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Renal transplantation in patients with HIV

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Abstract

HIV infection has been a major global health problem for almost three decades. With the introduction of highly active anti-retroviral therapy in 1996, and the advent of effective prophylaxis and management of opportunistic infections, AIDS mortality has decreased markedly. In developed countries, this once fatal infection is now being treated as a chronic condition. As a result, rate of morbidity and mortality from other medical conditions leading to end-stage liver, kidney and heart disease is steadily increasing in individuals with HIV. Presence of HIV infection used to be viewed as a contraindication to transplantation for multiple reasons:,concerns for exacerbation of an already immunocompromised state by administration of additional immunosuppressants; the use of a limited supply of donor organs with unknown long-term outcomes; and, the risk of viral transmission to the surgical and medical staff. This Review examines open questions on kidney transplantation in patients infected with HIV-1 and clinical strategies that have resulted in good outcomes. It also describes the clinical concerns associated with the treatment of renal transplant recipients with HIV.

Introduction

Since the early years of the AIDS epidemic, the medical and scientific community has been aware of various renal diseases that develop in patients with HIV.[1,2] Renal diseases directly related to HIV infection include HIV-associated nephropathy (HIVAN), immune complex diseases, and thrombotic microangiopathy. Although the widespread used of highly active antiretroviral therapy (HAART) has decreased the incidence of HIV-related renal disease,[3] the overall prevalence of renal disease continues to increase among patients with HIV.[4,5] Potential explanations include inadequate HAART, drug toxicity, increased survival rates leading to an increase in the proportion of elderly patients, and chronic viral co-infections (i.e. viral hepatitis)..[6,7]

The most aggressive HIV-related renal disease is HIVAN, which occurs in approximately 10% of patients with HIV.[8] These patients can progress to end-stage renal disease (ESRD) within weeks to months. Although the etiology of HIVAN is not completely understood, direct infection of HIV-1 of renal epithelial cells is associated with the onset of the disease.[9] This variant of focal sclerosing glomerulonephritis is diagnosed by kidney biopsy and afflicts mainly patients of sub-Saharan African descent.[10,11] HIVAN is currently the third most common etiology of ESRD among African Americans aged 20–64 years after diabetes and hypertension.[12,13] Co-infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) is also common, and affected patients are at risk of developing viral hepatitis-associated

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glomerulonephritis. Nearly 1% of all patients with ESRD in the US and Europe are estimated to have HIV.[5,14]

Nephrotoxicity could be induced or exacerbated by anti-retroviral medications, such as ritonavir, as well as infection prophylaxis medications such as trimethoprim sulfamethoxazole. Some drugs routinely administered to patients with HIV (i.e. indinavir, atazanavir, sulfadiazine, ciprofloxacin and intravenous aciclovir) can also precipitate in the renal tubular lumen, thereby causing renal failure.[7,15] Tenofovir and adefovir, which are HAART medications also used in the management of lamivudine-resistant HBV, are potentially nephrotoxic agents. Calcineurin inhibitors (CNIs) used in immunosuppressive therapy, such as ciclosporin and tacrolimus, are nephrotoxic, both directly and, by causing vasoconstriction and increasing blood pressure, indirectly. The toxicity of CNIs can be exacerbated by inhibition of the cytochrome P450 system by other HAART agents such as protease inhibitors (PIs) and agents commonly used for fungal prophylaxis and treatment, such as fluconazole. In addition, some HAART agents can induce insulin resistance, diabetes mellitus, hypertension and hyperlipidemia,[16] all of which are major risk factors for ESRD in the US.

Notably, however, survival of patients on dialysis who have HIV has improved in patients whose disease is under control on HAART (e.g., those with high $CD4^+$ T-cell counts) and is now similar to that of patients who are not infected with HIV.[17,18] Kidney transplantation in patients without HIV is known to result in better survival rates than continuing dialysis.[19] Given the advances in treatment of HIV over the past decades, investigating the safety and efficacy of renal transplantation in patients with HIV has become a research priority.

Early outcomes of transplantation

The first prospective study performed in the HAART era followed 10 patients with kidney transplants who had not undergone induction therapy and whose maintenance therapy included ciclosporin and mycophenolate mofetil (MMF). These patients had been selected for transplantation because they had no history of opportunistic infections and HIV virus was undetectable. This study demonstrated similar one-year patient and graft survival rates to patients without HIV;[20] however, more than half the study participants experienced acute rejection, which required aggressive treatment with an anti-lymphocyte globulin.[20,21] Subsequent retrospective analyses, case reports and small prospective studies include a study of the outcomes in 63 patients with HIV with deceased-donor-kidney-transplants and 37 with living-donor-kidney transplants from the US Scientific Registry of Transplant Recipients,[22] a report of 47 patients with HIV in the US Kidney Data System,[23] and a review of 18 patients transplanted at four US transplant center through 2003.[24] Early results from these studies indicate that patient and graft outcomes are similar to those reported for patients without HIV, although allograft rejection rates are higher. Roland *et al*. [25] prospectively followed 18 kidney transplant recipients with HIV for over 3 years and observed that the incidence of rejection episodes at 1-year and 3-years was 52% and 70%, respectively. In spite of the high rejection rates, however, patient and graft survival rates were 94% and 83% at 3 years. Other encouraging reports demonstrate comparable patient and graft survival rates in patients with and without HIV.[26,27,28,29]

Rates of acute rejection of renal transplants in patients with HIV range from 13% to 67%.[20,21,26-29] Protocol biopsies at one institution also demonstrated subacute rejection rates of 29%.[31] In addition, numerous studies have reported a higher acute rejection rate in patients of sub-Saharan African descent than in those from other ethnic backgrounds.[20,21,28,29] The etiology of such high rejection rates is unclear, although dysregulation of the immune system or insufficient immunosuppression are two possible causes. Data from a prospective

study by Kumar *et al*.[31] demonstrated that induction therapy by anti-CD25 antibody administration and maintenance therapy with sirolimus resulted in a decreased rejection rate; however, the 1-year patient and graft survival rates were similar to those in other high risk populations, 85% and 75%, respectively. Other encouraging preliminary data come from a small retrospective study that examined outcomes in eight renal allograft recipients with HIV. Study participants had undergone induction therapy with an anti-interleukin-2 receptor antibody and maintenance therapy with ciclosporin, MMF and prednisone. At a median follow-up of 15 months, patient and graft survival rates were 100% and 88%, respectively, and the rate of acute rejection was 13%.[29] In both of these studies, the patients did not show any HIV infection progression, although results require further verification with longer follow-up and larger cohort of patients than those examined.

Despite high rates of acute rejection, kidney transplantation has proven a successful renal replacement treatment modality for patients with HIV. Although patient and graft survival rates at three years are comparable with those observed in patients without HIV, the high number of early rejection episodes might have a negative effect on the long-term graft function of patients with HIV. Reducing rejection rates, therefore, will be a primary goal in future research, and collaborative research efforts are currently underway to investigate the etiology of acute rejection in these patients.

Patient selection criteria

The criteria that patients with HIV must satisfy to be eligible for transplantation continue to evolve as experience in managing transplant recipients with HIV accumulates. Traditionally, selection criteria were predicated on the concern that immunosuppressing patients with HIV would accelerate progression of HIV to AIDS. This effect on progression has however not materialized in practice, and the selection criteria for suitable allograft recipients are progressively being liberalized. Potential eligibility requirements for solid organ transplantation in patients with HIV are based on the North American and European transplantation criteria for patients without HIV (see Table 1). Mandated requisites include a prolonged period of abstinence from alcohol and narcotics, and demonstration of social support. Eligibility criteria specific to patients with HIV include defined minimum levels of $CD4^+$ T-cell counts and nondetectable levels of HIV viral load, absence of specific patterns of HIV viral resistance and absence of history of or ongoing specific opportunistic infections.[30,31] Most transplantation centers require recipients to have a $CD4^+$ T-cell count greater than 200 cells/ml.[32] Given that in children, the percentage of $CD4^+$ T-cell is a better reflection of an intact immune system,[33] pediatric patients 1–2 years of age or 2–10 years of age, the requirements in the US NIH multicenter trial require a $CD4^+$ T-cell percentage greater than 30% and 20%, respectively. Evidence also suggests that the ratio of $CD4^+$ to $CD8^+$ T-cells could be used as a surrogate of HIV-1 infection in pediatric patients.[34]

A history of opportunistic infections is no longer considered an automatic exclusion criterion in most European countries and North America, as long as the opportunistic infections can be treated successfully in immunosuppressed patients. In the NIH multicenter prospective trial, opportunistic infections which remain a contraindication for solid organ transplantation in general include chronic cryptosporidiosis, progressive multifocal leukoencephalopathy, and systemic Kaposi's sarcoma, whereas a history of tissue-invasive cytomegalovirus infection is no longer considered a contraindication given the availability of effective therapies. Consideration for transplantation of patients with resolved visceral Kaposi's sarcoma is based on the efficacy of sirolimus—a commonly used immunosuppressive agent—in treating the sarcoma.[35,36,37]

A clinical challenge in managing kidney transplant recipients with HIV is the relatively high frequency of co-infection with HBV and HCV. Approximately 30% of patients with HIV have hepatitis C co-infection[38] and approximately 10% hepatitis B co-infection.[39] In patients with either co-infection, the extent of liver damage needs to be assessed before consideration for kidney transplantation. Management strategies for patients with HIV who have minimal liver disease but have HBV or HCV infection can be challenging (see below). However, data suggest that treatment with HAART or MMF might help slow progression of liver disease[40] and improve survival rates after renal transplantation.[41]

Donor selection criteria

A major source of concern in renal transplantation is that the duration of time spent on the transplantation waiting list continues to increase as demand for organs soars while the supply of deceased-donor organs remains stable. One study of the United Network for Organ Sharing (UNOS) database demonstrated that lower death-censored graft survival at one year in patients with HIV and renal transplants from deceased donors older than 50 years of age and with cold ischemia time longer than 16 hours.[42] One strategy to address these problems is to use organs from living donors. Another is to use kidneys from 'infectious-high-risk'deceased donors—individuals who tested negative for HIV, HBV and HCV, but, based on social history, could have acquired the infections shortly before becoming kidney donors. Many recipients of renal transplants with HIV received organs from these donors. The use of extended-criteria deceased donors is appropriate for elderly patients with HIV (using the same recipient criteria as those for patients without HIV). Currently, the use of pediatric en-bloc kidneys is not recommended because of the high risk of rejection and the possibility that these small kidneys might not tolerate this rejection insult.

Strategies for immunosuppression

As mentioned, the reasonable belief that immunosuppression could result in progression of HIV disease has in the past discouraged transplantation in people with HIV. However, many agents currently used for post-transplantation maintenance immunosuppression (e.g. MMF, ciclosporin, tacrolimus, and sirolimus) have anti-retroviral properties. MMF virostatic action is thought to result from the depletion it causes of guanoside nucleosides, which are necessary for the virus lifecycle.[43,44] Ciclosporin and tacrolimus have well-documented antiretroviral effects through selective inhibition of infected cell growth[45,46]. These agents interfere with HIV pathogenic protein functions, which ultimately results in the reduction of virus formation.[47] Ciclosporin and tacrolimus can however cause glucose intolerance, which can be exacerbated by administration of sirolimus.

Since many patients with renal allografts, particularly those with HIV, experience some degree of renal insufficiency, sirolimus, an inhibitor of the mammalian target of rapamycin and an anti-proliferative agent, has been considered as an alternative to CNIs. Similarly to CNIs, sirolimus also exerts some antiretroviral activity through suppression of T-cell activation, suppression of professional antigen presenting cell function, and disruption of infective virion replication [34,35] Sirolimus also decreases the expression of C-C chemokine receptor type 5 on monocytes and lymphocytes, thus potentially preventing the HIV virus from entering these cells and replicating.[36]

In the initial clinical trials of organ transplantation in patients with HIV,[20, 21] immunosuppressive regimens focused on maintenance therapy with agents with known anti-retroviral qualities. This therapy consisted of a combination of steroids, a CNI and MMF. However, organ recipients with HIV can mount an alloimmune response[20,21] and renal transplant recipients with HIV have a higher rejection rate than their counterparts without

HIV.[20,21] For this reason, induction therapy with interleukin-2 receptor inhibitor has been introduced.[26,27] Whether induction with even more potent immunosuppressants than interleukin-2 receptor inhibitor will be required is unknown. Nonetheless, most transplantation centers are reluctant to utilize lymphocyte depleting agents for induction, as these agents severely deplete $CD4^+$ T-cells for several months. Nonetheless, these these potentdepleting agents have successfully reversed aggressive rejection in several patients.[21]

Drug interactions

In most centers, allograft recipients with HIV receive the same HAART regimens they received before transplantation. Early studies demonstrate that using this strategy HIV does not progress to AIDS.[20,25,27] If, for any reason, patients are unable to take one or more of their HAART drugs, HAART should be discontinued immediately to avoid development of drug-resistant HIV strains. Initial experience suggests that transplant recipients with HIV can tolerate HAART withdrawal for several weeks without changes in viral load and $CD4^+$ T-cell counts.[20,48]

Management of solid organ transplantation in patients with HIV is complicated by multiple drug interactions between HAART agents and immunosuppressants. The most notable drug interaction occurs between antiretroviral medications and immunosuppressive agents that induce or inhibit the P-glycoprotein efflux transporters and cytochrome p450 3A (CYP3A4) metabolizing enzymes found in the gut and liver. These interactions can lead to unexpected increases or decreases in drug plasma levels, and result intoxic side-effects, organ rejection or HIV disease breakthrough. CNIs, such as ciclosporin, and PIs inhibit both P-glycoprotein and CYP3A4 activity. This results in increased levels of circulating drugs due to an increase in cross-membrane drug transport and a decrease in drug metabolism, respectively. Non-nucleoside reverse transcriptase inhibitors (NNRTIs), such as efavirenz, can markedly induce CYP3A4 activity increasing drug metabolism and leading to decreased plasma drug levels.[49,50]

These pharmacologic interactions are well documented in a study describing the pharmacokinetics and dosing modifications of ciclosporin, sirolimus and tacrolimus in 35 liver or kidney transplant recipients on NNRTIs, PIs or both.[51] Patients on PIs and ciclosporin required only 20% of the immunosuppressant dose administered to renal transplant recipients without HIV. Low doses of ritonavir, a potent inhibitor of both P-glycoprotein and CYP3A4, is often used to increase or “boost” other PI levels. Patients on a ritonavir-boosted PI regimen required even lower doses of immunosuppressants than patients on other HAART regimens. In patients on tacrolimus or sirolimus, not only was the immunosuppressant dose markedly decreased, but the dosing interval increased more than five-fold. Similar findings have been demonstrated by other investigators in liver transplant recipients.[52,53,54,55] Notably, azole antifungals and macrolide antibiotics also inhibit the CYP3A4 system.[56]

Additional potential interactions between HAART and immunosuppression regimens should be kept in mind. Patients taking steroids are usually taking proton pump inhibitors, which can reduce intestinal absorption of the PI atazanavir and, thus, the drug’s plasma concentration.[57,58] Patients on proton pump inhibitors and atazanavir require, therefore, PI treatment to be boosted by the administration of ritonavir.[59] *In vitro* evidence suggests that MMF is antagonistic to the anti-HIV replication effects of zidovudine and stavudine[53], so these drug combinations should probably be avoided. Zidovudine is also the only myelotoxic HAART agent, and when combined with another myelotoxic agent such as MMF could have additive myelosuppressive effects.

Management of comorbities

HBV

HBV resistance to lamivudine is common in kidney transplant recipients who have been on lamivudine-containing HAART regimens. These patients require therapy with tenofovir or other appropriate antivirals. Containment of lamivudine-resistant hepatitis B post-transplantation in kidney recipients with HIV and HBV has not been problematic with the increasing number of anti-HBV agents available.

HCV

Post-transplantation immunosuppression exacerbates hepatitis C infection in kidney allograft recipients, which makes the management of patients with HIV–HCV co-infection particularly challenging. Clearance of HCV with interferon ribaviron therapy should be attempted before transplantation. Although efficacy of this approach is poor[60] (particularly in patients infected with the most common phenotype of the HCV virus, genotype 1) this attempt is worthwhile, since HCV clearance post-transplantation with interferon therapy increases the risk of organ rejection in a recipient population that is already particularly subject to this outcome.[48,61] Early data on kidney transplantation in patients with HIV and HCV have shown acceptable outcomes, but the long-term influence on rates of rejection and progression of HCV are being closely monitored in the NIH multicenter prospective trial[62]

Bone metabolism disorders

Renal transplant recipients with HIV are at particularly high risk of low bone mineral density and abnormal bone metabolism.[63,64] These abnormalities are secondary to multiple factors, including: renal-failure-associated hyperparathyroidism leading to osteitis fibrosa cystica; low vitamin D levels leading to low bone turnover; metabolic acidosis and reduced patient physical activity leading to osteoporosis; administration of post-transplantation medications such as steroids ; HIV-associated low androgen levels in both men and women; [65,66] and administration of antiretrovirals, such as tenofovir and didanosine, which have been associated with reduced bone mass.[67] Dual-energy X-ray absorptiometry data from the University of California San Francisco (unpublished data from the NIH trial) shows low bone mass density both before and after transplantation. If tolerated, hormone therapy or administration of bisphosphonates can be implemented to try and restore bone mass levels.

Managing risk of comorbidities

Prophylaxis to prevent co-infections

Renal transplant recipients with HIV should receive the standard post-transplantation prophylaxis regimens that are used in all transplant recipients. These regimens include prophylaxis for *Cytomegalovirus,* fungal infections, and *Pneumocystis carinii* pneumonia during the early post-operative period. If patients receive treatment with lymphocyte-depleting regimens for management of rejection, the prophylaxis regimens should be resumed for 3–6 months after discontinuation of the anti-rejection treatment (See Table 2). [21,62] For patients with HIV, lifelong prophylaxis with trimethoprim-sulfamethoxazole for *Pneumocystis carinii* pneumonia is recommended by most transplantation centers. For patients allergic to sulfonamides, dapsone or atovaquone are viable alternative options. For patients with $CD4^+$ T-cell counts under 75 cells/ml, prophylaxis for Mycobacterium avium complex is also recommended until the $CD4^+$ T-cell counts rebound. Transplant recipients with HIV should also receive vaccinations according to HIV guidelines.[68]

Cardiovascular diseases

Individuals with HIV are at high risk of cardiovascular diseases. Individuals with ESRD often have high blood pressure, even if that was not the etiology of their renal failure.[69] PIs disturb lipid metabolism, an effect that leads to high levels of cholesterol and triglyceride and causes insulin resistance.[70] CNIs administered after transplantation cause vasoconstriction and abnormal vascular remodeling,[71] whereas steroids, ciclosporin, and tacrolimus are diabetogenic.[72] Atorvastatin or pravastatin should be preferred to other statins as HMG-CoA reductase inhibitors, as they have less CYP3A and P-glycoprotein inhibitor activity. Combination treatment of statins with other lipid lowering agents, such as fibrates, may increase the risk of myotoxicity.[73]

Cancer

Patients with HIV are at increased risk of virus-mediated cancers such as Kaposi's sarcoma, non-Hodgkins lymphoma, human-papilloma-virus-associated cervical and anal cancers, and liver cancer.[74,75] Since the advent of HAART, Kaposi's sarcoma and non-Hodgkins lymphoma rates have declined;[76] however, hepatocellular carcinoma rates have increased. Although the reason for the increasing incidence of hepatocellular carcinoma is unclear, it is in part related to the increased longevity of patients with HIV co-infected with HBV or HCV.[77] Regular surveillance for hepatocellular carcinoma is warranted for patients with HIV and HCV or HBV. If the carcinoma develops, patients should be offered all conventional therapies, including liver transplantation. Human-papilloma-virus-associated cervical and anal cancers are a major concern in people with HIV, as both the risk for carcinoma and the growth of the carcinoma can be exacerbated by immunosuppression. Routine Pap smears and colonoscopies should ideally be performed in renal transplant recipients with HIV.[78]

Conclusions

Recognition that introduction of HAART has turned HIV into a chronic condition has been a gradual process in the transplantation community.[79]. Multiple studies have reported promising outcomes at 3–5 years after kidney transplantations in patients treated with HAART,.[24,27,29] In these patients, HIV load remains suppressed, $CD4^+$ T-cell counts remain stable, and opportunistic infections do not seem to increase considerably. However, rates of acute organ rejections are increased in these patients, and an NIH prospective multi-center trial is currently underway exploring the long-term effects that these acute rejections have on graft survival. Co-infection with HIV and HCV is a major concern in renal transplant recipients, both in terms of treatment options and long-term effects on progression of liver disease.

In general, the management of comorbities and their increased risk is crucial in the treatment of these patients. The importance of having a team of specialists looking after renal allograft recipients with HIV cannot be overemphasized. At the very least, this team should include HIV and infectious disease specialists, pharmacists, nephrologists, transplant surgeons, primary care physicians and transplant coordinators or nephrology nurses to help manage the information flow between the patients and the caregivers.[31,80] Regardless of concerns, however, evidence clearly indicates that the exclusion of patients with HIV from kidney transplantation can no longer be justified.

Key points

- Renal transplantation is both safe and effective in patients with HIV

- Rejection rates in patients with HIV are increased, although these rejections respond to therapy
- Several interactions between highly active antiretroviral therapy drugs and immunosuppressants exist, and they should be taken into careful consideration when devising immunosuppression regimens
- Management of co-infection with HCV and HIV is challenging, with more rapid progression of liver disease in affected patients
- Treatment and patient oversight by team of specialists is critically important to the management of renal transplant recipients with HIV

Box 1

Proposed selection criteria for renal transplantation candidates with HIV-1 infection[62]

Exclusion criteria

- Age <1 year
- Detectable HIV-1 RNA
- History of progressive multifocal leukoencephalopathy, chronic intestinal cryptosporidiosis of at least 1-month-duration, lymphoma (Burkitt's, immunoblastic or brain)
- History of multi-drug resistant fungal infection (e.g. resistant *Candida krusei* or *Candida glabrata* infection) not expected to respond to available oral antifungal agents
- History of any neoplasm except those specified in the inclusion criteria below
- Substance use as per local transplantation policy
- Advanced cardiac or pulmonary disease as per local transplantation policy
- Anatomic abnormalities precluding transplantation
- 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 co-infection, unless candidate is being listed for combined liver and kidney transplant
- Substantial wasting and/or malnutrition
- Concomitant conditions that, in the judgment of care providers, preclude transplantation or immunosuppression

Inclusion criteria

- Meeting standard criteria for inclusion in renal transplantation list
- $CD4^+$ T-cell count ≥200/ml at any time in the 16 weeks before transplantation.
- No change in antiretroviral regimen for 3 months before transplantation
- Primary medical care provider has expertise in HIV treatment
- Ability and willingness to comply with immunosuppression protocol and antiretroviral therapy

- Ability and willingness to undergo prophylaxis for pneumocystis pneumonia, herpes virus and fungal infection
- If hepatitis C co-infection is present, ability and willingness to undergo frequent post-transplantation monitoring including hepatitis C treatment as mandated by medical care provider and collection of liver biopsy samples
- 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's 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
- 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 provide 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 beta pregnancy test 14 days before transplantation. All candidates must practice barrier contraception

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Table 1

Recommended prophylaxis regimens for renal transplantation candidates with HIV

Condition	Primary prophylaxis*	Secondary prophylaxis‡
Pneumocystis carinii pneumonia	Indicated for life; to be initiated immediately upon inclusion in transplantation list Preferred treatment: Trimethoprim-sulfamethoxazole Alternatives: Dapsone—if not glucose-6-phosphate dehydrogenase-deficient— or Atovaquone	Same as for primary prophylaxis
Toxoplasmosis	Indicated with positive toxoplasmosis immunoglobulin G and $CD4^+$ T-cell counts ≤200/ml Preferred treatment: Trimethoprim-sulfamethoxazole Alternatives: Atovaquone or sulfadiazine + pyrimethamine + leucovorin Discontinue with $CD4^+$ T-cell >200/ml for 3–6 consecutive months	Indicated with $CD4^+$ T-cell counts ≤200/ml Treatment: Sulfadiazine + pyrimethamine + leucovorin Discontinue with $CD4^+$ T-cell >200/ml for 3–6 consecutive months§
Mycobacterium avium complex	Indicated when $CD4^+$ T-cell counts ≤50/ml Preferred treatment: Azithromycin 1200 mg/week Alternative: Clarithromycin Discontinue with $CD4^+$ T-cell count >100/ml for 3–6 consecutive months	Indicated with $CD4^+$ T-cell counts ≤50/ml Treatment: Clarithromycin + ethambutol Discontinue with $CD4^+$ T-cell count>100/ml for 3–6 consecutive months
Cytomegalovirus	No HIV-specific indication	Indicated with $CD4^+$ T-cell counts <75–100/ml Preferred treatment: Valganciclovir Alternatives: Foscarnet or cidofovir Discontinue with $CD4^+$ T-cell counts >200/mL for 3–6 consecutive months§
Extrapulmonary cryptococcus infection	No HIV-specific indication	Indicated with $CD4^+$ T-cell counts <200/ml Treatment: Fluconazole Discontinue with $CD4^+$ T-cell counts >200 for 3–6 consecutive months
Histoplasmosis	No HIV-specific indication	Indicated for life regardless of $CD4^+$ T-cell count Treatment: Itraconazole

*No history of infection. Additional alternatives, drug interactions and dosing in renal insufficiency are available elsewhere.[81]

‡Prior history of the infection. Additional alternatives, drug interactions and dosing in renal insufficiency are available elsewhere.[81]

§Secondary prophylaxis should also be reinstituted immediately post-transplantation for one month and during the treatment of acute rejection for one month following completion of the rejection therapy. If $CD4^+$ T-cell count is suppressed, continuation should be guided by the $CD4^+$ T-cell count.