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The problem of human immunodeficiency virus (HIV) infection and transplantation

Robert H. Rubin and Nina E. Tolkoff-Rubin

Infectious Disease and Dialysis-Transplantation Units of the Medical Service, Massachusetts General Hospital, Department of Medicine, Harvard Medical School, Boston, MA 02114, USA*

Abstract. The problem of human immunodeficiency virus (HIV) infection and that of the acquired immunodeficiency syndrome (AIDS) are becoming increasingly important in clinical transplantation. The epidemiologic characteristics of this infection are important factors in determining the impact of this infection on transplant patients: in particular, the presence of a transmissible virus in the blood, tissues, and body fluids of even asymptomatic individuals for prolonged periods; the role of lymphocyte activation in accelerating the pace and effects of HIV infection, with the transplant patient having more reasons for lymphocyte activation than other patient categories; and the possible contributions of immunosuppressive therapy to the course of HIV infection. Already, at least 20 cases of primary HIV infection conveyed by infected blood or allografts at the time of transplant have been noted; a similar number of transplants have been carried out in asymptomatic carriers of the virus. The initial impression is that the course of HIV infection in these patients is accelerated, but information is incomplete and an international registry for the study of this problem has been established.

Key words: Transplantation - AIDS - HIV infection.

The most dramatic medical event of the 1980s has been the advent of the hitherto unprecedented epidemic of opportunistic infection and malignancy now known as the acquired immunodeficiency syndrome (AIDS). As in most areas of medicine, AIDS is having and will continue to have an important impact on clinical transplantation. The epidemiologic exposures of the transplant patient, the use of immunosuppressive therapy for the life of the patient, the virtually universal presence of a variety of infectious agents in these patients, and the occurrence of allograft rejection all interact to produce a clinical condition in which AIDS is likely to be manifest. That this prediction has been fulfilled has already been documented in a series of reports in the literature [3, 8, 14, 15, 17, 21, 23, 24, 26, 29].

The purpose of this review is threefold: (1) to delineate the epidemiologic and pathogenetic reasons for the especially high risk of the transplant patient for this condition, (2) to outline what has thus far been clinically observed in this patient population, and (3) to suggest steps that might be taken to limit the influence of this epidemic on the practice of transplantation.

Epidemiologic considerations

Since AIDS was first described in 1981, nearly 75000 cases have been documented throughout the world, with a mortality rate in these individuals approaching 100% within three years of diagnosis. The etiologic agent of AIDS, the human immunodeficiency virus (HIV), previously known variously as the lymphadenopathy-associated virus, the T-cell leukemia virus type III, and the AIDS-associated retrovirus), is thought to infect an additional 1-2 million Americans, thousands of Europeans and, perhaps, millions of Africans. This asymptomatic but infected population is thought to serve both as the reservoir from which future cases of

* In cooperation with the Registry for the Study of AIDS in Transplantation

Offprint requests to: R. H. Rubin

AIDS will emerge and as the major source of future spread of the virus [9].

The epidemiologic aspects of HIV infection are determined by the following general characteristics: (1) HIV has a prolonged viremic phase in both symptomatic and asymptomatic individuals; (2) HIV is present in transmissible form in virtually all bodily fluids of infected individuals; (3) there is a high rate of asymptomatic but transmissible infection among individuals of high risk population groups; and (4) this asymptomatic, albeit infectious, state can persist for periods of years [1]. Not surprisingly, then, three modes of transmission of HIV have been defined:

1. *Inoculation with blood.* This method of inoculation includes transmission of HIV with blood and blood products, needle sharing among intravenous drug users, injection with a contaminated needle, and needle stick, open wound, and mucous membrane inoculation with *contaminated blood.*

2. *Sexual transmission.* Although the greatest impact of the AIDS epidemic has been observed among homosexual men, it is now clear that HIV can be transmitted heterosexually as well, from women to men as well as from men to women.

3. *Perinatal transmission.* HIV infection may be acquired by the neonate from an HIV-infected mother in three possible ways: (a) by infection in utero, (b) by the inoculation or ingestion of blood and other infected fluids during labor and delivery, and (c) by the ingestion of infected breast milk.

It should be emphasized that neither personal contacts that do not fit into one of these categories nor insect bites can transmit HIV from infected individuals to others [9, 26].

These observations are of the greatest importance for the practice of transplantation. Blood transfusion is clearly an effective means of transmitting HIV; the minimum risk of HIV infection occurring in the recipient of a unit of blood from an infected donor is at least 66% [30]. It should be emphasized that HIV transmission has been noted with the administration of whole blood, blood cellular components, plasma, and clotting factors. In contrast, immunoglobulin preparations, albumin, plasma protein fraction, and hepatitis B vaccine - all prepared from human blood - are without risk of transmitting HIV. In particular, immunoglobulin preparations that have contained antibodies to HIV do not contain infectious virus, unlike the previously listed blood components in which the presence of antibodies connotes infectivity. The difference here is that HIV is inactivated by the process of preparing immunoglobulin. Immunoglobulin preparations that are presently being marketed have an extra safeguard: they are prepared from units of blood that are antibody- and virus-negative [2, 26].

Although it has been suggested that the transmission of HIV with allografts is uncommon [8], more recent data suggest that transplanting an organ from an HIV-infected individual is as efficient a means of transmitting the virus as is transfusion [3, 14, 15, 24, 26, 29]. A recent experience in North Carolina [3] underlines this point.

A victim of a motor vehicle accident received 56 units of blood and blood products in a heroic attempt to save his life. Following the declaration of brain death, multi-organ donation was carried out. A blood specimen tested after the transfusions (and just prior to organ donation) was negative for HIV, although a specimen that was drawn prior to transfusion and that was later tested was floridly positive. The two organ recipients who survived for longer than three months (one kidney and one liver allograft recipient) developed evidence of primary HIV infection. Thus, although the amount of HIV in the circulation of the donor had been thoroughly diluted by the massive blood transfusions, the organs themselves all harbored sufficient amounts of virus to serve as efficient vectors of infection. Whether the virus conveyed with the allografts was present in residual traces of donor blood or in passenger leukocytes within the allografts themselves is currently unknown. Suffice it to say that organs and tissues of HIV-infected individuals are an extremely efficient means of transmitting HIV infection, and that transplant patients may be infected at the time of transplant with either blood transfusions or an allograft from an HIV-infected donor.

Pathogenetic considerations

The causative agent of AIDS, the human immunodeficiency virus, belongs to a group of non-transforming, cytopathic retroviruses called the lentiviruses. Other viruses of this group include visna virus (a sheep virus), caprine arthritis encephalitis virus (a goat virus), the simian T cell lymphotropic virus type III (STLV-III, which affects non-human primates), and another group of human T cell lymphotropic retroviruses more closely related to STLV-III than HIV, termed HIV-2 (which has been isolated from humans in West Africa). The first two of these produce chronic neurodegenerative diseases, whereas the latter two produce an immunodeficiency syn-

drome. It is noteworthy that HIV infection in man has both effects: a profound immunodeficiency and a progressive degeneration of the central nervous system [11]. It is likely that other retroviruses of this type with similar effects will be discovered in the next several years.

The primary targets of HIV are the CD4+ helper/inducer lymphocytes. Indeed, the CD4 molecule itself appears to be the receptor for the virus, with specific binding between it and the gp 120 major envelope protein of the virus accounting for this critical first step. The virus then enters the cell and is uncoated, with the viral genomic RNA then transcribed into DNA by viral reverse transcriptase. This DNA is circularized and integrated into the host cell genome by a virus-encoded enzyme during cell division, although much of the DNA remains unintegrated in the cytoplasm. The important point to be emphasized is that HIV replication in the resting cell is restricted and at a low level; the infected cell at this point remains alive. However, when this cell is activated, transcription occurs, followed by protein synthesis and the production of mature virions. It is at this point that the host lymphocyte is killed [6, 11, 12, 13, 19, 20, 21].

Thus, the two critical steps here are the initial interaction of the virus with the CD4+ lymphocytes and then the shifting into a high rate of viral production and cell destruction upon activation of the cells. In vitro, lymphocyte activation that results in these events has been shown to occur with mitogenic, antigenic, or allogeneic stimulation [11, 16, 31]. It is at this stage that the transplant recipient is likely to be particularly vulnerable to HIV infection. The opportunities for lymphocyte stimulation are particularly great in the transplant patient, such opportunities including allograft rejection, blood transfusions, and a plethora of infectious agents, but most especially such viruses as cytomegalovirus, Epstein-Barr virus, and the hepatitis viruses [26]. An example of the kind of acceleration of HIV infection that could be occurring in the transplant patient is that which has been shown to occur in vitro when HIV is combined with cytomegalovirus, a virus that is ubiquitous in transplant patients. Although under normal conditions lymphocytes support cytomegalovirus growth very poorly, when T cells are first infected with HIV, productive cytomegalovirus infection can occur. This synergy between the two viruses will then result in cell death and a more rapid depletion of the lymphocyte population [9].

The mechanisms by which productive HIV infection of activated CD4+ lymphocytes results in the striking depletion of this cell population, which is the prime component of the immunodeficiency that is characteristic of AIDS, are not completely understood at present. However, when considering the impact of HIV infection on the transplant patient, it is reasonable to postulate that the myriad of ways in which the CD4+ helper/inducer lymphocyte population can be activated in this clinical setting can only accentuate the effects of the virus on these patients. Therefore, it would be surprising if the clinical course in such individuals were not accelerated, particularly when the immunosuppressive effects of anti-rejection therapy are added to the equation [26].

The second group of cells to be infected with HIV are certain populations of monocytes and macrophages, perhaps those that express the CD4 antigen. Once infected with HIV, these cells are relatively resistant to cytotoxicity and remain alive for quite a long time. It is thought that HIV-infected monocytes and macrophages serve as an important reservoir of HIV within the individual and that they are the means by which HIV infection of the central nervous system is accomplished, resulting in the subacute encephalitis and other neurologic syndromes seen in so many patients with AIDS. In addition, it has been suggested that HIV infection of these cells results in a monocyte chemotactic defect which, in the case of the alveolar macrophage population, may account for the high rate of *Pneumocystis carinii* pneumonia observed in AIDS patients. Since cytomegalovirus infection is similarly related to alveolar macrophage dysfunction, as is exogenous immunosuppressive therapy, we would hypothesize that this is another aspect of HIV infection that might have an increased impact on the transplant patient. Monocyte infection with HIV also may result in the release of such cytokines as interleukin-1 and tumor necrosis factor, which may account for both the chronic fevers and the weight loss observed in AIDS patients [10, 11, 22, 26, 28].

B-lymphocytes are the third cell population influenced by HIV infection. Rather than being directly infected by the virus, B-lymphocytes undergo polyclonal activation when exposed to HIV. This results in a dysregulation of immunoglobulin synthesis which is characterized by the following: a polyclonal hyperglobulinemia, a poor antibody response to a variety of antigens but especially to the polysaccharide capsules of such organisms as *Streptococcus pneumoniae* and *Haemophilus influenzae type B*, and the occurrence of such autoimmune phenomena as immune thrombocytopenia and hemolytic anemia [5, 11]. In the transplant patient, overwhelming pneumococcal sepsis, akin to that observed in asplenic individuals, has been observed.

Diagnosis of human immunodeficiency virus infection

At present, the isolation of HIV from infected individuals is a research tool not appropriate for routine diagnostic use. The cornerstone of current diagnostic efforts aimed at identifying HIV infection is the demonstration of antibodies in the sera specific for viral antigens. It should be emphasized that anyone who truly has an antibody which is directed against HIV and which is demonstrable in his or her serum can be assumed to be infected with HIV and to harbor it in transmissible form in his blood, body fluids, and tissues. The presently used diagnostic strategy employs a rapid ELISA assay to detect antibodies against viral envelope proteins as a screening test. Any positives are then verified by a Western blot analysis. This second step is particularly important as the present generation of ELISA tests utilizes viruses grown in human cell lines as the source of their reagent. This reagent is contaminated with variable amounts of human histocompatibility antigens. Multiparous women and recipients of past transfusions or transplants may have false-positive responses due to the presence of antibodies to histocompatibility antigens which are present on the cell line in which the virus is grown (chiefly DR-4). Many transplant candidates fall into these categories and thus have false-positive results. Newer ELISA assays, utilizing recombinant antigens and thus free of contamination with histocompatibility antigens, should eliminate this problem. However, until these are in general use, verification of ELISA positivity by a Western blot analysis should be regarded as essential for every potential transplant donor and recipient [7, 26].

Typically, one to three months after infection with HIV, antibodies to the virus appear. They remain until the terminal stages of AIDS and may then disappear. Many individuals, including transplant patients, will, at the time of seroconversion, have a mononucleosis syndrome quite similar to that produced by cytomegalovirus and Epstein-Barr virus [15, 26]. However, in the past year, it has become increasingly clear that this typical pattern of seroconversion may not be universal and that more prolonged periods of viral infection (and, potentially, transmissibility) in the face of a negative ELISA antibody test may exist [1, 25]. Thus, in geographic areas with high rates of HIV infection, HIV has been isolated from 7-15% of antibody-negative homosexual men [18, 25]. In a recent Finnish prospective study, evidence of HIV infection could be found in some individuals 6-14 months prior to seroconversion, as measured by conventional ELISA assays for HIV envelope proteins. The frequency of these delays in antibody production still remains to be determined.

Recently, we observed a liver transplant patient whose course suggests that individuals receiving immunosuppressive therapy may have an even more delayed antibody response to the virus. This patient underwent successful liver transplantation in October, 1984 (prior to the availability of HIV ELISA testing) for end-stage liver disease due to non A, non B hepatitis. Retrospective testing some months later revealed that he had received one unit of blood at the time of transplantation from a donor subsequently shown to be infected with HIV. The transplant patient remained well - seronegative for HIV - until July 1987, when he presented with *Pneumocystis carinii* pneumonia. Testing for HIV antibody by ELISA was again negative. He recovered from the pneumonia and presented again in October 1987, with oral candidal infection and oral ulcerations due to herpes simplex virus. Serologic testing for HIV antibody by both ELISA and Western blot were now floridly positive. Since this monogamously heterosexual, non-drug-using individual had no other known risk factors for HIV infection, it is presumed that he acquired his infection at the time of transplant and that there was a time interval of three years in this chronically immunosuppressed individual before an antibody response to the virus by currently available tests could be documented.

These observations have considerable importance for clinical transplantation [1, 18, 25, 26]. There is now considerable evidence that the p24 antigen of HIV can be found in the circulation before the appearance of antibodies, as can antibodies to such HIV antigens as core and regulatory proteins prior to the development of circulating antibodies to envelope proteins, as measured in the current ELISA assays. The availability of assays for circulating p24 antigen and for these other antibodies should be extremely useful in two aspects of transplantation: the screening of donors and the testing of those transplant patients in whom HIV infection is suspected but where antibody response, as measured by the standard envelope protein assay, may be depressed.

Clinical effects of HIV infection on transplant patients

HIV infection in transplant patients can be divided into two general categories: primary HIV infection acquired at the time of transplantation, in which HIV-infected blood or an HIV-infected organ transmitted the virus to a previously uninfected and sero-

negative individual and secondary HIV infection, in which an asymptomatic but HIV-infected seropositive individual undergoes transplantation [26].

Primary HIV infection

Primary HIV infection has now been well documented to occur in transplant recipients. Sources of infection have included blood transfusions, kidney allografts, and liver allografts. Among kidney transplant recipients, it is important to emphasize that HIV infection has been transmitted with allografts obtained from both living related and cadaveric donors. In all instances, the blood or allograft donor was subsequently shown to be HIV seropositive or, when donor sera was unavailable for testing, to belong to a population group at high risk for HIV infection (male homosexual, hemophiliac, or intravenous drug user) [3, 8, 14, 15, 17, 21, 24, 26, 29]. Similarly, fatal AIDS related to transfusion has been reported 2.5 years after otherwise successful bone marrow transplantation [4]. It should be presumed that other tissues from HIV-infected donors can transmit the infection as well. For example, the virus can be isolated from corneal tissue of individuals with even asymptomatic HIV infection [27].

The clinical manifestations of primary HIV infection in transplant patients have been very similar to those observed in non-transplant patients. The most commonly reported abnormality has been a mononucleosis-like syndrome characterized by unexplained fevers, profound leukopenia, and lymphopenia with and without splenomegaly 2-7 weeks post-transplant. As in non-transplant patients, this syndrome is usually associated with the development of measurable anti-HIV antibody in the serum. Both the timing of this syndrome and its clinical manifestations closely resemble and may be indistinguishable from post-transplant cytomegalovirus infection. Other manifestations of primary HIV infection in the transplant patient have included the following: prolonged asymptomatic carriage of the virus, AIDS-related complex, conjugal spread of the virus to spouses, and full-blown AIDS, with both opportunistic infection and Kaposi's sarcoma being noted. If anything, *Pneumocystis carinii* pneumonia has been even more common in transplant patients with AIDS than in other patients with AIDS, which is not surprising given the occurrence of *Pneumocystis* pneumonia in transplant patients without AIDS. Although the information available to date is quite fragmentary, the incubation period between infection and the appearance of clinical AIDS may be shortened in the transplant patient. Similarly, the duration of survival after the onset of AIDS may also be more limited in these patients. This is consistent with the hypothesis that inhibition of interleukin-2 production by immunosuppressive therapy enhances viral expression and promotes cell death. Despite the suggestion that cyclosporine therapy might have some benefits in patients with AIDS, the experience thus far in transplant patients appears to provide little support for this theory [3, 8, 14, 15, 17, 21, 24, 26, 29].

Prevention of primary HIV infection

At least theoretically, primary infection of the transplant patient with HIV should be totally preventable provided an adequate epidemiologic history is obtained and an adequate serologic evaluation is carried out on prospective donors. The following recommendations are to be emphasized:

1. All potential allograft donors - both living related and cadaveric - should be screened for HIV infection by way of a rapid ELISA antibody test. A negative ELISA test for antibodies to HIV envelope proteins in an individual with a negative history for risk factors for HIV infection is an adequate screen for proceeding with organ donation *provided an appropriate blood specimen is utilized for the test.* The North Carolina experience cited above, where a false-negative result was obtained because the serum tested was one drawn only after 56 units of blood and blood products had diluted the patient's own anti-HIV antibody, underlines the necessity of only testing appropriate specimens if the risk of primary HIV infection is to be completely eliminated from clinical transplantation [3].

2. Because the currently available screening antibody tests for HIV have a small but definite false-negative rate, caution must be taken in approaching the use of potential donors from one of the population groups at high risk for HIV infection *even in the face of a negative ELISA antibody test for envelope proteins.* Such high risk groups will vary with each geographic locale and with the incidence of HIV infection in the particular group in the particular locale. However, in general, these groups include homosexual or bisexual men, intravenous drug users, hemophiliacs, individuals with a history of being prisoners in a correctional facility in which AIDS infection has been documented and, perhaps, immigrants from Central Africa or the Caribbean. If there is a pressing need to consider such individuals as donors, as for a life-saving cardiac transplant or for a living related kidney transplant for a highly sensitized recipient, then further serologic testing should be carried out. Such testing, ideally, should

include testing for the p24 antigen, antibody testing by Western blot, and/or testing for the antibodies to the core and regulatory proteins of HIV.

3. A high priority should be given to the deployment of the tests to detect p24 antigen and antibodies to the core and regulatory proteins for the routine testing of potential allograft donors as soon as possible.

Asymptomatic HIV infection in transplant candidates

A far more difficult problem is the issue of the clinical management of the patient in whom end-stage renal, liver, or cardiac disease develops in the context of asymptomatic HIV infection and who is thus seropositive for the virus. Published experience with this problem as well as information we have gathered as part of the Registry for the Study of AIDS in Transplantation (see below) have led to the following observations [23, 26, 29]:

1. We are aware of 6 kidney and 10 liver allograft recipients who were seropositive for HIV prior to transplant. Of these, 3 of the kidney and 6 of the liver recipients died of infection 2-30 months post-transplant. These poor results among HIV seropositive individuals stand in direct contrast with the greater than 70% one-year survival rate among HIV seronegative liver transplant patients and the greater than 90% one-year survival rate among seronegative renal transplant patients currently being observed at many transplant centers. The possibility that even some of the survivors will yet succumb to opportunistic infection or malignancy remains a major concern for physicians and patients involved in clinical organ transplantation.

2. Virtually all the deaths in such individuals have been related to infection, including *Pneumocystis carinii* pneumonia, systemic fungal, bacterial, and cytomegalovirus infection, as well as recurrent localized herpes simplex and candidal infection. Beginning attempts to utilize either trimethoprim-sulfamethoxazole prophylaxis against *Pneumocystis* or azidothymidine against HIV have already revealed that such therapies will be associated with at least as high a rate of side effects in this patient population as in other HIV-infected populations.

3. Asymptomatic individuals who are seropositive for HIV prior to transplant have considerable rejection activity post-transplantation even when full dose immunosuppressive regimens have been employed; that is, any hopes that such individuals could be managed with lesser amounts of immunosuppressive therapy because of their HIV infection have not been fulfilled. It is probable that this rejection activity has at least two detrimental effects on the course of HIV infection. First, it is likely that activation of CD4+ lymphocytes during the course of rejection will potentiate the effects of the HIV infection (see above). Second, the increased immunosuppressive therapy required to treat rejection in these patients will add to the patient's net state of immunosuppression and would be undesirable; one would like to avoid this.

Recommendations for the management of asymptomatic carriers of HIV

What then should be the position of the transplant community towards patients who - if they were not HIV-positive - would be deemed excellent candidates for transplantation? It is clear that in this extremely important area our information is very incomplete. At the present time, we would make the following very tentative recommendations [26]:

1. Although the number of individuals studied thus far is quite small, dialysis rather than transplantation appears in most such circumstances to offer the best available treatment for end-stage renal disease in patients seropositive for HIV.

2. In patients with liver or cardiac failure for whom no potential alternative life-support system is as yet available, it may be reasonable to attempt transplantation. However, because of concerns about excess cost and the inappropriate allocation of scarce organs, this should be carried out only at centers with experience both in organ transplantation and in AIDS/HIV investigation.

3. Because the initial impression has been that the course of these patients can be greatly abbreviated from the period of asymptomatic infection to life-threatening opportunistic infection, and from that moment to death when transplanted, such patients appear to be prime candidates for experimental therapies thought to be effective against AIDS and HIV.

4. A registry is needed to serve as a repository of detailed information regarding the experience with transplantation in persons with HIV infection. Such a registry would serve as an invaluable international resource of clinical information relevant to this problem. Issues such as the possible value of different anti-HIV strategies, anti-cytomegalovirus prophylaxis, and trimethoprim-sulfamethoxazole and anti-candidal prophylaxis could all be addressed in this fashion. Fortunately, no one transplant center is likely, in the near future, to have extensive experi-

ence with HIV-infected patients. However, it is likely that many transplant centers will have some experience. We would suggest that it is only by pooling our shared experience that we will learn how to deal with a problem that is already confronting us.

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