurses also believe that HIV-positive patients should not be considered for heart transplantation.⁸ Moreover, insurance companies have generally refused to pay for liver transplantation in HIV-infected patients.⁹⁻¹¹

ETHICAL CONSIDERATIONS

Even before the introduction of highly active antiretroviral therapy, a positive test for antibodies against

HIV was rarely, if ever, a legitimate criterion for withholding medical interventions other than transplantation. However, transplantation differs from other interventions with regard to both ethical and medical considerations. Because transplantable organs are scarce, determining the most ethical allocation system requires simultaneous considerations of efficacy, urgency, and equity.¹²

There are two distinct ethical questions about efficacy: Does transplantation benefit the individual patients? Would it benefit other patients more? With regard to the first question — the question of absolute efficacy — transplantation can certainly help HIV-positive patients with end-stage organ disease.¹³⁻²³ The second question — concerning relative efficacy — is rarely addressed in the distribution of plentiful resources, but there is a strong moral basis for posing this question when scarce resources are being allocated.^{24,25} We do not ask whether elderly persons should receive antihypertensive therapy, even though the benefits of long-term treatment are greater for younger persons. However, if transplantation provided substantially less benefit, in terms of survival and quality of life, for HIV-positive patients, then a policy of preferential allocation of organs to HIV-negative patients might be tenable.

Considerations of efficacy are factored into the allocation policies of the United Network for Organ Sharing in two ways: priority is given to candidates whose ABO blood group matches that of a donor, and in the case of kidney transplantation, HLA matching is an additional consideration.⁵ With the availability of highly active antiretroviral therapy, is it reasonable to suppose that HIV status might still influence efficacy as much as genetic compatibility?

Though there has been no systematic comparison of outcomes between HIV-positive and HIV-negative organ recipients, recent experience suggests that large differences are unlikely. All published reports of transplantation in HIV-positive patients who are receiving multidrug antiretroviral regimens have concluded that, in most cases, HIV infection does not affect the outcome of transplantation.²⁰⁻²³ There are several other, unpublished reports of favorable outcomes several years after transplantation in HIV-positive patients receiving antiretroviral therapy (Olthoff K: personal communication; and Stock P: personal communication).

Even if HIV-positive transplant recipients proved to have somewhat worse outcomes than HIV-negative recipients, relative efficacy is not the sole ethical criterion for determining candidacy. Medical urgency is another important criterion in heart, lung, and liver transplantation. This helps explain why patients who require rapid retransplantation routinely receive it,²⁴ even though expected survival is markedly diminished.^{24,26,27}

Equity (equal access to organs among patients with equivalent need) is also recognized as important by both transplantation specialists and the public.^{28,29} Thus, most programs offer organs to patients infected with hepatitis C virus (HCV), patients with diabetes, older patients (up to a point), and black patients, despite clear evidence that post-transplantation survival is diminished in each of these groups.³⁰⁻³⁸ On ethical grounds alone, there is no justification for providing organs to these groups of patients but not to patients infected with HIV.

MEDICAL CONSIDERATIONS

Might the questionable safety of transplantation in HIV-positive patients justify the discriminatory allocation system? There is an intuitive concern that immunosuppressive therapy might hasten the progression of HIV disease. However, the experience to date suggests that the use of standard immunosuppressive agents in patients with well-controlled HIV infection does not increase their susceptibility to opportunistic infections or malignant conditions.^{20,21,23} In fact, two common immunosuppressive agents, cyclosporine and tacrolimus, may actually improve outcomes in HIV-positive transplant recipients by inhibiting interleukin-2-dependent T-cell replication, by directly inhibiting HIV replication, or both.^{39,40}

There is also concern about potential interactions between antiretroviral and immunosuppressive agents. Protease inhibitors increase blood concentrations of tacrolimus and cyclosporine by inhibiting specific cytochrome P-450 enzymes.^{41,42} However, experienced centers routinely monitor blood levels of these agents and adjust doses accordingly. The pharmacokinetics of these interactions are similar to those in transplant recipients who require other concomitant medications (e.g., phenytoin) that may induce or inhibit the same enzymes.

Finally, physicians have been concerned that surgery itself might accelerate the progression of HIV disease. However, there is evidence that disease progression is unaffected by surgery, even major surgery requiring cardiac bypass.⁴³⁻⁴⁵

CONCERN ABOUT INTRAOPERATIVE TRANSMISSION OF HIV

Another concern is that HIV-positive patients might transmit the virus to members of the transplantation team. However, the risk of patient-to-surgeon transmission of HIV is extremely low and is substantially lower than the risk of transmission of many other infectious diseases, including HCV, which are present in many patients who undergo surgery.⁴⁶ Even if a member of a transplantation team were exposed to HIV, various postexposure regimens provide effective prophylaxis against infection.^{47,48}

Many argue that physicians are obligated to accept such small risks because of their unique responsibilities and privileges.⁴⁹⁻⁵¹ Indeed, several major medical associations, including the American College of Surgeons, contend that individual physicians have a duty to provide care to HIV-positive patients.⁵²⁻⁵⁴ There may also be a legal duty to provide treatment because HIV-positive persons are covered under the Americans with Disabilities Act.^{50,51}

OTHER ARGUMENTS AGAINST TRANSPLANTATION IN HIV-POSITIVE PATIENTS

Some may argue that it is wrong to expand the pool of eligible patients when the supply of organs is already inadequate. This argument erroneously assumes that patients with longer-established rights to receive organs should have priority over those with rights that have been established more recently. Equity dictates that no group of patients be penalized simply because medicine has only recently advanced to a point at which they may benefit from transplantation.

A final argument against transplanting organs in HIV-positive patients is that HIV infection is often, though by no means always, associated with intravenous-drug use or high-risk sexual practices. Such associations, however, have never been a legitimate reason to withhold medical interventions from patients.^{55,56} HCV is also commonly acquired through intravenous-drug use, and hepatitis B virus (HBV) is also commonly acquired through the same high-risk sexual practices as those associated with the transmission of HIV. Yet these diseases, along with alcoholic liver disease, remain the most common indications for liver transplantation in the United States. It is not the role of medicine to adjudicate the morality of personal behavior through selective treatment of life-threatening conditions.

THE BURDEN OF PROOF

It has been proposed that organs be offered to HIV-positive patients only in well-controlled studies until transplantation experts have shown that the outcomes are similar to those for uninfected patients. We disagree with this approach. Proof of relative efficacy has never been required for the initiation of new surgical procedures or for the expansion of indications for established procedures. There was certainly reason to suspect that HCV-positive patients would fare less well after liver transplantation than HCV-negative patients, but systematic comparisons were not required before these patients could receive organs in nonexperimental settings. It is therefore unjust to require such proof before offering transplantation to HIV-positive patients.

Still, some documentation of relative efficacy will eventually be needed to gain the acceptance of physicians, the public, and third-party payers. The best approach is to perform a substantial number of transplantations in HIV-positive patients at major centers and to record all pertinent data from their experience in widely accessible data bases. Investigators will then be able to compare the outcomes for HIV-positive transplant recipients with those for HIV-negative recipients who have similar demographic and disease-related characteristics. Such retrospective analyses are precisely how we learned about outcomes in HCV-positive patients.^{34,35}

PROVISION OF "MARGINAL" ORGANS

A counterproposal is that HIV-positive patients should first merit consideration for the transplantation of so-called marginal, or expanded-criteria, organs — those harvested from older donors, donors infected with HBV or HCV, and, as is increasingly common in renal transplantation, donors with diabetes or hypertension. The outcomes for recipients of marginal organs are typically worse than those for recipients of "ideal" organs.^{57,58} Therefore, in the absence of evidence that HIV-positive patients derive less benefit from transplantation than their HIV-negative counterparts, we see no justification for making HIV seropositivity an indication to use less viable organs. If an HIV-positive patient also happens to have a known risk factor for a poorer outcome, such as advanced coexisting disease or advanced age, then the use of a marginal organ should be considered in the same way as it would for a similar HIV-negative patient.

A CALL FOR CONSISTENCY

We believe it would be wrong to transplant an organ in a patient with terminal AIDS for the same reason that it would be wrong to transplant an organ in a patient with widely metastatic hepatocellular carcinoma: both patients would probably die from the coexisting illness before receiving any appreciable benefit from the new organ. However, a broad range of patients who are at low risk for progression to AIDS or AIDS-related death can be identified with the use of base-line CD4+ T-lymphocyte counts and HIV RNA levels.⁵⁹ Furthermore, because changes in the viral load after the initiation of therapy also predict progression to AIDS,⁶⁰ even patients who at one time met the diagnostic criteria for AIDS may benefit from transplantation if they subsequently receive treatment that provides good control of the disease.²⁰ Transplantation physicians must often make difficult decisions about how various coexisting conditions influence the likelihood that a patient will benefit from transplantation. The extent of HIV disease is simply another coexisting condition to consider.

Now is the time to remove barriers to transplantation in HIV-positive patients for whom it is otherwise indicated. We should not wait for evidence of relative efficacy to emerge. As with any new patient population, accumulating data will inform future analyses of the appropriateness of transplantation in HIV-positive patients.

Current considerations of efficacy in organ allocation can be summarized as follows. We have substantial evidence of diminished survival among HCV-positive patients, patients with diabetes, black patients, and patients requiring retransplantation, yet we do not prevent transplantation in these groups. In contrast, we have no evidence of poorer survival among otherwise healthy HIV-positive patients who are receiving antiretroviral therapy, yet both overt and covert barriers to transplantation remain. This contradiction is not justifiable according to any ethical theory. Instead, it indicates yet another way in which we continue to discriminate against HIV-positive persons.

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We are indebted to Drs. Emily Blumberg, Kim Olthoff, Jeffrey Punch, and Peter Stock for their candid discussions and insightful comments as we prepared the manuscript.

REFERENCES

1. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1998;338:853-60.
2. Mocroft A, Katlama C, Johnson AM, et al. AIDS across Europe, 1994-1998: the EUROSIDA study. *Lancet* 2000;356:291-6.
3. Kaplan JE, Hanson D, Dworkin MS, et al. Epidemiology of human immunodeficiency virus-associated opportunistic infections in the United States in the era of highly active antiretroviral therapy. *Clin Infect Dis* 2000;30:Suppl 1:S5-S14.
4. Bica I, McGovern B, Dhar R, et al. Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. *Clin Infect Dis* 2001;32:492-7.
5. Policies & bylaws. Alexandria, Va.: United Network for Organ Sharing, 2001. (Accessed July 3, 2002, at http://www.unos.org/frame_Default.asp?Category=aboutpolicies.)
6. Spital A. Should all human immunodeficiency virus-infected patients with end-stage renal disease be excluded from transplantation? The views of U.S. transplant centers. *Transplantation* 1998;65:1187-91.
7. Mullen MA, Kohut N, Sam M, Blendis L, Singer PA. Access to adult liver transplantation in Canada: a survey and ethical analysis. *CMAJ* 1996; 154:337-42.
8. Corley MC, Huff S, Sayles L, Short L. Patient and nurse criteria for heart transplant candidacy. *Med Surg Nurs* 1995;4:211-5.
9. Stryker J. HIV patients get fresh hopes for donor organs. *New York Times*. December 11, 2001:F6.

10. Smith S. Belynda Dunn, AIDS activist, dies after second liver transplantation. *Boston Globe*. March 13, 2002:B3.
11. HIV & transplant. Organ Transplantation Association, 2001. (Accessed July 3, 2002, at <http://organtx.org/hivtx.htm>.)
12. Ubel PA, Caplan AL. Geographic favoritism in liver transplantation — unfortunate or unfair? *N Engl J Med* 1998;339:1322-5.
13. Rubin RH, Jenkins RL, Shaw BW Jr, et al. The acquired immunodeficiency syndrome and transplantation. *Transplantation* 1987;44:1-4.
14. 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;44:21-4.
15. 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;47:134-40.
16. Poli F, Scalapogna M, Pizzi C, Mozzi F, Sirchia G. HIV infection in cadaveric renal allograft recipients in the North Italy Transplant Program. *Transplantation* 1989;47:724-5.
17. Erice A, Rhame FS, Heussner RC, Dunn DL, Balfour HH Jr. Human immunodeficiency virus infection in patients with solid-organ transplants: report of five cases and review. *Rev Infect Dis* 1991;13:537-47.
18. Tzakis AG, Cooper MH, Dummer JS, Ragni M, Ward JW, Starzl TE. Transplantation in HIV+ patients. *Transplantation* 1990;49:354-8.
19. Bouscarat F, Samuel D, Simon F, Debat P, Bismuth H, Saimot AG. An observational study of 11 French liver transplant recipients infected with human immunodeficiency virus type 1. *Clin Infect Dis* 1994;19:854-9.
20. Ragni MV, Dodson SF, Hunt SC, Bontempo FA, Fung JJ. Liver transplantation in a hemophilia patient with acquired immunodeficiency syndrome. *Blood* 1999;93:1113-4.
21. Prachalias AA, Pozniak A, Taylor C, et al. Liver transplantation in adults coinfecting with HIV. *Transplantation* 2001;72:1684-8.
22. Kuo PC. Reconsideration of HIV as a contraindication to transplantation. *Transplantation* 2001;71:1689.
23. Gow PJ, Mutimer D. Liver transplantation for an HIV-positive patient in the era of highly active antiretroviral therapy. *AIDS* 2001;15:291-2.
24. Ubel PA, Arnold RM, Caplan AL. Rationing failure: the ethical lessons of the retransplantation of scarce vital organs. *JAMA* 1993;270:2469-74.
25. Council on Ethical and Judicial Affairs, American Medical Association. Ethical considerations in the allocation of organs and other scarce medical resources among patients. *Arch Intern Med* 1995;155:29-40.
26. Dein JR, Oyer PE, Stinson EB, Starnes VA, Shumway NE. Cardiac retransplantation in the cyclosporine era. *Ann Thorac Surg* 1989;48:350-5.
27. Shaw BW Jr, Gordon RD, Iwatsuki S, Starzl TE. Hepatic retransplantation. *Transplant Proc* 1985;17:264-71.
28. Ubel PA, Lowenstein G. Distributing scarce livers: the moral reasoning of the general public. *Soc Sci Med* 1996;42:1049-55.
29. *Idem*. The efficacy and equity of retransplantation: an experimental survey of public attitudes. *Health Policy* 1995;34:145-51.
30. Valente JF, Hariharan S, Peddi VR, et al. Causes of renal allograft loss in black vs. white transplant recipients in the cyclosporine era. *Clin Transplant* 1997;11:231-6.
31. Kappes U, Schanz G, Gerhardt U, Matzkies F, Suwelack B, Hohage H. Influence of age on the prognosis of renal transplant recipients. *Am J Nephrol* 2001;21:259-63.
32. John PR, Thuluvath PJ. Outcome of liver transplantation in patients with diabetes mellitus: a case-control study. *Hepatology* 2001;34:889-95.
33. Revanur VK, Jardine AG, Kingsmore DB, Jaques BC, Hamilton DH, Jindal RM. Influence of diabetes mellitus on patient and graft survival in recipients of kidney transplantation. *Clin Transplant* 2001;15:89-94.
34. Nair S, Eustace J, Thuluvath PJ. Effect of race on outcome of orthotopic liver transplantation: a cohort study. *Lancet* 2002;359:287-93.
35. Forman LM, Lewis JD, Berlin JA, Feldman HI, Lucey MR. The association between hepatitis C infection and survival after orthotopic liver transplantation. *Gastroenterology* 2002;122:889-96.
36. Isaacs R, Nock SL, Spencer CE, et al. Racial disparities in renal transplant outcomes. *Am J Kidney Dis* 1999;34:706-12.
37. Hariharan S, Schroeder TJ, First MR. Effect of race on renal transplant outcome. *Clin Transplant* 1993;7:235-9.
38. Kasiske BL, Neylan JF III, Riggio RR, et al. The effect of race on access and outcome in transplantation. *N Engl J Med* 1991;324:302-7.
39. 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.
40. Kuo PC, Stock PG. Transplantation in the HIV+ patient. *Am J Transplant* 2001;1:13-7.
41. Schvarcz R, Rudbeck G, Soderdahl G, Stahle L. Interaction between nelfinavir and tacrolimus after orthotopic liver transplantation in a patient coinfecting with HIV and hepatitis C virus (HCV). *Transplantation* 2000;69:2194-5.
42. Sheikh AM, Wolf DC, Lebovics E, Goldberg R, Horowitz HW. Concomitant human immunodeficiency virus protease inhibitor therapy markedly reduces tacrolimus metabolism and increases blood levels. *Transplantation* 1999;68:307-9.
43. Lemma M, Vanelli P, Beretta L, Botta M, Antinori A, Santoli C. Cardiac surgery in HIV-positive intravenous drug addicts: influence of cardiopulmonary bypass on the progression to AIDS. *Thorac Cardiovasc Surg* 1992;40:279-82.
44. Sewell CA, Derr R, Anderson J. Operative complications in HIV-infected women undergoing gynecologic surgery. *J Reprod Med* 2001;46:199-204.
45. Astermark J, Lofqvist T, Schulman S, et al. Major surgery seems not to influence HIV disease progression in haemophilia patients. *Br J Haematol* 1998;103:10-4.
46. Goldberg D, Johnston J, Cameron S, et al. Risk of HIV transmission from patients to surgeons in the era of post-exposure prophylaxis. *J Hosp Infect* 2000;44:99-105.
47. Henderson DK. Postexposure chemoprophylaxis for occupational exposures to the human immunodeficiency virus. *JAMA* 1999;281:931-6.
48. Public Health Service. Updated U.S. Public Health Service guidelines for the management of occupational exposures to HBV, HCV, and HIV and recommendations for postexposure prophylaxis. *MMWR Morb Mortal Wkly Rep* 2001;50(RR-11):1-52.
49. Bayer R. AIDS and the duty to treat: risk, responsibility, and health care workers. *Bull N Y Acad Med* 1988;64:498-505.
50. Haley A, Brody B. Acquired immunodeficiency syndrome and the Americans with Disabilities Act: a legal duty to treat. *Am J Med* 1994;96:282-8.
51. Haley A. AIDS, surgery, and the Americans with Disabilities Act. *Arch Surg* 2000;135:51-4.
52. Health and Public Policy Committee, American College of Physicians, Infectious Diseases Society of America. The acquired immunodeficiency syndrome (AIDS) and infection with the human immunodeficiency virus (HIV). *Ann Intern Med* 1988;108:460-9.
53. Council on Ethical and Judicial Affairs. Ethical issues involved in the growing AIDS crisis. *JAMA* 1988;259:1360-1.
54. American College of Surgeons. Statement on the surgeon and HIV infection. *Bull Am Coll Surg* 1991;76:28-31.
55. Ubel PA. Transplantation in alcoholics: separating prognosis and responsibility from social biases. *Liver Transpl Surg* 1997;3:343-6.
56. Ubel PA, Jepson C, Baron J, Mohr T, McMorro S, Asch DA. The allocation of transplantable organs: do people want to punish patients for causing their illness? *Liver Transpl* 2001;7:600-7.
57. Ojo AO, Leichtman AB, Punch JD, et al. Impact of pre-existing donor hypertension and diabetes mellitus on cadaveric renal transplant outcomes. *Am J Kidney Dis* 2000;36:153-9.
58. Ojo AO, Hanson JA, Meier-Kriesche H, et al. Survival in recipients of marginal cadaveric donor kidneys compared with other recipients and wait-listed transplant candidates. *J Am Soc Nephrol* 2001;12:589-97.
59. Mellors JW, Munoz A, Giorgi JV, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med* 1997;126:946-54.
60. O'Brien WA, Hartigan PM, Daar ES, Simberkoff MS, Hamilton JD. Changes in plasma HIV RNA levels and CD4+ lymphocyte counts predict both response to antiretroviral therapy and therapeutic failure. *Ann Intern Med* 1997;126:939-45.

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