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Perspectives on Liver and Kidney Transplantation in the HIV-Infected Patient

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Abstract

HIV-infection is no longer an absolute contraindication for transplantation for patients with advanced kidney and liver failure. This article reviews the outcome data in the solid organ transplantation of HIV-infected patients that led to a change in thinking by the transplant community. We then review several emerging issues in the field such as eligibility criteria, selection of optimal immunosuppression agents and antiretroviral therapy in this population, and management of co-infection with Hepatitis B and Hepatitis C post-transplant.

Keywords

HIV; transplantation; Hepatitis B; Hepatitis C; liver; kidney

INTRODUCTION

Infection with human immunodeficiency virus (HIV) is no longer considered a contraindication for liver and kidney transplantation in patients with advanced organ failure. There were historic and legitimate fears that the immunosuppression needed following transplantation would exacerbate an already compromised immune system, and result in considerable mortality and morbidity in patients. There were also concerns that using scarce organs in this population would not be a good use of scarce resources (1, 2).

There are several factors that led to a positive change in thinking by the transplantation community. First, the remarkable advances in the treatment of HIV-infected patients over the past three decades have resulted in improved survival (3). Second, there has been a tremendous improvement in the understanding and implementation of the prophylaxis of opportunistic infections that afflict both populations of HIV patients as well as patients

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undergoing transplantation. Finally, there has been increasing proportion of HIV-infected patients with advanced kidney and liver disease, hence an increased demand for organs (3–5). Liver transplantation in the HIV-infected population has been driven mainly by complications of co-infection with hepatitis B (HBV) and hepatitis C virus (HCV), which both share similar modes of transmission as HIV. Liver disease is now a major cause of mortality in HIV-infected individuals. There has also been an increase in demand for kidney transplantation from HIV-associated nephropathy (HIVAN), immunoglobulin (Ig) A nephropathy, and glomerulonephritis as a result of HIV co-infection with HBV and HCV.

The initial published reports of outcomes of transplantation in HIV-infected patients came from single patient experiences or case series by single institutions (6, 7). Multiple centers providing retrospective and then prospective studies provided more robust and generalizable data (8–11). This increasing knowledge base has led to refinements in the way we select HIV-infected patients for transplantation, recommend particular antiretroviral agents, choose immunosuppressive regimens, and anticipate complications in these patients post-transplant. This paper will first review the latest outcomes in liver and kidney transplantation worldwide, focusing on the experiences in the era of highly active antiretroviral therapy (HAART). Then, in keeping with the theme of this issue of emerging infectious disease issues in solid organ transplantation, we will review some of the key issues and controversies that have recently arisen in the field.

OUTCOMES IN LIVER TRANSPLANTATION

Overall survival

Summarizing several of the early experiences of transplantation of HIV-infected persons since the widespread use of HAART in 1996, a report by the US Scientific Registry of Transplant Recipients (SRTR) described 1-year survival rates in liver transplant recipients from 60–100% (12–15). In the largest experience reported in this document (14), investigators combined data in HIV-infected patients undergoing transplantation from several centers in Pittsburgh, Miami, San Francisco, Minneapolis, and London. They then compared outcomes in this group to age and race matched cohort of HIV-uninfected transplant patients from the United Network for Organ Sharing (UNOS). There was no appreciable difference in cumulative survival at 1, 2 and 3 years in the HIV-infected patients (87%, 73%, and 73%) compared to the matched HIV-uninfected patients (87%, 82%, and 78%) (Table 1). Among the HIV-infected patients, lower survival was associated with HCV infection, not being able to tolerate HIV medications post-transplant, and CD4+ T cell counts <200 post-transplant. Although HCV infection was associated with higher mortality in HIV-infected patients, this was not statistically different from survival in the HIV-uninfected HCV-positive controls.

Hepatitis B

Outcomes in HIV-HBV co-infected patients are excellent following transplantation. The largest report compared the experience of a prospective cohort of 22 HIV-HBV co-infected patients transplanted between 2001–2007, with 20 HBV monoinfected patients (8). Patient/graft survival at 4 years was 85% in the HIV-HBV group compared with 100% in the HBV

mono-infected group post-transplantation (P=0.09). Following transplantation, all patients received hepatitis B immune globulin (HBIG) [continued indefinitely with a decrease in dose frequency after 12 months] as well as anti-HBV nucleoside or nucleotide analogues. All patients remained HBsAg and HBV DNA negative following transplantation (median follow-up of 3.5 years). The data in hepatitis B/HIV co-infected recipients demonstrates that if there is suitable control of the co-pathogen, HIV infection does not negatively impact allograft and patient survival. This is in contrast to the results following liver transplantation in HCV-HIV co-infected recipients, where the co-pathogen is more challenging to control.

Hepatitis C

Outcomes in HIV-HCV co-infected patients are more variable and depend on the selection criteria used. In a study of 84 HCV-HIV patients who underwent transplantation in Spain, 5-year survival rates were 54% compared with 71% in HCV monoinfected transplant patient controls (9). Another US prospective, multicenter study compared patient and graft survival for 89 HCV-HIV co-infected patients with two control groups (235 HCV mono-infected liver transplant patients, and all transplant recipients in the US who were 65 years or older) (11). Patient survival rates at 1 and 3 years were 76% and 60% in the HCV-HIV group compared with 92% and 79% in the HCV mono-infected liver transplant group. Graft survival at 3 years was 53% and 74% in both groups respectively. Independent predictors of graft loss among HCV-HIV transplant recipients included older age, combined kidney-liver transplant, an anti-HCV-positive donor and a body mass index <21 kg/m2. If HCV-HIV patients did not have a combined kidney-liver transplant or an anti-HCV-positive donor, and had a BMI of 21 kg/m2 or higher, patient and graft survival were similar to HCV mono-infected patients.

OUTCOMES IN KIDNEY TRANSPLANTATION

There have been several studies that demonstrate excellent survival in HIV-infected kidney transplant recipients (10, 15–18). In the largest of the published studies to date (N=150), investigators reported patient survival at 1 and 3 years of 95% and 88%, and allograft survival of 90% and 74% (10). The survival of HIV-infected kidney transplant recipients were between that of all kidney transplant recipients and those older than 65 years of age, as reported by the US Scientific Registry of Transplant Recipients (SRTR).

HIV-SPECIFIC OUTCOMES FOLLOWING TRANSPLANTATION

Studies have generally shown no evidence of HIV-disease progression to AIDS or HIV-opportunistic infections following transplant. However, depending on the type of immunosuppressive agents used, CD4+ T cell counts may be affected. In one prospective cohort study of kidney transplant recipients, HIV-infected patients who received induction with thymoglobulin had a higher median decline in CD4+ T cells at 1 year following transplant, compared to those who did not receive this agent (−239 versus −135 cells/mm3) (10). Reassuringly, at three years, there was no difference in the change of CD4+ T cells from baseline between the two groups.

There have been few HIV-associated opportunistic infections post-transplantation. In the US multicenter study of 125 HIV-infected liver and 150 kidney transplant patients, there have been only 4 cases of Kaposi's sarcoma, 2 cases of P. jiroveci pneumonia, 1 case of cryptosporidiosis, and 6 cases of esophageal Candidiasis. A history of opportunistic infections was not independently associated with mortality (19). In a Spanish study of 84 HCV-HIV co-infected liver transplant recipients, severe infection was an independent risk factor for mortality among these patients (HR 2.6, P<0.01) (9). However, there was no difference in the occurrence of infection as a cause of death when comparing the co-infected transplant patients to those who were HIV-uninfected (8% versus 6%).

EMERGING ISSUES

Eligibility criteria

Based on the accumulating data from observational studies, the eligibility criteria for potential HIV-infected transplant candidates is continuing to evolve (Table 2). In many senses, it is getting liberalized, particularly with respect to permitting a history of opportunistic infections in potential transplant candidates (2). However, opportunistic infections for which there are no reliable therapeutic options post-transplantation remain a contraindication to transplantation. These include progressive multifocal leukoencephalopathy, chronic cryptosporidiosis, primary central nervous system lymphoma, and drug-resistant fungal infections (such as Scedosporium prolificans).

However, long-term outcomes in HCV-HIV co-infected patients who have received liver transplants are leading to a refinement of selection criteria in this population. Potential HCV-HIV transplant candidates who have a BMI of at least 21 kg/m2 and do not need a concomitant kidney transplant may have a better probability of patient and graft survival than sicker patients (11). Older donors and donors who are HCV-infected are associated with eventual graft loss in this study, and should be used with caution in this population. Of note, the utilization of older donors yields poorer results in HCV monoinfected recipients as well.

The absolute CD4+ T-cell count continues to be an important component of potential candidates for transplantation. For kidney transplantation, most centers require that HIV-infected patients have a CD4+ T cell count greater than 200 cells/ml, any time in the 16 weeks prior to transplantation. For advanced liver disease HIV-infected patients, we permit a lower absolute CD4+ T cell cutoff of greater than 100 cells/ml (except if there is a history of opportunistic infection or malignancy in which case the cutoff is 200 cells/ml). This allows for presumed splenic sequestration of T lymphocytes, based on the observation of patients with portal hypertension and splenomegaly, particularly those with high Model for End-Stage Liver Disease (MELD) scores. For children, the percentage CD4+ T cells are more important. For children 1–2 years of age, the CD4+ percentage should be greater than 30. For children between 2–10 years, the CD4+ percentage should be greater than 20.

The HIV-1 RNA also continues to be important in the evaluation of potential transplant candidates who are HIV-infected. Most centers require that patients have an undetectable HIV RNA, based on the most recent level checked at least 16 weeks before the transplant

date. Some liver transplant candidates are unable to tolerate HAART because of drug-associated hepatotoxicity. In these cases, the requirement for an undetectable HIV RNA could be waived if an experienced HIV clinician can confidently predict that viral suppression could occur post transplantation with the available options.

Immunosuppression considerations

Multiple immunosuppressive regimens have been used in the treatment of HIV-infected patients post-transplant. However, it is not clear whether one regimen is superior to another. For induction, most centers avoid lymphocyte depleting regimens (i.e. thymoglobulin) for induction agents, given the profound effect on CD4+ T cells that these lymphocyte depleting agents can have. As a result of the high occurrence of rejection episodes in the HIV-infected kidney transplant population (10), many centers have used the interleukin-2 receptor inhibitors for induction therapy (2). Most centers have been able to avoid the use of lymphocyte depleting induction agents in the HIV-infected liver transplant patients, given that steroids and adjustments in maintenance therapy have been generally been successful in managing rejection episodes that arise.

Most centers use a maintenance therapy regimen of steroids, a calcineurin inhibitor (tacrolimus or cyclosporine A), and the antiproliferative agent mycophenolate mofetil (MMF). We use steroids at standard doses in the HIV-infected transplant recipient. Cyclosporine has been a common agent used because of both antiretroviral and immunomodulatory properties (20, 21). In addition, because of the lower risk of glucose intolerance compared with tacrolimus, cyclosporine was favored by many centers. However, there is recent evidence of an association of cyclosporine with graft rejection, although there was no impact on graft survival (10). We target similar calcineurin trough levels as in the HIV-uninfected transplant population. Like cyclosporine, MMF has antiretroviral properties, and synergize with didanosine, abacavir, and tenofovir (22, 23).

The TOR inhibitor sirolimus is an alternative to the calcineurin inhibitors and is of interest for several reasons. It is an effective antiproliferative agent for Kaposi’s sarcoma (24). Given these anti-cancer properties, it may also be useful in cases of patients who develop malignancies post-transplant (25). It also down-regulates the expression of CCR5 receptors on CD4+ T cells, and synergizes with the antiretroviral agents enfuvirtide and maraviroc which inhibit viral entry or CCR5 chemokine coreceptor-facilitated attachment (26). Also, because many HIV-infected patients have some degree of renal impairment that is HIV-associated or from other causes, sirolimus may be a useful agent when compared to the calcineurin inhibitors.

Antiretroviral considerations

As in other HIV-infected patients, we generally use three active drugs from among the classes of antiretroviral medications. These include the nucleoside analog reverse transcriptase inhibitors (NRTIs), the non-nucleoside analog reverse transcriptase inhibitors (NNRTIs), HIV-protease inhibitors (PIs), entry inhibitors and integrase inhibitors. The ultimate goal is to devise a regimen that can be delivered in the post-transplant setting which

will provide continuous suppression of HIV, ensure adequate therapeutic levels of the immunosuppressive medications and minimize overlapping drug toxicities (Table 3).

The ability to concomitantly administer both a potent antiretroviral regimen with a combination of immunosuppressive and opportunistic infection prophylactic drugs remains a challenge. This is because of multiple bidirectional drug interactions between antiretroviral and immunosuppressive regimens (27). The immunosuppressive agents (cyclosporine, tacrolimus and sirolimus) will require adjustment depending on which antiretroviral drug is chosen (Table 2). Protease inhibitors commonly inhibit the cytochrome P-450 3A4 (CYP450) system, and patients will require a decreased dose of immunosuppression (e.g., 1 mg tacrolimus orally weekly) (28). Patients on NNRTI-based regimens will require an increase in the dose of calcineurin inhibitors or sirolimus, because of the induction of P-450 3A4. The induction of P-450 3A4 by NNRTIs is not as strong as the inhibition by PIs. Therefore, when both a PI and an NNRTI are used, the doses of immunosuppression are adjusted as if a PI alone was used (i.e. reduction of the dose of immunosuppression).

There has been some systematic study of these drug interactions. One study reported the experience of 35 HIV-infected patients post-transplant who were on various drug regimens (NNRTIs, PIs, or both) (29). The investigators showed that patients on PIs needed lower doses of cyclosporine, tacrolimus or sirolimus using longer dosing intervals compared to those not on PIs. Adjustment was an ongoing process for those on PIs – the area under the curve (AUC) for cyclosporine continued to change over a two year period with continual need for dose adjustment. Conversely, patients on cyclosporine and efavirenz required higher doses of cyclosporine.

Chemokine receptors and transplantation

There has been great interest in evaluating the role of CCR5 chemokine receptor antagonists in transplantation. CCR5 is a co-receptor that HIV uses to enter the target cell. HIV-infected individuals who are homozygous for the CCR5 delta 32 mutation (1% of Caucasians) have a nonfunctional receptor and are highly resistant to HIV infection (30, 31). CCR5 also plays an important role in alloreactivity. There is some evidence that these individuals also have reduced rates of rejection and improved survival following transplantation. In one study of 1227 kidney transplant recipients, those who were homozygous for CCR5 delta 32 (2% of this population) had improved survival compared to those who were either heterozygous for CCR5 delta 32 or homozygous for wild-type CCR5 (32). In another study of 158 liver transplant recipients (33), patients who were homozygous for CCR5 delta 32 had no rejection episodes, compared to 13% of those homozygous for CCR5 delta 32, and 31% in the CCR5 wild-type patients. Modifying the CCR5 receptor pharmacologically with a CCR5 receptor antagonist may also be bene0ficial. Investigators added a 33-day course of the CCR5 receptor antagonist maraviroc to graft-versus-host-disease (GVHD) prophylaxis in 35 patients undergoing hematopoietic stem cell transplantation (34). An unusually low proportion of patients in this study developed grade III or IV GVHD by day 180 (6%). The mechanisms underlying these observations are unclear. In the GVHD study, investigators showed that maraviroc was associated with impaired lymphocyte chemotaxis without impact on lymphocyte function. As CCR5 receptor antagonists continue to be developed for HIV

treatment, there is promise for its future use in transplantation, even in individuals who are not HIV-infected.

Prophylaxis for opportunistic infections

Prophylaxis for cytomegalovirus (CMV), pneumocystis jiroveci pneumonia (PCP) and fungal infections is routinely given to all patients for several months following transplantation. In addition, we recommend additional opportunistic infection prophylaxis for the HIV-infected transplant patient (Table 4). Screening and treatment for latent tuberculosis infection follows routine guidelines in HIV-infected patients. Immunizations for HIV-infected patients are the same recommended for transplant patients who are not HIV-infected.

Management of Hepatitis B co-infection

Outcomes in the HBV-HIV transplant patients undergoing liver transplantation have been excellent as reviewed earlier. We recommend following the same guidelines for treatment of HBV post-transplant as in the published studies. This involves using hepatitis B immune globulin (HBIG)and antiretrovirals that also have activity against HBV. HBIG is continued indefinitely using a standard tapering protocol. Antiretrovirals that are commonly used include tenofovir plus either lamivudine or emtricitabine, and have HBV as well as HIV activity. In cases where entecavir may be needed for additional HBV activity post-transplant, it is important to ensure that HIV is concomitantly suppressed. This is because entecavir may select for HIV resistance, despite not having specific anti-HIV activity (35). This management strategy for the HBV-HIV patients had led to control of HBV recurrence post-transplant, and corresponding good outcomes in terms of patient and graft survival.

Management of Hepatitis C co-infection

In contrast to the excellent outcomes seen in the HBV-HIV transplant patients, HCV-HIV patients have had high rates of HCV recurrence following transplantation with lower patient and graft survival in general. In response to the poorer outcomes seen, some centers have revised their selection criteria as discussed earlier. In general, the current recommendations for management of HCV reactivation post-transplant are similar regardless of HIV status. We usually initiate HCV treatment when there is histologic evidence of progression or severe recurrence. There are challenges in using interferon and ribavirin post-transplant in a population at risk for thrombocytopenia and lymphopenia, and a high proportion of patients require growth products and antidepressants. There is limited experience so far with the new class of direct-acting HCV antivirals such as telapravir and boceprevir in this population. Although very promising in general, the use of these new agents will be complicated by substantial drug interactions (36) and there is limited data at this point to guide clinical practice in the HIV-HCV co-infected transplant patient. Interestingly, spontaneous clearance of HCV in several of the co-infected patients has been observed, though there has not been a good explanatory model.

Rejection

It is now well recognized that HIV-infected patients mount a vigorous alloimmune response post-transplant. This is supported by the observation that rejection rates in HIV-infected patients are 2–3 times that seen in HIV-uninfected patients post-transplant. In a multisite observational study of 150 HIV-infected kidney transplant patients, 1 and 3 year rejection rates were 31% and 41%, compared to a control rate of 12% in the general kidney transplant population (10). This fortunately did not seem to impact graft function in the period of time observed, since there was no statistical difference in graft function between the HIV-infected and uninfected populations. In a study of 89 HCV-HIV liver transplant recipients, 3 year rejection rates were39%, higher than the 24% of HIV-negative HCV patients observed (11). More than 50% of the rejection episodes occurred in the first 21 days following liver transplantation. The reasons for the higher rate of rejection seen in HIV-infected patients are likely multifactorial. Drug interactions between antiretroviral agents (particularly PIs) and calcineurin inhibitors may have led to lower total drug exposure of immunosuppression. Even though there was a careful attempt to adjust dosing of calcineurin inhibitors based on troughs, the substantially longer intervals between doses could have led to sub-therapeutic levels of drug. In the HIV kidney transplant study referenced above, use of cyclosporine was independently associated with rejection (10). In the HIV liver transplant study above, lower tacrolimus trough levels was associated with rejection (11). Alternatively, it could be that the immune activation and general immune dysregulation seen in HIV could have led to a heightened and nonspecific enhancement of alloimmunity. Utilization of integrase inhibitors, as well as avoidance of protease inhibitors, may minimize drug-drug interactions. More long term follow-up is needed to determine whether these episodes of rejection will translate into graft loss.

CONCLUSIONS

HIV-infection is not an absolute contraindication to kidney and liver transplantation in patients with advanced organ disease. Compared to the general transplant population, several observational studies have revealed equivalent patient and graft survival outcomes in kidney and selected liver transplants in the HIV-infected population. To ensure the best outcomes, patients need to be selected carefully with well-controlled HIV, and post-transplant complications need to be aggressively managed. As new information becomes available, selection criteria continues to be refined. Emerging issues in the HIV-infected transplant field include determining the best drug combinations of antiretrovirals and immunosuppressive medications to administer, optimally treating Hepatitis C recurrence following transplantation, and following long term outcomes in patients. As these cohorts mature, they will also give us valuable information about malignancies (particularly those that are virally mediated like HPV-associated neoplasia) in this growing population (37). Nevertheless, demand for organs continue to outstrip supply. Demand for organs will only increase as the HIV-infected population ages given comorbidities in this population such as hypertension, diabetes mellitus and chronic hepatitis. New ways of increasing organ availability such as transplantation of HIV-positive donors and recipients will continue to be hot discussion topics (38).

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Key Points

- Infection with human immunodeficiency virus (HIV) is no longer considered a contraindication for liver and kidney transplantation in patients with advanced organ failure.
- There were historic and legitimate fears that the immunosuppression needed following transplantation would exacerbate an already compromised immune system, and result in considerable mortality and morbidity in patients.
- There were also concerns that using scarce organs in this population would not be a good use of scarce resources (1, 2).

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Table 1

Rates of Patient and Graft Survival at 1 Year and 3 Years among HIV-infected compared to HIV-uninfected in published multicenter cohort studies.

			Patient survival (%)				Graft survival (%)				
			At 1 Year		At 3 Years		At 1 Year		At 3 Years		
Location	**Organ**	**N (HIV + patients)**	**HIV+**	**HIV−**	**HIV+**	**HIV−**	**HIV+**	**HIV−**	**HIV+**	**HIV−**	**Reference**
USA	Liver	24	87	87	73	78					(14)
USA	Liver (HBV)	22	85	100	85	100	85	100	85	100	(8)
Spain	Liver (HCV)	84	88	90	62	76	86	85	60	69	(9)
USA	Liver (HCV)	89	76	92	60	79	72	88	53	74	(11)
USA	Kidney	150	95		88		90		74		(10)

Missing values in table not provided in respective studies.

Table 2

Eligibility criteria for HIV-infected transplant candidates

Meet center-specific criteria for specific organ transplant
HIV-related criteria
Kidney: CD4+ T cell count > 200 cells/ul
Liver: CD4+ T cell count > 100 cells/ul (CD4+ T cell count > 200 cells/ul if history of OI or malignancy)
HIV RNA suppressed (or expect to be suppressed post-transplant)
Stable antiretroviral regimen
No active OI or neoplasm
No history of chronic cryptosporidiosis, primary CNS lymphoma or progressive multifocal leukoencephalopathy
Other
Liver (HCV): BMI> 21 kg/m2, no need for combined kidney transplant, no HCV+ donor

Table 3

Antiretroviral considerations in the transplant setting for specific drugs

Antiretroviral class/agent	General considerations	Adjustment in immunosuppression
Nucleoside analog reverse transcriptase inhibitors (NRTIs)	Avoid NRTIs with mitochondrial toxicity (e.g, didanosine, stavudine, and zidovudine) if MMF is used concomitantly.	None
Abacavir	Theoretically avoid if donor is HLA B5701+ because of risk of hypersensitivity reaction. Not commonly done in clinical practice at this point.	
Abacavir	Associated with decreased response to recurrent hepatitis C treatment (ribavirin phosphorylation impaired).	
Abacavir	May have synergistic effect against HIV if MMF concomitantly used. (23)	
Tenofovir	Associated with proximal tubular dysfunction and Fanconi syndrome in the non-transplant setting. Limited data regarding risk of renal toxicity following kidney transplantation.	
Tenofovir	May exacerbate osteopenia and osteoporosis associated with advanced liver and kidney disease pre-transplant and steroid use post-transplant.	
Zidovudine	May worsen bone marrow suppression if MMF is used at the same time.	
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		Will require increases in cyclosporine, tacrolimus or sirolimus
Nevirapine	Avoid in patients undergoing liver transplantation because of fears of drug associated hepatotoxicity.	
Integrase inhibitors		None
Raltegravir	Associated with low occurrence of rejection.	Favored. Relative absence of drug interactions post-transplant.
Protease inhibitors (PIs)	May exacerbate hyperlipidemia that occurs post-transplantation, as well as calcineurin inhibitor associated hyperglycemia.	Will require lower dose and increase in dosing interval of cyclosporine, tacrolimus or sirolimus
Atazanavir	Avoid. Proton pump inhibitors frequently required indefinitely post-transplant and this is contraindicated with atazanavir	

Key: MMF mycophenolate mofetil

Table 4

Opportunistic infection prophylaxis for HIV-infected transplant recipients

Opportunistic infection	**Preferred agent**	**Primary prophylaxis** *(1)*	**Secondary prophylaxis** *(2)*
Pneumocystis jiroveci pneumonia	Trimethoprim/Sulfamethoxaxole	Lifelong	Lifelong
Cytomegalovirus	Valganciclovir	No HIV-specific indication. Follow standard center specific prophylactic regimens for transplant recipients (e.g. 6 months valganciclovir for CMV-negative recipients of CMV-positive donors).	CD4+ T cell < 75–100 cells/ml Discontinue when CD4+ T cells > 200 cells/ml for 3–6 months
Cryptococcosis	Fluconazole	No HIV-specific indication	CD4+ T cell < 200 cells/ml Discontinue when CD4+ T cells > 200 cells/ml for 3–6 months
Mycobacterium avium complex	Azithromycin	CD4+ T cells < 50 cells/ml Discontinue when CD4+ T cells >100 cells/ml for 3–6 months	CD4+ T cell < 50 cells/ml Discontinue when CD4+ T cells > 100 cells/ml for 3–6 months
Toxoplasmosis	Trimethoprim/Sulfamethoxaxole	Toxoplasmosis IgG-positive donor or recipient CD4+ T cells < 100 cells/ml	CD4+ T cell < 200 cells/ml Discontinue when CD4+ T cells > 100 cells/ml for 3–6 months

(1) No history of infection

(2) Prior history of infection. Apart from following CD4+ T cell criteria, we recommend secondary prophylaxis for at least 1 month following transplantation, and for 1 month following treatment of rejection