How Feasible Is Renal Transplantation in HIV-Infected Patients?

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ABSTRACT

HIV infection has been considered for a long time an absolute contraindication to transplantation. The introduction of highly active antiretroviral therapy has led to improved immunovirological control and increased survival in HIV-infected patients. Renal transplantation can now be performed if these patients are on stable highly active antiretroviral therapy and achieve undetectable viral load and a sufficient CD4 level, in the absence of untreatable infections and cancers. Highly active antiretroviral therapy and immunosuppressive medication should be maintained for life in these patients, raising the problem of multiple drug-drug interactions. Thus, an increased rate of rejection was attributed to the difficulty of achieving sufficient immunosuppressive levels but also to the intrinsic immune system activation despite suppressed HIV RNA levels. HIV infection of the kidney allograft could constitute a renal viral reservoir that impacts long term graft survival. Future options are developing, such as transplanting organs from HIV-infected donors. With highly active antiretroviral therapy, patient and graft survival in HIV-infected kidney transplant recipients are improving and approaching that of non-infected controls.

Keywords: kidney transplant, HIV infection, highly active antiretroviral therapy, infection, rejection

INTRODUCTION

Human immunodeficiency infection virus (HIV) is one of the major infectious diseases of our time. Since the introduction of highly active antiretroviral therapy (HAART) in 1996, HIV-infected patients have better control of viral replication, and the mortality secondary to specific acquired immune deficiency syndrome (AIDS)-related complications and opportunistic infections has decreased. As HIV-infected patients live longer, chronic complications have increased, leading to terminal cardiac, liver and renal failure in these patients (1, 2). Accordingly, the need for renal replacement therapy – dialysis and renal transplantation – is continuously increasing.

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Renal disease in HIV

Several types of renal diseases may develop in HIV-infected patients. The main renal disease in HIV-infected patients is HIV-associated nephropathy (HIVAN) that represents the third most common etiology of end-stage renal disease (ESRD) in African-American patients in the United States (US) (3). Several pathogenic mechanisms of HIVAN have been proposed, such as the direct HIV-1 infection of renal glomerular and tubular epithelial cells and the expression of HIV genes in the infected renal cells. Host genetic factors, such as mutations of \textit{APOL1} and \textit{MYH9} in patients of African descent, play an important role in the pathogenesis of HIVAN. Subsequently, collapsing focal segmental glomerulosclerosis develops, associated clinically with the onset of nephrotic proteinuria and rapidly progressive renal failure (4). Treatment of HIVAN is represented by the antiretroviral therapy that has been associated with better renal outcomes in treated patients (5).

HIV infection induces abnormalities of B lymphocytes, with increased secretion of gammaglobulins and autoantibodies (6). Several immune-complex nephropathies may develop in HIV-infected patients. These may be related to circulating and \textit{in situ} HIV-antigen specific immune complexes or to coinfection with hepatitis B and C viruses (7).

Due to the efficacy of HAART, epidemiology of renal disease in HIV-infected patients is changing. The incidence of HIVAN is decreasing (from 80% in 1997 to 20% in 2004), while the incidence of nephropathies secondary to cardiovascular risk factors such as diabetes, hypertension and dyslipidemia is increasing (3, 8) (Figure 1).

Cardiovascular disease is an important cause of mortality in HIV-infected people and recent studies report a 1.5 times increase in cardiovascular events in this population (10, 11). Prevalence of traditional cardiovascular risk factors is increased in HIV-infected people. A study of 2386 HIV-infected patients reported that 40% were current smokers and 50% obese (12).

Highly active antiretroviral therapy, especially protease inhibitors and possibly abacavir, are associated with dyslipidemia, but HAART interruption leads to increased rate of cardiovascular events in HIV-infected patients (13). HIV infection itself is associated with proinflammatory markers and cytokines (hsCRP, IL-6) that promote cardiovascular disease (14). A high rate of viral replication and a low immunological control are associated with an increased risk of cardiovascular events in HIV-infected patients (15).

End-stage renal disease (ESRD) is more frequent in HIV-infected patients than in controls. A study reports that the risk of ESRD is four times higher in HIV-infected patients than in the general population (16). It is estimated that about 1.5% of all patients with ESRD are infected with HIV (17). Risk factors for ESRD in HIV-infected patients are black race, drug injection history, severe HIV infection with a high viral load and a low number of CD4 lymphocytes, hepatitis C coinfection and presence of cardiovascular risk factors such as diabetes, hypertension and dyslipidemia.18

HIV treatment with HAART stopped the steep increase in ESRD incidence in HIV-infected patients by decreasing HIVAN. Due to improved survival, ESRD incidence remains high in HIV-infected patients (19) (Figure 2).
Transplant recipient selection criteria

HIV-infected ESRD patients have been for a long time excluded from transplantation (21). However, with better antiretroviral therapy HIV-infected patients can achieve today a sufficient viral and immunological control that allows them to receive transplants and immunosuppression therapy. Nevertheless, renal transplantation in HIV-infected patients is challenging, because of problems related to immunosuppression in patients with ongoing HIV infection, drug-to-drug interactions (antiretrovirals and immunosuppressors) and the additional risk of infection and cancer.

Inclusion criteria for renal transplantation in HIV-infected patients comprise undetectable viral load under stable antiretroviral therapy, a minimal level of CD4 lymphocytes of 200 cells/mL and absence of untreatable opportunistic infections and cancers (22). All patients should undergo a psychiatric evaluation. Patients that consume alcohol should become abstinent for six months before transplantation. For drug users, a drug-free period of at least two years is recommended (23). Medical treatment inobservance is a contraindication to transplantation.

Interactions between immunosuppressors and antiretroviral therapy

There are multiple drug-drug interactions between HAART and immunosuppressive therapy. The main drugs used post transplantation are calcineurin inhibitors (CNI) – tacrolimus (TAC) and cyclosporine A (CSA) – and mammalian target of rapamycin inhibitors (mTOR) – sirolimus and everolimus. These drugs are metabolized in the liver by cytochrome P (CYP) 450 and also by the system of P-glycoprotein. Protease inhibitors (PIs), especially ritonavir, and also cobicistat, inhibit CYP450, causing large variations in through levels, potentially causing nephrotoxicity (24). Immunosuppressor doses have to be lowered and intervals between doses have to be increased (e.g., from twice a day to once a week), potentially causing rejection. Also, rejection episodes can be induced in HIV-infected kidney transplant (KT) recipients if PIs are withheld and immunosuppresor concentrations are steeply modified. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are inducers of CYP450 and decrease CNI levels, potentially causing rejection (25).

Newer antiretrovirals that do not interact with CYP450 have been developed, such as integrase inhibitors raltegravir and dolutegravir. Raltegravir is increasingly being used in HIV–infected KT recipients and is associated with good antiretroviral efficacy (26).

Doses of antiretrovirals have to be adapted in KT recipients, as most of them have a degree of residual renal failure. Tenofovir is contraindicated in patients with creatinine clearance under 60 mL/min and should be avoided in KT recipients, due to its potential of nephrotoxicity (27).

Immunosuppression and rejection

It has been believed that immunosuppression may accelerate HIV progression in kidney transplant recipients. Therefore, minimal immunosuppression was traditionally used in HIV-infected KT recipients. Transplant immunosuppression is composed of an initial induction treatment with potent immunosuppressors, followed by a maintenance treatment. Studies that did not use induction therapy at all in HIV-infected KT recipients were faced with an increased rate of acute rejection that imposed later the intensification of immunosuppression (28). Current British guidelines (22) recommend induction with an anti-interleukin-2 (anti-IL-2) antibody basiliximab. Maintenance immunosuppressive treatment should be comprised by calcineurin inhibitors (CNI), mycophenolate mofetil (MMF) and tapering corticosteroids.

Induction with anti thymocyte globulins (ATG) is generally avoided in HIV-infected KT recipients, due to the risk of depleting CD4 lymphocytes and developing secondary infections. In a study of 150 HIV-infected KT recipients, Stock et al found that ATG induction is associated with a double incidence of infections (0.9 vs 0.4, p=0.002) (29).

A recent study on 830 HIV-infected KT recipients challenges this opinion. Anti thymocyte globulins, that are potent agents, were associated with lower rates of infections than the lighter agent anti-IL-2 antibody. This was explained by the fact that patients receiving initially induction with the less potent anti-IL-2 antibody had higher rates of acute rejection (AR), consequently needing subsequent heavy immunosuppression (30). Another study of 516 HIV-infected KT re-
Acute rejection rates in HIV infected KT recipients are 3-5 fold higher that in non-infected controls, being as high as 50%. (29-30, 32-33). Causes are multifactorial – racial, pharmacologic and immunologic – and not completely understood. Black race (30), use of cyclosporine (29), sirolimus (30) and kidney grafts from deceased donors have been associated with increased rates of AR among HIV-infected KT recipients. Drug-drug interactions between HAART and CNI leading to insufficient immunosuppression in patients taking PIs have been associated with AR. HIV infection itself is associated with immune system dysregulation, despite good viral control with HAART. There is T cell activation despite suppressed viral loads (35). Markers of inflammation such as IL-1beta, IL-6, and hs-CRP are persistently elevated (36-37). A period of six months of negative viral loads under stable HAART is mandatory before transplantation in HIV-infected patients. A prolonged period of viral suppression before transplantation was recently proved to reduce post transplant rejection. In the study of Husson et al., it was found that, if the period of viral suppression was prolonged to two years, there was a 2.48-fold reduction in the post transplant AR rate (38).

**Post transplant infections**

Incidence of post transplant infectious complications in HIV-infected KT recipients is similar to that of non-infected controls, ranging from 38 to 55% (29, 39). Bacterial infections are dominant (69%), followed by fungal (9%), viral (6%) and protozoal (1%) infections. The majority (60%) of infections occur in the first six months post transplantation, which is the period of most intense immunosuppression (29). The etiology of opportunistic infections is similar to that seen in non-transplanted HIV-infected patients. Lifelong prophylaxis against *Pneumocystis* sp. is mandatory in all HIV-infected KT recipients. Depending on CD4 levels, prophylaxis may be necessary against other pathogens such as *Histoplasma, Coccioidioides, Cryptococcus* and *Mycobacterium avium* complex.

Viral hepatitis coinfection is frequent among HIV-infected KT recipients mostly because of history of intravenous drugs use in these patients (40). They have particularly worse outcomes post transplantation, with lower patient and graft survival that non-coinfected controls. In a study of 510 KT recipients, coinfeited HIV/HCV patients had worse graft survival at 5-years (52% versus 64%, p=0.02) and at 10 years (27% vs 36.2%, p=0.004) compared with HCV monoinfected controls. Patient survival was also lower among coinfeited HIV/HCV patients at five years (66.3% vs 78.6%, p<0.01) and at 10 years (29.3% vs 56.23%, p=0.002). Risk of death was 2.85 higher among coinfeited HIV/HCV KT recipients (p<0.001) (41).

Treatment of HIV/HCV coinfection post transplantation was particularly difficult in the period when only pegylated interferon and ribavirin were available, as interferon was contraindicated due to the increased risk of graft rejection and ribavirin alone had a low response rate (42). The new direct acting antiviral agents (DAAs) have revolutionized the treatment of HCV infection due to their high rate of virologic response of 90-95% (43). However, there are multiple drug-drug interactions between DAAs, HAART and immunosuppressants that complicate the use of these agents post transplantation.

**Cancers**

HIV-infected patients are frequently coinfeited with oncogenic viruses. Human papilloma virus (HPV) is associated with cervical and anal cancers. Ebstein-Barr virus (EBV) leads to non-Hodgkin lymphomas. Human Kaposi’s herpes virus 8 (HHV8) is associated with Kaposi’s sarcoma, especially in black race and Mediterranean patients. Treatment with HAART improves immunovirological control in HIV-infected patients and is associated with a decrease in the incidence of Kaposi’s sarcoma and EBV-associanted non-Hodgkin lymphoma (44).

**Kidney as a HIV reservoir**

At the moment of transplantation, all HIV-infected KT recipients must have undetectable HIV viral loads (<50 copies/mL). However, even in the presence of undetectable viral loads, HIV still can infect renal allografts. In the study of Canaud et al, (45) in patients with undetectable HIV RNA in the blood, HIV-1 infected 68% of renal allografts. Two patterns of HIV-1 infection in renal allografts were described. The most se-
vere form was the infection of podocytes, with loss of differentiation markers and development of podocyte apoptosis and progressive renal focal segmental glomerulosclerosis (FSGS). This was associated clinically with nephrotic proteinuria and renal graft failure. The second form was the infection by HIV-1 of renal tubular cells. This was more frequent than the glomerular form (62% vs 38%) and was associated with better graft outcomes. The mechanisms of this are not completely understood. One explanation is that, even with good viral control, transient episodes of viremia can arise (HIV blips). Other hypothesis is the transfection of HIV from HIV-infected T-cells of the recipient to the naïve renal cells of the kidney allograft (47). HIV infection of the renal epithelial cells constitutes a viral reservoir and has adverse consequences on renal allograft function (45).

**HIV-to–HIV transplantation**

A solution to donor shortage in HIV-infected population could be the use of organs from HIV-infected donors. The first four cases of renal transplantation from HIV-infected donors have been performed by Muller et al in 2010 in South Africa, with 100% graft and patient survival at one year (48). In 2015, the same author reported a series of 27 HIV-to-HIV transplantations (49). Patient survival rates at one, three and five years post transplantation were 84%, 84% and 74%, respectively. Graft survival rates were 93%, 84% and 84%, respectively. The median serum creatinine at one year was 1.3 mg/dL (IQR 1.2-1.3). The allograft rejection rate was 8% at one year and 22% at three years. Post transplantation patients had good immunovirological control and did not develop opportunistic infections. Overall, HIV-to-HIV transplantation seems to have favorable results. Issues may be represented by the possibility of acquiring a more virulent strain of HIV and the development of viral resistance. Infection of medical personnel while manipulating HIV-infected organs is another potential concern.

**Patient and graft survival**

Before the HAART era, patient and graft survival in HIV-infected KT recipients were inferior to that of HIV-negative controls (50). Introduction of HAART improved post transplant outcomes in HIV-infected KT recipients. In the study of Stock et al, patient survival rates were 94.6% at one year and 88.2% at three years. Graft survival rates were 90.4% and 73.7%, respectively. These results were comparable to that of older (>65 years) non-infected KT recipients from the large database of Scientific Registry of Transplant Recipients (SRTR) (29). In another recent study of SRTR database, 10 year outcomes were reported. HIV-infected KT recipients had similar outcomes to that of non-infected controls, but HIV/HCV coinfected KT recipients had worse outcomes (41). In European studies from France (51), Spain (52) and United Kingdom (53), patient survival of HIV-infected KT recipients was excellent, ranging from 91.3 to 100% at one and three years. Graft survival at one year ranged from 85 to 98% and at three years from 74 to 84.7%. These results were similar to HIV-negative controls.

**Multidisciplinary approach**

Management of HIV-infected KT recipients needs a multidisciplinary approach. The nephrologist has to deal with multiple post transplant issues such as impaired renal function, hydroelectrolytic disturbances, hypertension, acute and chronic rejection, etc. The surgeon has to manage post transplant urologic complications. Specific HIV complications and opportunistic infections have to be managed by a HIV-experienced infectionist. Complex drug-drug interactions between HAART and immunosuppressors need the advice of a pharmacist with experience in HIV care. A social assistant has to deal with specific social issues in these patients.

**CONCLUSIONS**

Renal transplantation in HIV-infected patients is a viable option in patients treated with HAART and with good immunovirological control. Some issues remain to be resolved, such as the multiple drug-drug interactions between HAART and immunosuppressors and the increased rates of rejection and infections. Patient and graft survival are somewhat lower than in non-infected KT recipients, but significantly higher than before the HAART era. A multidisciplinary approach of the management of these patients is mandatory for their care.

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