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Liver and Kidney Transplantation in HIV-Infected Patients

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Abstract

HIV infection has evolved into a chronic condition as a result of improvements in therapeutic options. Chronic exposure with HIV and associated co-pathogens as well as toxicities from prolonged therapy with antiviral medications has resulted in increased morbidity and mortality rates from end-stage liver and kidney disease in the HIV-infected population. Since the definitive treatment for end-stage organ failure is transplantation, demand has increased among HIV-infected patients. Although the transplant community has been slow to recognize HIV as a chronic condition, many transplant centers have eliminated HIV infection as a contraindication to transplantation as a result of better patient management and demand. This review examines the current clinical strategies and issues surrounding liver and kidney transplantation in HIV-infected patients **(AIDS Rev. 2009;11:190-204).**
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Key words

HCV. HBV. Transplant. Renal. Hepatic. End-stage organ failure.

Introduction

The advent of highly active antiretroviral therapy (HAART) has changed the course of HIV disease, which has evolved into a chronic condition. As a result, there is an increasing rate of morbidity and mortality from end-stage liver, kidney, and heart disease in HIV-infected people[1,2]. In the past, the presence of HIV was viewed as a contraindication to transplantation due to logical concerns that immunosuppression would exacerbate an already immunocompromised state. Other issues, such as the demand for the limited pool of donor organs in a group of patients with a limited expectancy for survival, the risk of infection of surgical staff, and the lack of expert care for such complex patients, also contributed to the controversy[3]. The transplant community has been slow to recognize the transition of HIV infection to a chronic condition. Unfortunately, delayed patient evaluation and enlistment on the transplant waitlist have contributed to high mortality rates on the waiting lists, thus contributing to the confusion surrounding the safety and efficacy of transplantation in HIV-infected subjects[4]. In light of the foreseeable increasing demand for transplantation as the definitive management of end-organ failure in these patients, this has prompted many transplant centers to eliminate HIV infection as a contraindication to transplantation. This limited review examines the current clinical strategies and issues surrounding liver and kidney transplantation in HIV-infected patients. In addition, the current clinical strategies that have resulted in good outcomes after solid organ transplantation in HIV-infected patients will be described. While transplantation for the management of bone marrow disease and cardiomyopathy secondary to HAART and HIV will not be discussed in this review, these are two areas that are slowly gaining acceptance in the transplant community[5,6].

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Demand for transplantation in HIV-infected patients

With the advent of HAART in 1996 and improved prophylaxis for opportunistic infections there has been a dramatic decline in mortality secondary to the progression of HIV to AIDS. As a result, HIV-infected patients are increasingly likely to experience comorbidities that

affect the general population. Thus, it is not surprising that HIV-infected patients now represent an increasing population on the kidney and liver transplant waiting lists[7,8].

Kidney disease associated with chronic HIV

Since the early years of the AIDS epidemic, the medical and scientific community has been aware of the various forms of renal disease in HIV-infected patients[9,10]. Renal diseases directly related to HIV infection include HIV-associated nephropathy (HIVAN), immune complex diseases, and thrombotic microangiopathy. Although the widespread use of HAART has decreased the incidence of HIV-related renal disease[10,11], the overall frequency of renal disease continues to increase in the HIV-infected population[8,12]. This is the result of long-term HAART therapy, drug toxicity, advancing age, and chronic viral infections (hepatitis viruses and HIV). A recent review article by Fine, et al. summarizes in detail the epidemiology, pathogenesis, and current management of renal disease in HIV-infected patients[13]. Some of these diseases, despite prompt diagnosis and aggressive treatment, ultimately progress to end-stage renal disease (ESRD).

The most aggressive HIV-related renal disease is HIVAN. Although up to 10% of HIV-infected patients will develop HIVAN[14], only a small fraction will develop ESRD and require kidney transplantation. If not urgently diagnosed and treated, these patients can rapidly progress to ESRD within weeks to months. The etiology of HIVAN is not well known, but multiple studies suggest that it is due to direct infection of HIV-1 on renal epithelial cells[15]. This variant of focal sclerosing glomerulonephritis is diagnosed by kidney biopsy and afflicts mainly patients of African descent[16-18]. Currently, HIVAN is the third most common etiology of ESRD among African Americans of 20-64 years of age, after diabetes and hypertension[19]. The estimated prevalence of subjects with HIV on dialysis is nearly 1% of the total ESRD population in the USA and Europe[20]. As a result of shared transmission modalities, coinfection with hepatitis B virus (HBV) or hepatitis C virus (HCV) is common and these patients are also at risk of developing hepatitis virus-associated glomerulonephritis. The HCV-associated glomerulonephritis is caused by the deposition of immune complex formation with HCV antigens in the glomerulus[21]. The goal in managing this disease is to reduce the HCV load with interferon therapy. According to a Spanish study, approximately 61% of HIV-infected patients on dialysis are coinfected with HCV[12]. This is a challenging disease to manage and currently increasing in frequency[12].

HIV-specific immune complex-mediated glomerulonephritis, such as immunoglobulin A nephritis and lupus-like disease, are not as aggressive as HIVAN. Immune complexes with HIV antigens have been found in the circulation and renal parenchyma of HIV-infected patients with immunoglobulin A nephritis[22,23]. Thrombotic microangiopathy is a rare renal disease that is due to viral-induced damage of endothelial cells, resulting in platelet activation and deposition of thromboses in the renal microvasculature[24].

Kidney disease may be exacerbated by nephrotoxicity related to multiple HAART and infection prophylaxis medications such as ritonavir and trimethoprim-sulfamethoxazole. Tenofovir and adefovir, alternative agents used in the management of lamivudine-resistant hepatitis B before and after liver transplantation, are also potentially nephrotoxic agents. Calcineurin inhibitors (CNI) such as cyclosporin A (CsA) or tacrolimus, used in immunosuppressive therapy, are also nephrotoxic. Medications can cause renal damage by precipitating as drug crystals in the renal tubular lumen (indinavir, atazanavir, sulfadiazine, ciprofloxacin, and intravenous acyclovir) and has recently been summarized[13,25].

HAART, which has been pivotal in controlling viral replication and prolonging survival, also causes metabolic derangements, specifically insulin resistance and diabetes mellitus, hypertension, and hyperlipidemia[26]. The long-term use of these medications may exacerbate pre-existing renal insufficiency and potentially lead to ESRD. Therefore, as HAART becomes increasingly more accessible and the HIV-infected population ages, the demand for renal transplantation as part of the management of HIV-related and HIV-unrelated ESRD will increase.

Liver disease associated with chronic HIV infection

Unlike renal disease, HIV does not directly cause liver disease. The main etiologies of liver disease in HIV-infected patients are secondary to coinfections with HBV[27] and HCV[28]. Early reports demonstrated the prevalence of end-stage liver disease (ESLD) in HIV-infected patients as the result of HCV and HBV coinfection to be 23-33[29] and 9%[30], respectively. Progression to cirrhosis is accelerated in HIV-infected subjects[31-36]. Soriano, et al. reported the median survival following decompensation of cirrhosis to be 13 months[36]. As a result, liver disease has become a major cause of death in HIV-infected subjects with HCV or HBV coinfection.

Despite effective control of HIV replication, the HAART regimen can be directly and indirectly hepatotoxic. Hepatotoxicity is a significant cause of morbidity, mortality, and treatment discontinuation in HIV-infected patients[37]. Because HAART consists of multiple medications, it is difficult to determine the contribution that each drug has on the development of hepatotoxicity. There are several reports describing pathogenic mechanisms of how specific HAART drugs may act to promote hepatotoxicity[38]. Nonnucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI) can cause direct hepatotoxicity, and indirect liver injury through drug interactions or immune-mediated responses. Nevirapine is an NNRTI reported to be associated with immune-mediated hepatotoxicity, severe allergic reactions such as Steven's Johnson syndrome or toxic epidermal necrolysis, and death[39]. Pregnant patients and patients with high CD4 counts are especially at a high risk of acquiring immune-mediated hepatotoxicity secondary to nevirapine[40,41]. Nucleoside analogs have been reported to cause mitochondrial toxicity and massive hepatic steatosis with lactic acidosis[41-43].

Protease inhibitors may indirectly damage the liver through induction of insulin resistance, and promote steatohepatitis[37]. HAART-assisted immune reconstitution can indirectly exacerbate liver insufficiency by promoting immune restoration hepatitis in the setting of HBV or HCV coinfection. The frequent use of lamivudine as a component of HAART therapy can lead to the development of lamivudine-resistant HBV and rapid decompensation of liver function[44,45]. Although not as common, medications used as prophylaxis or treatment for opportunistic infections, such as trimethoprim/sulfamethoxazole, isoniazid, rifampicin, and fluconazole, have been shown to cause liver dysfunction in a direct or indirect manner[46,47]. For the all of these reasons, it is clear that the number of HIV-infected people with decompensated liver disease will continue to increase both as a direct result of viral coinfection as well as the indirect impact of the medications used to treat HIV infection. Thus, further increases in the demand for liver transplantation in people with HIV should also be expected.

Early outcomes of transplantation in HIV-infected recipients

Early reports of kidney and liver transplants performed in HIV-infected recipients during the HAART era demonstrated comparable results to HIV-uninfected recipients in selected patients. These pilot trials have set the foundation for kidney and liver transplantation in the HIV-infected patient.

Kidney transplant

In the first prospective pilot trial of kidney transplants in people infected with HIV, the selection criteria were conservative[48]. Patients with a history of opportunistic infections were excluded. In addition, recipients had to have a CD4 count > 200 cells/µl and a non-detectable HIV viral load on a stable antiretroviral regimen. In this selected group of recipients, the short-term allograft and patient survival rates were comparable to non HIV-infected kidney transplant recipients. The HIV disease remained under excellent control without evidence of progression. An unexpected finding was a relatively high incidence of rejection. A significant number of these rejection episodes required lymphocyte-depleting regimens in order to control moderate to severe rejection[49]. This aggressive anti-rejection therapy was well tolerated and provided effective reversal of the rejection episodes, but the long-term impact of these early rejection episodes is unknown.

Several retrospective analyses, case reports, and small prospective studies also demonstrate patient and graft survival in selected HIV-infected patients to be similar to those seen in HIV-uninfected patients[12,48-56]. One recent prospective cohort study of kidney recipients followed for over three years showed graft and patient survival rates at three years of 94 and 83%, respectively. However, the same study demonstrated a rejection incidence at one and three years of 52 and 70%, respectively[50]. Acute rejection rates following kidney transplantation in HIV-infected recipients were reported to range from 43 to 67%[48,50,52,54]. Higher acute rejection rates have been observed in patients of African descent[48,50,52,54]. The etiology of such a high rejection rate is unclear. Dysregulation of the immune system or insufficient immunosuppression are two possibilities.

More recent studies demonstrate that induction by anti-CD25 antibody and maintenance on sirolimus results in a lower rejection rate; however, the one-year patient and graft survival was 85 and 75%[52]. Another a small retrospective study examined the outcomes of eight renal allograft HIV-positive recipients, induced with an anti-interleukin-2 receptor antibody and maintained on CsA, mycophenolate mofetil (MMF), and prednisone, with a median follow-up time of 15 months. They reported patient and graft survival to be 100 and

88%, respectively, and an acute rejection rate of 13%[54]. In both of these studies, the patients did not demonstrate any progression of their HIV disease. Although the data from these two studies are promising, both require further verification with longer follow-up and a larger cohort of patients. Table 1 summarizes the main characteristics of graft and patient survival following kidney transplantation in HIV-infected patients.

Liver transplantation

Early retrospective studies on outcomes following liver transplantation in people with HIV were limited by a lack of information regarding HIV viral loads and CD4 T-cell counts. Successful liver transplantation in HIV-infected recipients has been documented in a retrospective review from the Scientific Registry of Transplant Recipients [55]. The one-year survival rate ranged between 60-100%[33,48,50,55,57-73]. The largest of these studies compared pooled data on HIV-infected liver transplant recipients from multiple centers (University of California San Francisco, University of Miami, University of Pittsburgh, University of Minnesota, and King's College) to the United Network for Organ Sharing (UNOS) database cohort of age- and race-matched HIV-uninfected recipients[60]. The cumulative survival at one, two, and three years in HIV-infected recipients (87, 73, and 73%, respectively) was comparable to HIV-uninfected recipients (87, 82 and 78%, respectively)[60]. Poorer survival was associated with HCV infection, posttransplant HIV medication intolerance, and a posttransplant CD4 count < 200 cells/µl. A recent prospective trial reported one- and three-year liver graft survival of 82 and 64%, respectively[50]. Multiple studies consistently observed that despite stable CD4 counts and HIV RNA loads, viral hepatitis recurred in the majority of the HCV-coinfected patients but not in the recipients coinfected with HBV.

Clearly, the most significant morbidity associated with liver transplantation in HCV/HIV-coinfected patients has been the inability to control posttransplant HCV recurrence. One French study reported a two-year survival rate of 70% in HIV/HCV-coinfected patients, but a 90% survival rate in HIV/HBV-coinfected patients[66]. In their report they observed that HCV recurrence was more severe in HIV-coinfected patients[66]. A French study showed HCV/HIV-coinfected and HCV-monoinfected recipients to have a five-year survival rate of 51 and 81%, respectively[65]. One study from the USA reported a five-year patient survival rate of 33% in HCV/HIV-coinfected patients and 72% in HCV-monoinfected patients[62]. They also reported that the predictors of mortality in coinfected patients are African descent, pretransplant Model for End-Stage Liver Disease (MELD) score of more than 20, intolerance to HAART posttransplantation, and high posttransplant HCV viral load[62]. Table 1 summarizes the main characteristics of graft and patient survival following liver transplantation in the HIV setting.

Unlike HCV/HIV-coinfected patients, HBV infection has been well controlled posttransplantation in recipients coinfected with HIV and HBV. With the advent of an increasing number of agents effective in the treatment of lamivudine resistance, the recurrence of HBV infection in recipients with lamivudine resistance has been prevented posttransplantation in lamivudine-resistant hepatitis B recipients[50,68].

Selection criteria

The acceptance criteria for proceeding with transplantation in the HIV-infected patient continue to evolve as results from early studies become available. Traditionally, the selection criteria were built around concerns that providing further immunosuppression to the HIV-infected recipient would accelerate their progression of HIV to AIDS. There were also concerns with regards to limited resources in a group a recipients with unknown survival. Due to promising results from multiple trials, further insight into pharmacology, closer monitoring, and evolving management of HIV and immunosuppression, the acceptance criteria continues to be liberalized. Table 2 records the main selection criteria currently used for kidney and liver transplantation.

HIV factors

The University of California, San Francisco (UCSF) criteria for solid organ transplantation in HIV-infected patients are based on established North American and European transplantation criteria in HIV-uninfected patients, including prolonged period of abstinence from alcohol and narcotics, sufficient rehabilitation, and demonstration of social support. The criteria are also based on CD4 T-cell counts, HIV viral load, and the history and presence of specific opportunistic infections[48,50,68,74].

To proceed with a kidney transplant, most centers require adult recipients to have CD4 T-cell counts > 200 cells/µl[75]. For liver transplant recipients, the CD4 T-cell count must be > 100 cells/µl. T-cell counts are decreased for liver transplantation candidates, as

Table 1. Patient and graft survival rates in kidney and liver transplant recipients with HIV

Kidney														
					Patient					Graft				
		(n)	Study design		1 year	2 year	3 year	4 year	Other	1 year	2 year	3 year	4 year	Other
Roland, et al. 2008[50]	USA	18	Prospective		94%		94%			83%		83%		
Gruber, et al. 2008[54]	USA	8	Retrospective						100% (Mdn = 15 months)					88% (Mdn = 15 months)
Kumar, et al. 2005[52]	USA	40	Prospective		85%	82%				75%	71%			
Pelletier, et al. 2004[55]	USA	63	Retrospective	Deceased donor	92%	89%				84%	84%			
		37		Living donor	95%	90%				92%	74%			
Tan, et al. 2004[51]	USA	4	Prospective	Deceased donor					100% (M = 49 months)					50% (M = 49 months)
		3		Living donor/on alemtuzumab					100% (M = 246 days; Mdn = 262 days)	100%	100%	100%	100%	100% (M = 246 days; Mdn = 262 days)
Abbott, et al. 2004[53]	USA	47	Retrospective				96%		Past 3 years beyond tx.			98%		Past 3 years beyond tx.
Trullas, et al. 2005[56]	Spain	7			100%		100%			85.7-100%		85.7-100%		
Liver														
					Patient					Graft				
		(n)	Study design		1 year	2 year	3 year	4 year	Other	1 year	2 year	3 year	4 year	Other
Testillano, et al. 2009[69]	Spain	12	Prospective	HCV	83%	75%	62%							
Roland, et al. 2008[50]	USA	11	Prospective		91%		64%			82%		64%		
Duclos-Vallée, et al. 2008[65]	France	35	Prospective	HCV		73%			51% (5 years)					
Di Benedetto, et al. 2008[70]	Italy	10	Prospective		65%	65%	65%			54%	54%	54%		

(Continue)

Table 1. Patient and graft survival rates in kidney and liver transplant recipients with HIV *(continued)*

Liver															
					Patient					Graft					
		(n)	Study design		1 year	2 year	3 year	4 year	Other	1 year	2 year	3 year	4 year	Other
Mindikoglu, et al. 2008[33]	USA	138	Retrospective			70%	66%							
Castaing, et al 2007[66]	France		Prospective	HBV		90%								
				HCV		70%								
Castells, et al. 2007[71]	Spain	9	Prospective	HCV			87%							
Wojcik, et al. 2007[63]	Germany	4	Prospective	HCV	100%	100%	100%	100%	100% (M = 41 months; Mdn = 45 months)	100%	100%	100%	100%	100% (M = 41 months; Mdn = 45 months)
Vennarecci, et al. 2007[72]	Italy	12	Prospective		83%	58%	58%							
Schreibman, et al. 2007[57]	USA	15	Retrospective		73%	73%	73%							
Terrault, et al. 2006[68]	USA	4	Retrospective	HBV	100%	100%	100%	100%	100% (Mdn = 31 months)	100%	100%	100%	100%	100% (Mdn = 31 months)
de Vera, et al. 2006[62]	USA	27	Prospective	HCV	67%		56%		33% (5 years)	63%		52%		31% (5 years)
Vogel, et al. 2005[61]	Germany	7	Retrospective						86% (n=6) (M = 30 months; Mdn = 24 months)					86% (n=5) (M = 30 months; Mdn = 24 months)
Radecke, et al. 2005[73]	Germany	5	Prospective	HCV/HBV/ HCV-HBV					40% (M = 26 months)					
Pelletier, et al. 2004[55]	USA	87	Retrospective		75%			69%		70%			65%	
Ragni, et al. 2003[60]	USA	24	Prospective		87%	73%	73%							
Prachalias, et al. 2001[59]	United Kingdom	5	Retrospective						40% (Mdn = 15 months)					

M: mean; Mdn: median, Tx: transplantation.

Table 2. Inclusion and exclusion criteria for kidney and liver transplant candidates infected with HIV (www.natap.org)

Inclusion criteria	
Kidney	**Liver**
Meeting standard criteria for inclusion in renal transplantation list.	Meeting standard criteria for inclusion liver transplantation list.
Primary medical care provider has expertise in HIV treatment.	Primary medical care provider has expertise in HIV treatment.
CD4 T-cell counts ≥ 200/µl at any time 16 weeks before transplantation.	CD4 T-cell counts ≥ 100/µl within 3 months of transplantation; case-by-case evaluation if patient on interferon therapy. Paediatric population: Age 1-2 year ≥ 30 % T-cells; Age 2-10 years ≥ 20 % T-cells
HIV viral load undetectable.	HIV viral load preferred to be undetectable; case-by-case evaluation if patient had to transiently stop HAART due to liver toxicity; HIV virus must be controllable posttransplant.
No change in antiretroviral regiment for 3 months before transplantation.	Patient should not have multidrug resistant HIV.
Ability and willingness to comply with immunosuppressive protocol and antiretroviral therapy.	Ability and willingness to comply with immunosuppressive protocol and antiretroviral therapy.
Ability and willingness to undergo prophylaxis for pneumocystis pneumonia, herpes virus and fungal infection.	Ability and willingness to undergo prophylaxis for pneumocystis pneumonia, herpes virus and fungal infection.
If hepatitis C coinfection is present, ability and willingness to undergo frequent posttransplantation monitoring and treatment as mandated by medical care provider and collection of liver biopsy samples.	HIV/HCV-coinfected patients preferred to have lower MELD scores, higher body/mass indices and absence of renal sufficiency. HIV/HBV-coinfected patients preferred to have HBV that is predicted to be controllable posttransplantation, preferrably not multidrug resistant.
If a history of pulmonary coccidiodomycosis exists, patient must be disease-free for at least 5 years before transplantation.	If a history of pulmonary coccidiodomycosis exists, patient must be disease-free for at least 5 years before transplantation.
If a history of neoplasms such as cutaneous Kaposi sarcoma, in situ anogenital carcinoma, adequately treated basal or squamous cell carcinoma of the skin or solid tumors treated with curative therapy exists, the patient must be disease-free for at least 5 years before transplantation.	If a history of neoplasms such as cutaneous Kaposi sarcoma, in situ anogenital carcinoma, adequately treated basal or squamous cell carcinoma of the skin or solid tumors treated with curative therapy exists, the patient must be disease-free for at least 5 years before transplantation.
If a history of renal cell carcinoma exists, patient must be disease-free for at least 2 years before transplantation	Patients with history of Kaposi's sarcoma (KS) require a recent high-resolution CT scan without evidence of pulmonary KS.
Ability to provide informed consent. For children under the age of 7 years, only the parent can provide consent. For children aged 7-12 years, the parental or legally responsible person must provid informed consent and the minor must sign an assent. In the case of a minor between ages 13 and 18 years, the minor and parent)s) must provide informed consent.	Ability to provide informed consent. For children under the age of 7 years, only the parent can provide consent. For children aged 7-12 years, the parental or legally responsible person must provid informed consent and the minor must sign an assent. In the case of a minor between ages 13 and 18 years, the minor and parent(s) must provide informed consent.
Female candidates of child-bearing potential must have a negative serum human chorionic gonadotropin chain-β pregnancy test 2 weeks before transpalntation. All candidates must practice barrier contraception.	Female candidates of child-bearing potential must have a negative serum human chorionic gonadotropin chain-β pregnancy test 2 weeks before transpalntation. All candidates must practice barrier contraception.

(Continue)

Table 2. Inclusion and exclusion criteria for kidney and liver transplant candidates infected with HIV (www.natap.org) *(continued)*

Exclusion criteria	
Kidney	**Liver**
Age < 1 year	Age < 1 year
History of progressive multifocal leukoencephalopathy, chronic cryptosporidiosis, AIDS-associated lymphoma (Burkitt, immunoblastic or brain), multidrug-resistant fungal infection.	History of progressive multifocal leukoencephalopathy, chronic cryptosporidiosis, AIDS associated lymphoma (Burkitt, immunoblastic or brain), multidrug-resistant fungal infection.
History of neoplasm except those specified in inclusion criteria.	History of neoplasm except those specified in inclusion criteria.
Substance use as per local transplantation policy.	Substance use as per local transplantation policy.
Advanced cardiac or pulmonary disease as per local transplantation policy.	Advanced cardiac or pulmonary disease as per local transplantation policy.
Anatomic abnormalities precluding transplantation.	Anatomic abnormalities precluding transplantation.
Substantial wasting and/or malnutrition.	Substantial wasting and/or malnutrition.
Concomitant conditions that, in the judgement of care providers, preclude transplantation or immunosuppression.	Concomitant conditions that, in the judgement of care providers, preclude transplantation or immunosuppression.
Use of interleukin-2 or granulocyte-macrophage colony-stimulating factor in the 6 months before transplantation.	
Cirrhosis on liver biopsy in patients with hepatitis C coinfection, unless candidate is being listed for combined liver and kidney transplant.	

patients with end-stage liver disease and portal hypertension have some splenic sequestration of T-lymphocytes secondary to splenomegaly[76]. Unlike adults, the percentage of CD4 T-cells is a better reflection of the pediatric intact immune system[77]. For children 1-2 years of age, and 2-10 years of age, the CD4 T-cell should be greater than 30 and 20%, respectively[78]. An undetectable HIV viral load at the time of liver and kidney transplantation is a most desirable goal for the surgical team in the event of a needle stick injury; however, many liver transplant recipients are unable to achieve an undetectable HIV viral load due to medication intolerance and temporary discontinuation of HAART. In these patients, a decision to proceed with transplant is dependent on the ability to suppress the virus post-transplantation. This decision is facilitated by input from an HIV provider and is in part related to the resistance of the HIV virus to antiretroviral agents.

Opportunistic infections

A history of opportunistic infections is no longer considered as exclusion criteria in most European countries and North America, as long as the opportunistic infections can be treated successfully. Therefore, infections that remain contraindications include progressive multifocal leukoencephalopathy, chronic cryptosporidiosis, and drug-resistant fungal infections. Tissue-invasive cytomegalovirus disease is no longer a contraindication as it can be controlled with oral antiviral agents.

Most clinical trials currently include patients with resolved cutaneous Kaposi's sarcoma (KS); however, HIV-infected patients with a history of visceral KS are usually excluded. This is an exclusion criterion because of experience in HIV-uninfected transplant patients who develop KS. Historically, cessation of immunosuppression in order to control the KS was required. The support for proceeding with transplantation in HIV-infected patients comes from isolated case reports demonstrating that prompt initiation of HAART and reconstitution of the immune system can control the KS. Moreover, sirolimus, a vascular endothelial growth factor inhibitor and immunosuppressant agent, can be used to treat KS and maintain immunosuppression[79].

Disease severity

The MELD scoring system is routinely used to predict the survival probability of a patient with ESLD on the waiting list[80]. This score is used in the allocation process, with higher MELD scores (sicker patients) receiving priority for liver transplantation Unfortunately, HIV-infected candidates may deteriorate at a lower MELD score than their HIV-uninfected counterparts[35,68,81]. To expedite transplantation at lower MELD scores, options include the use of living donors as well as serologically negative "high infectious risk" deceased donors that would not be used in HIV-uninfected candidates. Additionally, as with HCV-monoinfected patients, donors that are HCV-positive without evidence of active hepatitis or fibrosis have been utilized in the coinfected recipients. Hopefully, future recognition of these facts will encourage earlier referral and a decrease in the high death rate of HIV-infected liver transplant candidates while on the waiting list[82].

With the advent of tenofovir and adefovir, hesitancy in proceeding with transplantation in lamivudine-resistant HBV-coinfected patients is no longer an issue. Better selection of HIV/HCV-coinfected patients to obtain better outcomes in this challenging group of transplant candidates will require analysis of large prospective trials. To this end, a cooperative effort with 17 centers, sponsored by the UCSF and supported by NIAID/NIH, has been created with the aim to evaluate the safety and efficacy of solid organ transplantation in people with HIV disease by conducting a prospective, multicenter cohort study of HIV-infected patients who undergo kidney and liver transplantation (www.HIVtransplant.com).

Medication management

Strategies for immunosuppression

During the initial trials of transplantation in people with HIV, it was hypothesized that the HIV-positive recipient would require less immunosuppression as a result of an already immunocompromised state. Ironically, HIV-infected renal recipients may have higher rejection rates than their HIV-uninfected counterparts[48,49]. Interestingly, unlike renal transplant recipients, early liver transplant studies demonstrate similar acute rejection rates in HIV-infected and HIV-uninfected recipients[50,60]. The etiology of this aggressive, early rejection in HIV-infected renal transplant recipients is unclear. Possibilities include HIV-mediated dysregulation of the immune response, and inadequate exposure to immunosuppressive drugs due to the complex pharmacokinetic interactions between the immunosuppressive drugs and the antiretroviral agents. The impetus to prevent acute rejection has lead to further development and evaluation of immunosuppressive strategies.

During the early trials, induction immunosuppression with antibody depleting agents was avoided due to concerns of further depleting the T-lymphocytes. Maintenance immunosuppressive agents with antiretroviral properties were used. For most of the trials, maintenance immunosuppression has consisted of steroids, MMF, and a CNI. In addition to its antiproliferative properties, MMF has virostatic action, which is thought to result from the depletion of guanosine nucleosides necessary for the completion of the virus lifecycle, and the inhibition of immune activation and cellular proliferation[83,84]. Cyclosporin A and tacrolimus are two calcineurin /nuclear factor of activated T-cell inhibitors that have a prominent role in most maintenance regimens[85,86]. Both of these drugs have well-documented antiretroviral effects through selective inhibition of infected cell growth and interference with HIV pathogenic protein functions resulting in the reduction of virus formation. Both of these CNI are diabetogenic, and this may be further exacerbated when used in conjunction with the diabetogenic PI used in HAART regimens.

As a result of the unexpectedly high rates of rejection episodes, as well as the severity of these early rejection episodes, a significant number of the kidney transplant recipients have received thymoglobulin for treatment[49]. This polyclonal antibody treatment has been successful in terms of resolving the rejection episodes, but depletes the $CD4^+$ T-lymphocytes. The $CD4^+$ T-cell count remains significantly depleted for up to 3-6 months, and aggressive prophylaxis against opportunistic infections is required during this time[49,87]. The long-term impact of these early rejection episodes on kidney function remains a concern. In an effort to prevent early rejection, induction with IL-2 receptor antibodies (daclizumab, basiliximab) has been implemented at many sites performing kidney transplants in HIV-infected patients[52]. This treatment is well tolerated and does not deplete the $CD4^+$ T-cells. The efficacy of IL-2 receptor antibodies is unclear. Most centers remain reluctant to provide induction with thymoglobulin. In addition to providing induction therapy, efforts to maintain adequate levels of CNI may help decrease the high rates of rejection. Maintenance of adequate

CNI levels is challenging in patients on NNRTI as the induction of the cytochrome P450 system leads to low CNI levels. A major challenge has been related to the potent inhibition of the cytochrome P450 system in patients on PI resulting in toxic levels of the immunosuppressive agents (see section on pharmacokinetic interactions).

Since many HIV-infected and renal transplant patients experience some degree of renal insufficiency, sirolimus, a target of rapamycin (TOR) inhibitor and antiproliferative agent, has been considered as an alternative to CNI[88]. Although sirolimus is considered less nephrotoxic and diabetogenic than CNI, recent data suggests no difference in renal function in those subjects taking CNI or sirolimus, and use of sirolimus was associated with higher triglyceride levels[132]. Similar to CNI, sirolimus exerts some antiretroviral activity through suppression of T-cell activation, suppression of professional antigen-presenting cell function, and disruption of infective virion replication. Sirolimus also decreases the expression of CCR5 receptor on monocytes and lymphocytes, thus potentially preventing the virus from entering the cells and replicating[89]. Finally, sirolimus is the agent of choice in recipients with KS posttransplantation. Sirolimus inhibits vascular endothelial growth factor and is therefore effective in the treatment of this vascular tumor[79].

Strategies for HAART

Most U.S. transplant centers currently performing solid organ transplants in people with HIV infection require stable HIV disease. For that reason, it makes sense to maintain the potential recipients on the regimen they were on at the time of the referral since that regimen resulted in stable HIV disease. Early studies demonstrated that transplant recipients, regardless of their HAART regimen, did not have progression of their HIV to AIDS[50,90]. This suggested that antiretroviral dosing has been adequate regardless of the type of agents used for HAART or the impact of CNI on the cytochrome P450 system and HAART metabolism.

After transplantation, if the patient becomes hepatotoxic, neuropathic, or experiences any toxic effects of HAART, all the agents can be discontinued temporarily to avoid development of HIV drug-resistant strains. Based on initial experience, stopping HAART for several weeks does not increase the viral load and CD4 T-cell count[50,90]. In fact, recent studies report that it is safe to interrupt HAART therapy for 48 weeks in patients with CD4 T-cell counts > 350 cells/μl[91,92]. Following a drug holiday and resolution of the toxic event, a different HAART regimen should be introduced based on recommendations from the HIV providers.

Pharmacokinetic interactions

Management of solid organ transplantation in HIV-infected patients is complicated by pharmacokinetic interactions that create substantial changes in drug plasma levels. Without intensive monitoring and titration of drug levels, toxic side-effects, organ rejection, or HIV disease breakthrough can occur. Many of these interactions are mediated by the interactions between the membrane efflux transporter P-glycoprotein (P-gp) and the intracellular metabolizing enzymes system cytochrome p450 3A4 (CYP3A4) found in the intestine and liver[93,94]. Calcineurin inhibitors such as CsA and PI inhibit both P-gp and CYP3A4 activity, leading to increased intestinal uptake and decreased hepatic metabolism and excretion of both CsA and the PI. On the other hand, NNRTI induce CYP3A4 activity, decreasing CNI levels[93,94]. These effects are well documented in a recent study describing the pharmacokinetics and dosing modifications of cyclosporine, sirolimus, and tacrolimus in 35 liver or kidney transplant recipients on NNRTI, PI, or both NNRTI and PI[95]. Compared to non HIV-infected renal transplant patients or those on NNRTI, patients on PI and CsA required only 20% of the dose given to the noninfected group. Those subjects on ritonavir-boosted regimens required even less. And for those subjects on tacrolimus or sirolimus, not only was the dose markedly decreased, but the dosing interval increased more than fivefold. Similar findings have been demonstrated by other investigators in liver transplant recipients. In addition, azole antifungal (fluconazole used frequently to treat *Candida* infections) and macrolide antibiotics (clarithromycin and azithromycin frequently used to treat *Mycobacterium Avium* complex) inhibit the CYP3A4 system[96].

Steroids are commonly used in conjunction with other PI in immunosuppressive therapy or in the treatment of rejection episodes. They have complex induction and inhibition interactions on metabolic and transport systems; therefore, these patients must be monitored closely to ensure optimal treatment[97]. In addition, patients taking steroids are usually taking proton pump inhibitors, which can reduce atazanavir absorption and plasma concentration[98,99]. Therefore, patients on proton pump inhibitors benefit from ritonavir-boosted regimens with atazanavir[100].

Management strategies for coinfection with viral hepatitis

HBV management

The current success of liver transplantation in HBV-mediated liver disease can be attributed to advances in the ability to control posttransplant HBV reinfection. Because most HBV/HIV patients have lamivudine-resistant HBV from prior use of lamivudine in their HAART regimen[98], there were initial concerns that HBV/HIV-coinfected patients would be at an increased risk for uncontrolled posttransplant reinfection[101-105].

The medications currently approved for the treatment of chronic hepatitis B are interferon, lamivudine, adefovir, entecavir, telbivudine, emtricitabine, and tenofovir[106]. Despite reports demonstrating that interferon-α therapy decreases the incidence of HBV cirrhosis regardless of HIV status or serologic response[107], this therapy is not frequently administered in HIV-infected transplant patients due to associated thrombocytopenia, anemia, leucopenia, and relatively limited ineffectiveness in HIV/HBV-coinfected patients[107,108]. Ideally, if the HIV/HBV-coinfected patient requires HBV infection treatment, but does not require HIV treatment, a 12-month course of pegylated interferon-α therapy is recommended, followed by long-term nucleoside analog antiviral therapy[27]. Currently, successful prevention of HBV recurrence posttransplantation can be achieved in HIV/HBV-coinfected patients with prophylactic therapy consisting of hepatitis B immunoglobulin (HBIg), and lamivudine with tenofovir or adefovir[68]. Currently, HBIg therapy is administered indefinitely, with posttransplant dosing guided by antibody titer levels[68].

Because it is critical to prevent HBV reinfection in this early period, it is recommended to start anti-HBV medications as soon as possible. Unfortunately, many liver transplant recipients are unable to tolerate HAART therapy in the early posttransplant period. Because lamivudine, tenofovir, emtricitabine, and entecavir have both anti-HIV and anti-HBV properties, it is crucial to temporarily discontinue these medications until HAART can be reestablished to prevent the development of HIV-resistant strains. Adefovir, at HBV treatment doses, and telbivudine are two attractive alternatives as they do not have anti-HIV properties and should not contribute to the development of HIV-resistant strains[28]. Once HAART can be reinitiated posttransplantation, the strategy to prevent HBV recurrence should include HBIg and lamivudine, with or without adefovir and/or tenofovir as before transplant, with the appropriate dose adjustment for renal insufficiency[68,90].

HCV management

Liver disease is now the leading cause of death in HIV/HCV-infected patients[34,35]. Unlike the success experienced by HIV/HBV transplant patients, rapid recurrence of HCV post liver transplantation continues to be a major problem in HIV/HCV recipients[65]. The reasons for this inability to control rapid recurrence are not well defined. There are controversial reports suggesting the significance of HBV in coinfected HIV/HCV patients in influencing the progression of liver fibrosis and response to interferon therapy[109-112]. One study has documented successful control of HCV recurrence using posttransplant administration of interferon and ribavirin therapy in HIV/HCV-coinfected liver recipients[63]. Other studies have not supported the early use of interferon and ribavirin following liver transplantation for preventing HCV recurrence[65,113-115]. The complex pharmacokinetics and hepatotoxicities in patients on antiretroviral agents and immunosuppressive therapy makes interferon and ribavirin therapy challenging to administer in the early periods posttransplantation. Most centers are introducing interferon/ribavirin therapy only when there is histologic evidence of progressive HCV disease.

Some centers prefer the use of CsA over tacrolimus for immunosuppression maintenance therapy in HIV/HCV-coinfected patients as it has both anti-HCV and anti-HIV properties[116]. Steroids should be administered judiciously in HIV/HCV-coinfected recipients as steroid boluses have been shown to exacerbate HCV disease[117]. Interestingly, there have been several reports on spontaneous clearance of HCV in HCV/HIV-coinfected patients as well as HCV/HIV-coinfected recipients following transplantation[118-121]. Although patients undergoing liver transplantation for HCV coinfection have poorer outcomes than patients with HBV coinfection, it is premature to abandon transplantation in this population. Some of the recipients have done extremely well, and in light of HCV viral clearance in some coinfected recipients (both spontaneous and following interferon therapy), further mechanistic studies will be required to yield better insights into the management of HIV/HCV-coinfected patients.

HIV-specific healthcare issues

Prophylaxis for opportunistic infection

During the early postoperative period, all transplant recipients, regardless of their HIV status, are administered prophylaxis for cytomegalovirus, fungal infections,

and *Pneumocystis Carinii* pneumonia. In addition, HIV-infected recipients should also receive prophylaxis for *Mycobacterium Avium* complex when CD4 counts drop below 75 cells/µl. Several recent reviews of prophylaxis for the HIV transplant population have recently been published[90,122].

Immunization strategies between HIV-infected and HIV-uninfected transplant recipients are similar. This includes administration of vaccinations against pneumococcal hepatitis A and B prior to transplantation and initiation of immunosuppression. Adult patients who have not had chicken pox should not receive varicella vaccine, but immunoglobulin G treatment after exposure. Household contacts are advised not to receive any live-attenuated vaccines such as oral polio or smallpox inoculations.

HIV-associated malignancy risks in the transplant recipient

The HIV-infected patients are susceptible to cancers specific to HIV infection, cancers associated with immunosuppression, and cancers that are common to their HIV-uninfected counterparts. The HIV-infected patients have an increased risk of cancer due to their immunosuppressed state[123-125]. Kaposi's sarcoma (KS) and non-Hodgkin's lymphoma (NHL) have been associated with an immunodeficient state and are hallmarks of AIDS. Since the advent of HAART, KS and NHL rates have declined[126]; however, hepatocellular carcinoma (HCC) rates have increased. The rise in HCC incidence may be due to direct exacerbation of HCC disease by HIV, or the result of the increased lifespan of HBV- or HCV-coinfected patients as the result of the widespread of HAART[127]. For these reasons, regular surveillance for HCC is essential for these patients. If they acquire HCC, they should be offered all conventional therapies, including transplantation.

Viral-mediated cancers, such as cervical, anal, and liver cancer, are also seen at increased frequency, but the association with the immunodeficient state is unclear. Interestingly, melanoma, known to be exacerbated by an immunosuppressed state, is more frequent in non-HIV transplanted recipients than in non-transplanted HIV patients[128]. However, an increased incidence of non-melanoma skin cancers, such as basal cell and squamous cell carcinoma, has been observed[129].

Currently, the impact of immunosuppression on the progression of human papillomavirus (HPV)-mediated anal and cervical lesions is unknown. As these patients have a tenfold increased risk of cervical and anal cancers, it is prudent for them to undergo routine screening. The results of the efficacy of HPV vaccines are still pending, but hopefully this will change the incidence of these diseases. There are currently no national screening guidelines. The UCSF screening guidelines recommends that these patients should be screened with PAP smears of the cervix and/or anal canal annually. This is followed with repeat smears and colposcopy and/or anoscopy, depending on the stage of the lesion (www.analcancerinfo.ucsf.edu).

As observed in HIV-uninfected patients, heavy tobacco use and alcohol consumption also contribute to the development of lung, liver, and stomach cancers in this population[123,128]. A recent meta-analysis of HIV-infected transplant recipients reports that there is no increased rate of common epithelial cancers, such as prostate and breast cancer, as compared to HIV-uninfected transplant recipients. However, there is an increased rate of brain and testicular cancer in the HIV-infected population as compared to the HIV-uninfected transplant recipients[128]. As HIV-infected individuals continue to achieve a normal life expectancy, and transplantation becomes further recognized as a treatment option for these patients, the care for these individuals should include screening for cancers common in the aging population and transplant recipients.

Conclusions

The transplant community has been slow to recognize the efficacy of HAART in changing the course of HIV infection into a chronic condition. As HAART becomes more accessible to new HIV patients and as the current population continues to age, the transplant community will need to address the increasing need for transplantation as the definitive management of increasing liver and kidney failure associated with HIV-related and HIV-unrelated comorbidities. Multiple studies continue to report promising outcomes of HAART-treated HIV patients with kidney and liver allografts. In these patients, HIV viral load remains suppressed, CD4 counts remain stable, and there appears to be no significant increase in opportunistic infections.

Ongoing areas of investigation include the optimization of strategies to prevent rejection especially in renal transplant recipients, control of HCV recurrence following liver transplantation in HIV-coinfected recipients, and monitoring for malignancies in these subjects whose HIV infection already makes them prone to develop cancer.

The NIH has recognized the need to evaluate transplantation as a therapy for HIV-infected patients and has an ongoing U.S. multicenter trial to evaluate the safety and efficacy of liver and kidney transplantation in this population. Third-party payers are increasingly supporting transplantation in HIV-infected patients with well-controlled disease. Both UNOS and the U.S. Veterans Affairs Administration approve of transplantation in HIV-infected subjects[130]. Some European countries have also provided guidelines for transplantation in HIV-infected subjects[131]. Improved awareness that HIV is no longer a contraindication for transplantation, and multinational research support in this area holds promise for better treatment of end-stage liver and renal disease in the HIV-infected population.

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