

## BRIEF REPORT

## Successful Cardiac Transplantation in an HIV-1–Infected Patient with Advanced Disease

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**A**DVANCES IN THE MANAGEMENT OF HUMAN IMMUNODEFICIENCY VIRUS (HIV) infection — specifically, the introduction of highly active antiretroviral therapy — have dramatically delayed the progression of disease, enhanced immunologic function, and reduced mortality.<sup>1</sup> Coincident with these trends has been an increase in mortality due to end-organ failure, rather than from other life-threatening causes related to HIV.<sup>2</sup> Therapy for end-organ failure has generally been supportive, but during the past few years, a small number of solid-organ transplantations, mostly of kidneys and livers, in patients known to be HIV-positive have been reported.<sup>3–5</sup> Recently, on both ethical and scientific grounds, some have called for solid-organ transplantation in HIV-positive patients to be initiated at major transplantation centers and to be viewed similarly to transplantation in other patients.<sup>6,7</sup> We report the 24-month follow-up of a patient infected with HIV type 1 (HIV-1) who underwent cardiac transplantation when his serologic status was known.

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## CASE REPORT

The patient (Dr. Robert Zackin) is a 39-year-old man who was given a diagnosis of the acquired immunodeficiency syndrome (AIDS) in March 1992, when he had *Pneumocystis carinii* pneumonia. Retrospectively, it was estimated that he had become infected with HIV early in 1986. His CD4 cell count at the time of diagnosis was 20 cells per cubic millimeter. In October 1992, Kaposi's sarcoma of the hard palate was diagnosed on biopsy; the lesion was excised. When pulmonary involvement subsequently developed in 1994, treatment with liposomal daunorubicin was begun; this treatment continued through 1995, and there was an excellent clinical response. The course of chemotherapy was complicated by several episodes of profound leukopenia and anemia; anemia was treated with erythropoietin. Several opportunistic infections developed in 1993 and 1994, including disseminated *Mycobacterium avium* complex and cytomegalovirus infection of the gastrointestinal tract, for which the patient was treated medically.

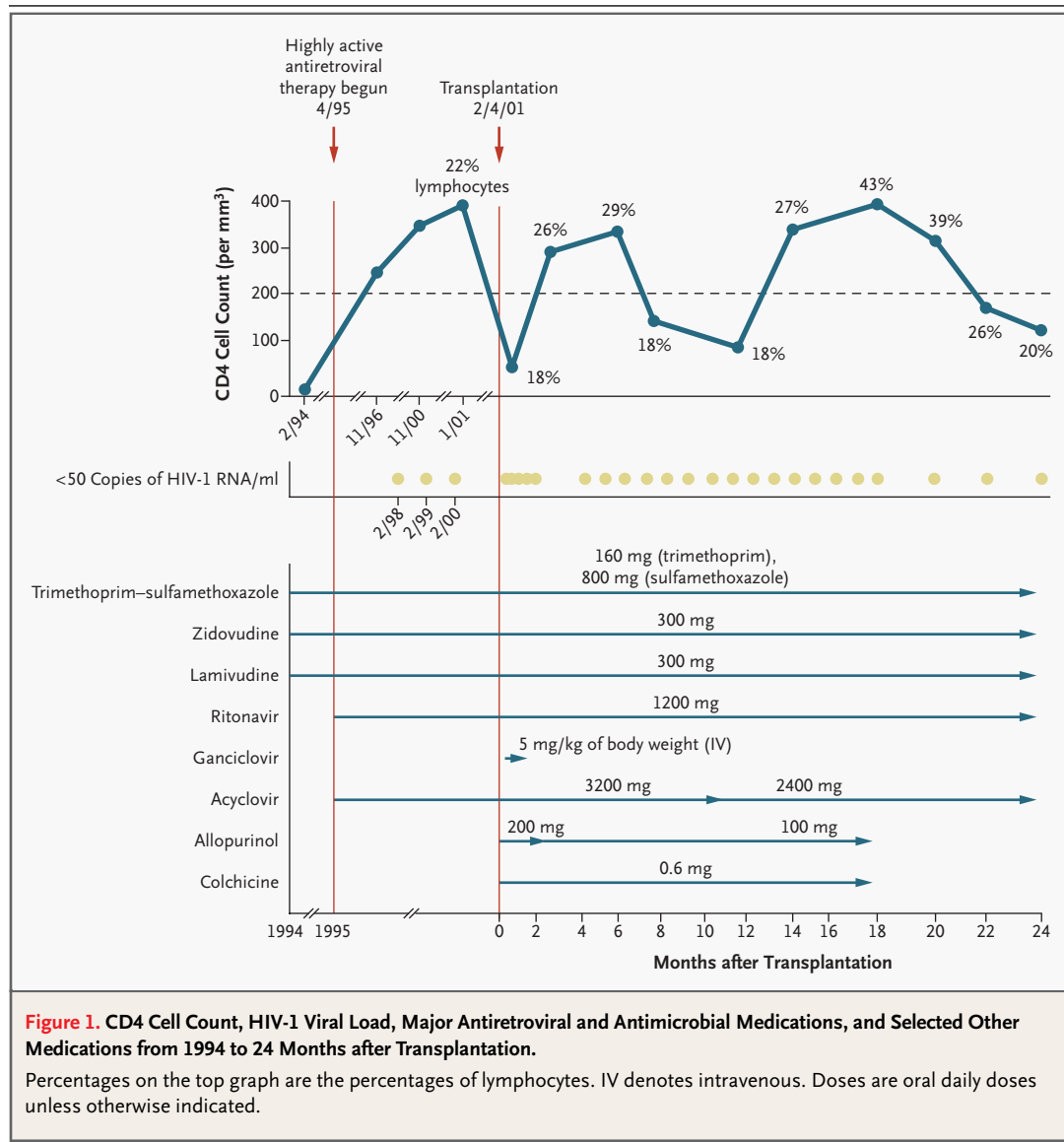
In the fall of 1995, progressive shortness of breath developed. Echocardiography revealed an ejection fraction of less than 25 percent. Liposomal daunorubicin therapy was discontinued, and paclitaxel therapy was initiated for continued management of Kaposi's sarcoma. Treatment with paclitaxel continued through the summer of 1996. In October 1999, the ejection fraction was less than 10 percent, and continuous dobutamine infusion was initiated for the management of dilated cardiomyopathy.

The nadir in the patient's CD4 cell count was 0 cells per cubic millimeter in April 1994. He began to receive antiretroviral therapy in 1992; his history of antiretroviral ther-

apy since 1994 is summarized in Figure 1. From 1992 to 1995, he was treated exclusively with nucleoside analogues in varying combinations of zidovudine, lamivudine, and stavudine. Protease-inhibitor-based therapy was initiated in June 1995, with ritonavir, an investigational agent, added to a stable regimen of zidovudine and lamivudine. HIV-1 RNA has remained suppressed, with a plasma level below the limit of quantitation (50 copies of HIV-1 RNA per milliliter). The CD4 cell count gradually increased to 250 cells per cubic millimeter or higher beginning in October 1996, several months after chemotherapy was discontinued. Through the remainder of the clinical course, no further opportunist

infections developed, nor was there a relapse of Kaposi's sarcoma.

In January 2001, the patient was evaluated at the Cleveland Clinic Foundation for possible cardiac transplantation. The base-line values for immunologic and cardiac variables are shown in Figure 1 and Table 1. Largely because of the critical nature of the case, the patient's excellent response to combination antiretroviral therapy, and the belief that the dilated cardiomyopathy had most likely resulted from daunorubicin toxicity, the patient was placed on the waiting list for cardiac transplantation. He was admitted to the hospital on January 15 to await a suitable donor. During this time, an intraaortic



**Table 1.** Cardiac Hemodynamics, Endomyocardial Biopsy Results, and Antirejection Therapy.\*

Date	Oral Dose of Cyclosporine	Whole-Blood Cyclosporine Level	Daily Oral Dose of Prednisone	Daily Oral Dose of Mycophenolate Mofetil	Daily Oral Dose of Azathioprine	Grade of Cardiac Rejection on Biopsy	Treatment for Rejection	Serum Creatinine Concentration	Pulmonary-Capillary Wedge Pressure	Cardiac Output
	mg	ng/ml		mg				mg/dl	mm Hg	liters/min/m <sup>2</sup>
Jan. 16, 2001 (before transplantation)								2.1	25	3.9
April 2, 2001	75 every other day	250	20	750		2–3A	Prednisone orally, 100 mg × 3 days	1.4	10	9.6†
April 17, 2001	50 every other day	523	20	750		1A		2.1	12	
April 30, 2001	50 every other day	333	20	750		2–3A	Prednisone orally, 100 mg × 3 days	1.9		
May 14, 2001	50 every other day	435	20	750		2–3A	Methylprednisolone IV, 1000 mg × 3 days	2.3		
June 25, 2001	50 every other day	512	20	1250		2	Prednisone orally, 100 mg × 3 days	2.5	6	
Sept. 10, 2001	25 daily	310	18	1250		2	Prednisone orally, 100 mg × 3 days	2.4	5	
Jan. 7, 2002	25 daily	372	15	1000		2–3A	Prednisone orally, 100 mg × 3 days	2.5	5	
Jan. 28, 2002	25 daily	325	12		50	2		2.2		9.1‡
Aug. 7, 2002	25 daily	296	5		25	1A		2.7	6	

\* Transplantation was performed on February 4, 2001. IV denotes intravenous.

† Cardiac output was measured on March 1, 2001.

‡ Cardiac output was measured on March 1, 2002.

balloon pump was required for cardiac support. On February 4, 2001, the patient underwent successful orthotopic cardiac transplantation.

## RESULTS

### CLINICAL COURSE AFTER TRANSPLANTATION

The patient's cardiac, immunologic, and virologic status and medications after transplantation are also summarized in Figure 1 and Table 1. After surgery, there was a marked and immediate improvement in cardiac function, followed by a gradual, sustained improvement in functional capacity that has

so far lasted more than 24 months. Thus far, there have been no opportunistic infections since the cardiac transplantation, despite occasional decreases in the CD4 cell count to less than 100 cells per cubic millimeter.

The clinical course has been marked, however, by frequent episodes of rejection (ranging from grade 0 to grade 3A<sup>8</sup>), revealed by serial endomyocardial biopsies; these episodes have not been associated with hemodynamic changes and have been treated with intermittent glucocorticoids (the data are summarized in Table 1). Other complications after transplantation have included an exacerbation

of gouty arthritis, recurrent anal condyloma, and the development in March 2002 of anemia (hematocrit, 25 percent) that was initially attributed to distal esophagitis–gastritis on endoscopic examination in April 2002. The patient recently became transfusion-dependent, despite the resumption of erythropoietin therapy (Table 2), and currently requires transfusions of packed red cells every two to three weeks. Ehrlichia was diagnosed in October 2002; symptoms resolved after doxycycline therapy. Despite immunosuppression after the transplantation, the plasma HIV-1 RNA levels have remained below the limit of quantitation (<50 copies of HIV-1 RNA per milliliter). Careful monitoring has uncovered no development or reactivation of opportunistic infections (Table 2). The patient continues to work full-time and to exercise regularly.

#### PHARMACOKINETICS

The patient had been receiving an antiretroviral regimen including the protease inhibitor ritonavir, a drug known to be a potent inhibitor of cytochrome P-450 3A4 metabolizing enzyme in the liver and gut, as well as a P-glycoprotein inhibitor for cyclosporine that would be predicted to prolong the half-life of cyclosporine.<sup>9,10</sup> In an effort to avoid toxic effects of cyclosporine, an escalating-dose regimen based on a two-compartment cyclosporine model<sup>11,12</sup> was used to establish therapeutic, nontoxic doses. A conservative intravenous infusion of 0.32 mg per kilogram of body weight per day resulted in very low whole-blood cyclosporine levels of 31 ng per milliliter 6 hours into the infusion and 45 ng per milliliter 10 hours into the infusion.<sup>13,14</sup> An increase to 0.99 mg per kilogram per day resulted in a level of

**Table 2. Opportunistic Infections and Clinical Events before and after Cardiac Transplantation.\***

Event	Before Transplantation (3/20/92–2/3/01)	After Transplantation (2/4/01–3/30/03)
Kaposi's sarcoma	Hard palate, 10/92; given daunorubicin therapy Pulmonary involvement, 1994; given liposomal daunorubicin therapy	No clinical reactivation; PCR assays for HHV-8 remain negative
Disseminated <i>Mycobacterium avium</i> complex	1993; given ofloxacin, ethambutol, clarithromycin	No reactivation; blood cultures remain negative
Cytomegalovirus disease	Perirectal ulceration, 1994; given ganciclovir, followed by foscarnet for resistant infection	No reactivation; PCR for cytomegalovirus DNA remains negative
Fungal infections	None	No clinical infection; serum cryptococcal antigen tests and fungal blood cultures remain negative
Lymphoproliferative and lymphoma syndromes	None; positive for IgG to viral capsid antigen	None clinically; serial PCR for Epstein–Barr virus DNA (in blood): initially negative; 20 copies/100,000 B cells detected in 11/02; asymptomatic
Anemia	Stable chronic anemia with erythropoietin therapy	Resolved, erythropoietin discontinued; new-onset ana- emia in 3/02; no hemolysis; negative PCR for parvo- virus B19; erythropoietin therapy resumed — 4000 units subcutaneously 3 times/wk; distal esophagitis on endoscopy; alendronate discontinued; no tumor seen on colonoscopy; no cytomegalovirus disease; condylomata acuminata in anal canal; on bone mar- row biopsy (11/02), normocellular marrow, relative erythroid hypoplasia, no tumor seen; on flow cyto- metry, no phenotypic changes suggestive of lymphoma; patient remains transfusion-dependent; zidovudine discontinued; erythropoietin discontinued (3/02) due to lack of response
Immune thrombocytopenia	None	Platelet count, 21,000 in 3/03; antiplatelet antibody present; azathioprine discontinued; high-dose prednisone therapy initiated

\* HHV-8 denotes human herpesvirus 8, and PCR polymerase chain reaction.

244 ng per milliliter 14.5 hours later. Serial monitoring of whole-blood cyclosporine levels was performed daily from the first intravenous infusion through day 2 of oral cyclosporine therapy, and then on days 4 and 7 of oral therapy. The results of this modeling (data not shown) indicate that there was an increase in the bioavailability of cyclosporine to 90 percent by best-fit determination (normal bioavailability, approximately 30 to 40 percent) and that the elimination half-life increased from 18.7 hours on day 2 to 71.7 hours on day 7 of oral cyclosporine therapy. Subsequent adjustments of the dose and corresponding cyclosporine levels are shown in Table 1.

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#### DISCUSSION

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The early experience with solid-organ transplantation in HIV-infected patients has involved kidneys and livers and has generally been restricted to immunocompetent patients (nadir CD4 count, >250 cells, with no previous opportunistic infections); preliminary reports suggest that HIV infection does not adversely affect the outcome.<sup>3,4,6,15</sup> The need for cardiac transplantation in patients with HIV disease is at present measurably smaller than that for liver or kidney transplantation, and only a few reports of cardiac transplantations in HIV-infected patients have been published.<sup>16-18</sup> Before it became routine practice to test for HIV in potential transplant recipients, several patients who had undergone cardiac transplantation were later found to be HIV-infected; all had poor outcomes.

Arguments against performing solid-organ transplantation in HIV-infected patients have included both scientific and ethical objections. The scientific objections have generally fallen into two categories — those surrounding the untoward effects of post-transplantation immunosuppression and those related to the formidable pharmacokinetic hurdles imposed by complex drug interactions between protease-inhibitor-based antiretroviral therapy and the calcineurin antagonists used after transplantation. Our case report contributes to the scientific debate by providing limited evidence that a patient with a history of advanced AIDS, with subsequent immune recovery associated with the initiation of therapy with a protease inhibitor, can undergo successful cardiac transplantation and recover, without serious sequelae. This finding supports both the investigation of cardiac transplantation in immunocompetent patients and the practice of sol-

id-organ transplantation in general in patients with advanced but controlled HIV disease.

Of all recipients of solid-organ transplants, recipients of cardiac transplants receive an immunosuppressive regimen that is among the most potent. Despite the fact that our patient had, at one time, been profoundly immunosuppressed and had incurred further immunosuppressive insults from chemotherapy through 1996, he ultimately had a response to the addition of a protease inhibitor. By the time his chemotherapy was discontinued in 1996, his clinical course was marked by a sustained immune response that allowed him to remain free of further opportunistic infections and permitted the HIV-1 viral load to be maintained below the level of quantitation. This degree of control of HIV-1 disease persisted even through the challenges of immune activation posed by cardiopulmonary bypass and intraaortic balloon support,<sup>19,20</sup> as well as through immunosuppressive therapy after transplantation that involved glucocorticoids, calcineurin antagonists, and antimetabolites.

Because of the patient's history of advanced Kaposi's sarcoma, there was also concern about the possible reactivation of human herpesvirus 8, but none has been found on serial monitoring of blood by a sensitive polymerase-chain-reaction technique.<sup>21</sup> Careful monitoring for the reactivation of other opportunistic and endogenous pathogens has also failed to reveal any evidence of such infections (Table 2). Only 21 months after transplantation was low-level expression of Epstein-Barr virus detected in peripheral blood (Table 2). This expression was unassociated with signs or symptoms of clinical infection, and the levels of 20 to 40 copies per 100,000 B cells were in the range detected in healthy persons with latent Epstein-Barr virus infection and far below the range generally associated with post-transplantation lymphoproliferative syndromes.<sup>22,23</sup>

The principal complication after transplantation in our patient has been unusually frequent and persistent episodes of rejection, detected on endomyocardial biopsy (Table 1). During the first year after transplantation, there were six treated episodes of rejection, four of which were classified as histologic grade 2 to 3A<sup>8</sup> and two of which were classified histologic grade 2. Treatment of these episodes of rejection has consisted of glucocorticoid boluses. In addition, the dose of prednisone has been tapered much more gradually than is usual. Therefore, the patient has had a much higher level of exposure to

glucocorticoids than most recipients of heart transplants.

The pharmacokinetic hurdles imposed by our patient's antiretroviral regimen that included full-dose ritonavir were not inconsequential, and consideration was given during the period before transplantation to switching to a drug that is less inhibitory of the cytochrome P-450 system. Because of the clinical success of the patient's therapy, it was decided that ritonavir therapy should be continued and that pharmacokinetic modeling should be undertaken to address the major adjustments required in the dose of cyclosporine. With dramatic reductions in the dose of cyclosporine based on this modeling, drug levels have nonetheless been a matter of concern. Despite the use of a dose of 25 mg once daily, troughs in the whole-blood cyclosporine level have remained in the range of 198 to 531 ng per milliliter, and the most recent measurement of the serum creatinine concentration was 2.7 mg per deciliter.

Ethical issues need to be considered, including the appropriateness of expanding the pool of eligi-

ble recipients by including patients with an indication for which transplantation has unproven success, at a time when there are inadequate numbers of organs available. If HIV-infected patients are now expected to live long and productive lives when they are successfully treated, then they should not be penalized for the advances in medicine that may allow them to benefit from transplantation. The argument that such organs would be "wasted" would be supported only if transplantation is demonstrably less successful in HIV-infected patients than in other recipients. So far, kidney and liver transplantations do not appear to be less successful in this population.<sup>7</sup> To date, no other HIV-infected patients have been referred to our facility for evaluation for cardiac transplantation. Ours is only a single case, and the patient's long-term clinical course is as yet unknown. It continues to be critical to report the results of ongoing clinical trials as well as individual cases in order to further our knowledge about organ transplantation in HIV-infected patients.

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