American Journal of Transplantation 2013; 13: 169–178
Wiley Periodicals Inc.

doi: 10.1111/ajt.12109

Special Article

Human Immunodeficiency Virus in Solid Organ Transplantation

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Key words: Drug resistance, drug interaction, highly active antiretroviral therapy, human immunodeficiency virus, reverse transcriptase inhibitor, viral load

Abbreviations: BMI, body mass index; CNI, calcineurin inhibitor; CMV, cytomegalovirus; HAART, highly active antiretroviral therapy; HAV, hepatitis a virus; HBV, hepatitis b virus; HCV, hepatitis c virus; HIV, human immunodeficiency virus; HPV, human papillomavirus; LTBI, latent tuberculosis infection; MAC, mycobacterium avium complex; MELD, model for end stage liver disease; mTOR, mammalian target of rapamycin; NNRT, non nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; OI, opportunistic infection; PI, protease inhibitor; TB, tuberculosis.

Epidemiology

With the advent of highly active antiretroviral therapy in the mid-1990s, the patterns of morbidity and mortality in patients with human immunodeficiency virus (HIV) infection have changed. HIV associated complications and opportunistic infections have declined and end stage renal disease and cirrhosis have become increasingly important causes of patient death (1,2). Consequently, interest in organ transplantation in HIV infected patients has increased and the number of transplants in this population as well as the regional expansion of this practice have steadily increased since 1999 (3).

Currently, the vast majority of transplant recipients with HIV are known to have HIV infection before transplant. Donor derived HIV infection has occurred rarely both before the advent of universal testing of donors for HIV and more recently due to the failure of standard testing to identify HIV infection in deceased and live donors (4–7). In an unknown number of cases, HIV has been acquired after transplantation.

Liver and kidney transplants are the most common transplant procedures performed in patients with HIV, reflecting the common occurrence of end stage renal disease and liver cirrhosis in this patient population. HIV associated nephropathy has become an important cause of end stage renal failure, especially in people of African ancestry, and people infected with HIV also have increased incidences of hepatitis associated glomerulonephritis, membranous nephropathy, IgA nephropathy, and drug related nephrotoxicity (8). Because of common infection pathways, HIV often co-exists with both hepatitis C virus and hepatitis B virus, both of which seem to have accelerated progression to cirrhosis in co-infected individuals with diminished responses and intolerance to therapy (9). Although cardiovascular disease has become an increasingly common cause of death in HIV infected patients, heart transplants are still rare in this population (1,10–13). Reports of lung transplantation and pancreas transplantation are also uncommon (12,14,15).

Historically, outcomes in HIV infected patients before HAART were generally poor when compared with patients without HIV infection (16). Recent prospective and retrospective studies both in the United States and Europe have showed improved renal transplant outcomes in the HAART era with patient and graft survival rates falling in between those of uninfected patients and transplant recipients >65 years of age (17–20). Moreover, one study involving the largest single center experience in HIV infected patients revealed superior survival when compared with maintenance on dialysis (21,22). Results in liver transplantation vary based on the underlying disease. HIV infected individuals transplanted for chronic hepatitis C have been found to have decreased survival when compared with their HIV infected counterparts transplanted for other indications, whose survival may be comparable to non-HIV infected liver transplant recipients (23–28). Information regarding transplantation of other organs has been limited to anecdotal reports and small case series. Based on limited data, successful outcomes have been noted in a limited number of HIV infected recipients of cardiac, combined kidney–pancreas transplants, and lung transplants (10–15). Combined liver and kidney transplants may be more likely to result in worse outcomes, however, especially in patients co-infected with HIV and HCV (24).

Regardless of the organ transplanted, the outcomes have been notable for the uncommon occurrence of AIDS

Table 1: Criteria for transplantation in HIV infected individuals

	Kidney transplant	Liver transplant	Heart transplant	Lung transplant	Kidney-pancreas transplant
Meet center specific inclusion criteria	X	X	X	X	X
CD4 count > 100 cells/uL, <200 cells/uL (without history of OI)	NR	X	NR	NR	NR
CD4 count > 200 cells/uL during 3 months before transplantation	X	X[1]	X	X	X
Undetectable HIV viral load while receiving antiretroviral therapy	X	X	X	X	X
Detectable HIV viral load due to intolerance of HAART, HIV can be suppressed post-tx	NR	X	NR	NR	NR
Documented compliance with a stable antiretroviral regimen	X	X	X	X	X
Absence of active opportunistic infection and malignancy[2]	X	X	X	X	X
Absence of chronic wasting or severe malnutrition	X	X[3]	X	X	X
History of hepatitis B or C with lack of evidence of advanced fibrosis or cirrhosis	X	NA	[4]	[4]	X
Acceptance of life-long *Pneumocystis* prophylaxis	X	X	X	X	X
Donor free of hepatitis C	X[5]	X[5]	X	X	X
Appropriate follow-up with providers experienced in the management of HIV	X	X	X	X	X
Ready access to immunosuppressive medication therapeutic drug monitoring	X	X	X	X	X

NA = not applicable; NR = not recommended.
[1]With a history of AIDS defining illness such as opportunistic infection or malignancy.
[2]Patients with a previous history of progressive multifocal leukoencephalopathy, chronic interstitial cryptosporidiosis, primary central nervous system lymphoma, and visceral Kaposi's sarcoma were excluded from the study.
[3]BMI > 21.
[4]Absence of data, although patients with controlled hepatitis B may be considered. Extreme caution for hepatitis C infected patients.
[5]HCV infected donors may be considered for HCV infected recipients on an individual basis.

defining occurrences when standard prophylaxis for opportunistic infections is used. Although outcomes have been generally good, rejection rates have been noted to be significantly higher in HIV infected individuals (18,20,24,29). In some studies, HIV infected liver transplant recipients have had significant recurrences of hepatitis C which have adversely affected patient outcomes (24,26,30).

Risk Factors

To limit the potential impact of HIV on transplant outcomes, most centers have required patients to have well-controlled HIV infection before transplantation. Suggested criteria for transplantation in HIV infected individuals are noted in Table 1 and mirror those used for the NIH sponsored collaborative trial of transplantation in HIV infected individuals (18,24). These criteria reflect the requirement for stable HIV infection at the time of transplant, without any evidence of active opportunistic infections or uncontrolled HIV viremia. An exception may be made for patients with end stage liver disease and intolerance of antiretrovirals related to severe liver disease but HIV genotypic and phenotypic testing that is predictive of viral suppression on resumption of HAART. Although there are no data to establish a time period for which individuals need to sustain these criteria, we recommend a minimum of 3 months (III).

Whether prolonged waiting times may affect outcomes after transplantation is debatable. Early reports suggested that pretransplant survival for liver candidates was diminished in HIV infected individuals when compared with others awaiting liver transplantation, despite equivalent MELD scores (31). Subsequent studies have not confirmed these results, instead showing that MELD was an accurate predictor of wait list mortality in HIV patients, similar to its use in HIV uninfected candidates, and a later survey suggests that hemophiliacs may be at increased risk for death due to accelerated MELD (32,33). After renal transplantation, diminished allograft survival has been noted in recipients of older donor organs and organs with prolonged ischemic time as well as delayed graft function, rejection, and receipt of antithymocyte globulin (18,34). Live kidney donor organs were associated with better outcomes (18). In liver transplant recipients, HCV positive recipients had reduced survival compared with HBV infected recipients (24,25,27). Factors associated with reduced patient and graft survival in patients coinfected with HIV and HCV included older donor age, higher donor risk index, combined liver and kidney transplant, use of an HCV infected donor, higher MELD at transplant, HCV genotype 1 and BMI < 21 (24,29). Patients whose HCV and HIV are undetectable at the time of transplant seem to have improved survival compared to those with detectable virus (25,29).

Significantly increased rejection rates (two- to threefold) have been noted throughout the posttransplant period in both kidney and liver recipients (18,20,29). The etiology of the higher rejection rates remains

unclear; innate immune system dysregulation in the HIV infected recipient and inadequate exposure to immunosuppressive agents secondary to pharmacokinetic interactions with HAART have both been considered to be contributory.

In liver transplant recipients, the biggest impact on patient survival has been the recurrence of hepatitis C infection with progression to cirrhosis (24,26,29). Older recipients and male recipients may have less severe HCV recurrence; the most significant factor associated with recurrent HCV seems to be rejection (24). Because of the rapid progression to cirrhosis, current management strategies include the earlier introduction of treatment for hepatitis C infection (30). Whether this strategy will sufficiently reduce the impact of hepatitis C on outcome to balance the potential risk of rejection associated with interferon is unknown. Of note, there have been several reports of the spontaneous clearance of hepatitis C infection after transplantation (35).

Opportunistic infections and other AIDS defining conditions have been uncommonly reported after transplantation. Instead, HIV infected recipients more commonly experience bacterial infections typically found in HIV uninfected patients (18–20,36). Patients typically experience transient declines in the CD4+ T cell counts after transplantation, but these transient declines do not seem to have an impact on infection risk (18,29,37). Moreover, T cell responses after transplantation both directed at HIV and at herpesviruses have been shown to be stable or expanded, reflecting an increase in immune reactivity (38). A major exception to this both *in vitro* and clinically has been related to the administration of anti-thymocyte globulin either for induction or treatment of rejection. This has been associated with prolonged declines in CD4+ T cell counts, loss of polyfunctional T cell antiviral cytotoxic T lymphocyte responses and the subsequent development of life-threatening bacterial infections (38,39). HIV viremia is generally well controlled with occasional transient episodes of viremia and less frequent persistent HIV viremia (18,29).

Although most reports have focused on infection and rejection, several other complications have also been noted. Malignancies have been uncommon, but those associated with human papillomavirus have been noted more frequently (18,40). Patients with hepatocellular carcinoma have been successfully transplanted with only one study suggesting a trend toward decreased survival in HIV infected recipients with hepatocellular cancer when compared with HIV negative recipients (24,41). It is unclear if there is an increased risk of vascular thrombosis; a single center reported an increased incidence of vascular complications involving arterial and venous systems (42).

Diagnostic Strategies Posttransplant in the HIV Positive Recipient

As with other transplant recipients, the cause of allograft dysfunction may not be apparent based on clinical presentation or laboratory testing. Medications, rejection, disease recurrence and superinfection may all be contributory. Consequently, allograft biopsies should be considered for persistently elevated serum creatinine (kidney transplant recipients) and liver associated enzymes (liver recipients) (II-2). Because liver enzymes may not be reflective of ongoing liver damage related to hepatitis C infection, standard protocol biopsies at 6-month intervals should be considered in liver recipients (III). Because liver enzymes may not reflect the degree of damage in renal transplant candidates co-infected with hepatitis B or C, all candidates for renal transplantation with hepatitis co-infection should undergo liver biopsy before listing (III). Patients with cirrhosis should be carefully evaluated for risk for hepatic decompensation and potentially excluded unless they could be considered for combined liver and kidney transplant (III).

To maintain virologic control of HIV infection, it is recommended that quantitative HIV RNA and CD4+ T cell counts be measured regularly, with the first assays at 1 month after transplant and subsequent studies every 2–3 months thereafter. More frequent monitoring may be necessary in patients receiving depleting antibodies to determine the need for anti-infective prophylaxis (III). If patients have persistent HIV viremia, resistance testing should be performed (genotypic and phenotypic) to determine treatment options (III).

Treatment Considerations in the HIV Positive Transplant Recipient

One of the most intriguing outcomes, seen consistently across all HIV positive transplant studies, is the surprisingly high rejection rates, which are in excess of 30% in renal recipients and nearly twice those of HIV negative liver recipients (18,24). Consequently polyclonal depleting antibodies especially antithymocyte globulin (rabbit) (rATG) have been considered for use in HIV infected kidney transplant recipients. Unfortunately, data regarding the long-term safety of such use is lacking. In addition, the use of these agents must be balanced against the increased risk of graft loss seen with anti-thymocyte globulin use in the HIV-TR study, as well as the infectious complications seen when used at higher doses for rejection (18,39). Use of rATG as an induction agent results in a similar rapid and profound depletion of CD4 + T cells compared to what is seen in the non-HIV population (18,43).

The optimal maintenance immunosuppressive regimen for the HIV-infected transplant recipient is currently unknown.

Early data suggested that cyclosporine may be the preferred calcineurin inhibitor (CNI) due to its potential antiviral activity against HIV. However, data from the large scale HIV-TR kidney study now suggest that tacrolimus is the optimal CNI as higher tacrolimus levels correlated with lower rejection rates when compared with cyclosporine (II-2) (18). Mycophenolate mofetil is the more potent antiproliferative (compared to azathioprine) and may therefore be more effective in preventing rejection in this high risk population (III). An added benefit of mycophenolate is its potential to suppress HIV replication, especially in combination with nucleoside reverse transcriptase inhibitors such as abacavir (44). Sirolimus, an mTOR inhibitor, has been shown *in vitro* to enhance the antiviral activity of enfuvirtide, efavirenz and the CCR5 inhibitors (45). Although these agents have been used in standard treatment regimens for patients with HIV, the potential benefit of using them in transplant recipients with HIV warrants further investigation.

One of the most challenging treatment issues in HIV infected transplant recipients has been managing the numerous drug interactions associated with antiretrovirals and immunosuppressive agents (46). Before transplantation, HIV infected individuals should be on a stable treatment regimen, which should be continued through the peritransplant period to limit the impact of complex drug interactions (III). Patients receiving a protease inhibitor (PI)-based ARV regimen will require significant dose adjustments of both CNI and mTOR inhibitors (47) (II-2). Tacrolimus should be initiated in patients remaining on PIs through the peritransplant period with a mini-load of 1–2 mg. Daily tacrolimus levels should be monitored and the patient should be redosed with 0.5 mg 3–5 days later when the tacrolimus level plateaus in the therapeutic range consistent with organ specific targets (III). Patients receiving boosted PI regimens typically require only 0.375–0.5 mg of tacrolimus once or twice a week to maintain therapeutic targets (46). (II-2) A similar degree of adjustment is necessary when boosted PIs are used with sirolimus (III). A sirolimus dose adjustment down to 0.5–1 mg once weekly has been reported (47). Use of cyclosporine in combination with boosted PIs is simpler because available formulations allow for administration of the substantially lower daily doses required when PIs are used. To maintain therapeutic targets, patients receiving boosted PI regimens generally require modified cyclosporine doses in the range of 15–25 mg twice daily (46). Regardless of the choice of CNI, pharmacokinetic (PK) studies evaluating the impact of boosted PIs on tacrolimus and cyclosporine exposure have shown that the peak CNI levels are blunted when these agents are used together (48,49) (II-2). Additional research is ongoing to evaluate whether this altered PK profile may be a contributing factor to the higher rejection rates seen in this population.

The potential for drug interactions also exist with the NNRTIs nevirapine, etravirine and efavirenz due to their ability to induce clearance of drugs metabolized by CYP3A; rilpivirine does not seem to have the same effect on CNI clearance. Published reports detailing the impact of efavirenz and nevirapine on CNI kinetics are conflicting. The majority of the available data implies that minimal or no dose adjustments are necessary. However, the study by Frasseto et al. reported that patients receiving efavirenz required twice the dose of cyclosporine to achieve therapeutic levels (46). Consequently, close monitoring of immunosuppressive levels is critical in all patients with HIV and should begin on the first day posttransplantation with daily follow-up until levels have stabilized (II-2).

The choice of antiretrovirals should take into account the potential for increased toxicity or diminished bioavailability after transplantation (III). To diminish the risk of mitochondrial toxicity and lactic acidosis, stavudine and didanosine should be avoided (III). Zidovudine may be associated with increased risk of anemia in patients receiving interferon. Atazanavir may have diminished absorption in transplant patients, who commonly receive gastric acid suppression and can be associated with hyperbilirubinemia which may confound posttransplant assessments; consequently it is preferable to avoid this protease inhibitor (III). Use of the integrase inhibitor raltegravir offers the advantage of having no drug interactions and minimal toxicity (50). Unfortunately, that advantage comes at the cost of a lower barrier to resistance. The recently approved once daily integrase inhibitor combination containing elvitegravir, cobicistat, emtricitabine and tenofovir has a higher barrier for resistance than raltegravir but has a significant potential for drug interactions (51). The pharmacokinetic booster cobicistat is a structural analog of ritonavir and has been shown in *in vitro* studies to inhibit CYP3A to a similar degree. Promising data exist with the use of maraviroc, which has a theoretic potential for reduction of the risk of rejection (52). Enfuvirtide also has the advantage of not having any drug interactions with the CNIs or mTOR inhibitors. However, enfuvirtide's subcutaneous administration will likely continue to limit its use (III). A summary of the potential pharmacokinetic interactions that may occur between HAART therapy and immunosuppressants is provided in Table 2.

Treatment of hepatitis B before and after transplantation is essential in transplant recipients who are co-infected with hepatitis B (53) (II-2). Numerous agents, including lamivudine, adefovir, tenofovir, emtricitabine and entecavir have all been used successfully. Standard management has also included the use of hepatitis B immune globulin to maintain titers >200 IU/mL (the goal titer may vary relative to time from transplantation). Lamivudine resistance in hepatitis B has been common in patients co-infected with hepatitis B and HIV as a result of prolonged usage of lamivudine as a component of HAART therapy. Despite the presence of lamivudine resistance in the majority of HIV-hepatitis B co-infected patients, outcomes in these patients have been excellent with the administration of antiretrovirals with appropriate hepatitis B virus coverage (27). In HIV infected

Table 2: Potential pharmacokinetic drug interactions between antiretrovirals and immunosuppressants

	Glucocorticoids	Calcineurin inhibitors	Antimetabolites	mTOR inhibitors
NNRTIs	↓	↓	NI	↓
NRTIs	NE	NI	NI[1]	NE
Unboosted protease inhibitors[2]	↑↑	↑↑	NI	↑↑
Boosted protease inhibitors[2]	↑↑	↑↑↑	NI	↑↑↑
Integrase inhibitors[3]	NE	NI	NE	NI
CCR5-antagonists	NE	NE	NE	NE
Fusion inhibitors	NE	NE	NE	NE

NE = no interaction expected based on theoretical considerations; NI = no interaction found in clinical studies. ↓ = slight potential for decreased exposure due to CYP induction; ↑↑ = known significant drug interaction resulting in increased exposure due to CYP inhibition; ↑↑↑ = known severe drug interaction resulting in increased exposure due to CYP inhibition.

[1]Use of the NRTIs lamivudine, didanosine and abacavir in combination with mycophenolate products may result in an increased risk of lactic acidosis and mitochondrial toxicity. The combination of mycophenolate with zidovudine and stavudine has been found to be antagonistic.

[2]The degree of CYP inhibition may vary across the class of protease inhibitors.

[3]Integrase inhibitors combined with drugs that inhibit the CYP3A system such as cobicistat will likely result in increased exposure of glucocorticoids, calcineurin inhibitors and mTOR inhibitors. Data are currently unavailable on these combinations.

patients who are not undergoing transplantation, combination therapy with tenofovir and lamivudine or emtricitabine has been noted to decrease the development of resistance (54). Combination therapy has been recommended in published clinical guidelines for co-infected recipients unrelated to transplant status (55); this approach is appropriate for co-infected transplant recipients as well (III). Termination of antihepatitis B therapy should be avoided as it may result in a hepatitis flare (III).

Treatment of hepatitis C infection has been more difficult. Whenever possible, hepatitis C infected patients should be assessed for potential treatment before transplant to diminish the hepatitis C viral load, thereby potentially decreasing the risk of post transplant recurrence (III). The addition of telaprevir and boceprevir to standard therapy with pegylated interferon/ribavirin has resulted in significant improvements in sustained viral response rates, even in the HCV/HIV population (56,57). Significant drug interactions exist between the HCV protease inhibitors and various HIV protease inhibitors. To avoid subtherapeutic exposure in HIV and HCV therapy, changes in the ARV regimen may be required before initiation of treatment with telaprevir or boceprevir (58). Most patients will probably not tolerate this before transplantation, however.

After transplantation, patients should be considered for treatment based on liver biopsy results revealing early fibrosis and evidence of progression of recurrent hepatitis C infection; the optimal timing for this is unknown (III). Thus far, combination therapy with interferon and ribavirin has been used sporadically in co-infected transplant recipients with variable responses; toxicity and increased rejection occurrence have been limiting factors (59–61). Data are presently lacking on the impact of the drug interaction between CNIs and telaprevir or boceprevir in HIV infected patients receiving protease inhibitors for treatment of their HIV. Use of telaprevir alone results in the need for similar dose adjustments, as seen with ritonavir boosted protease inhibitors (62). The interaction between boceprevir and the CNIs is not nearly as strong as that seen with telaprevir (63). Currently no formal recommendations exist for the use of combination therapy for HCV with protease inhibitors after transplantation, especially in HIV infected patients. Given the potential for an even greater risk for rejection in HIV patients being treated with interferon and ribavirin, patients on interferon and ribavirin should be closely monitored for rejection (III). The optimal timing and duration of hepatitis C treatment is currently unknown.

Preventative Measures in the HIV+ Transplant Population

Because HIV infected patients undergoing transplantation are presumed to potentially have an augmented risk of developing opportunistic infections due to the addition of exogenous immunosuppression, prophylactic regimens for prevention of opportunistic infections have been recommended (37) (III). Recommendations for opportunistic infection prophylaxis in the HIV infected transplant population are outlined in Table 3. These recommendations differ slightly from the 2009 MMWR publication as the cutoffs for initiation of primary prophylaxis of *Toxoplasma* and *Mycobacterium avium* were higher in the original NIH protocol for transplantation of HIV+ individuals than in the more recent MMWR guidelines (37,55). In addition, the HIV-TR protocol called for lifelong *Pneumocystis* prophylaxis. Whether HIV infected transplant recipients require this more aggressive prophylactic approach is not known; although it is notable that most studies report low incidences of opportunistic infections in recipients using this prophylaxis protocol.

Similar to HIV negative transplant candidates, vaccination status should be assessed before transplantation and

Table 3: Preventative measures in HIV+ transplant recipients—Opportunistic infection prophylaxis

Opportunistic infection	Primary prophylaxis (patients with no prior history of infection)	Regimen	Additional comments
Pneumocystis pneumonia[1]	Indicated for life (III)	Sulfamethoxazole/trimethoprim (Bactrim) 1 double strength (800/160) or single strength (400/80)PO daily	Alternatives: Bactrim DS three times a week, dapsone 100 mg QD (contraindicated if G6PD deficient). If Bactrim or dapsone allergic consider atovaquone 1500 mg PO daily or aerosolized pentamidine 300 mg via nebulizer monthly
Toxoplasma gondii[1]	Toxoplasmosis IgG+ subjects with CD4+ T cell count $\leq$ 200 or any recipient of an organ from a donor seropositive for toxoplasmosis (II-2)	Preferred primary px: Bactrim DS once daily Alternatives: Bactrim SS 1 tab PO QD or dapsone 100 mg PO daily + pyrimethamine 50 mg PO QD + leucovorin 25 mg PO QD or atovaquone 1500 mg PO QD Preferred secondary px: pyrimethamine 25 mg PO QD plus sulfadiazine 100 mg/kg PO QD plus leucovorin 25 mg PO QD. Separate PCP prophylaxis should be discontinued if this regimen is used.	Alternative: for patients who cannot tolerate sulfa drugs pyrimethamine 25 mg PO QD plus clindamycin 300 mg PO QID. Note that only the combination of pyrimethamine plus sulfadiazine seems to provide protection against PCP, thus PCP prophylaxis must be continued with this regimen
Mycobacterium avium Complex (MAC)[1]	Indicated when CD4+ T cell count $\leq$ 75. Discontinue when CD4 count is >100 cells/μL for 6 months (III)	Primary px: Preferred: azithromycin 1200 mg PO weekly Alternative: clarithromycin 500 mg PO BID or rifabutin 300 mg PO QD. Secondary px: Preferred: azithromycin 600 mg PO QD in combination with ethambutol 15 mg/kg/day. Regimen may be modified based on previous MAC treatment. Alternative: clarithromycin 500 mg PO BID plus ethambutol 15 mg/kg/day	Significant drug interactions exist with clarithromycin and rifabutin, monitor immunosuppression levels closely. Rifabutin must be administered at one-half the usual daily dose (i.e., reduce from 300 mg to 150 mg PO QD) with protease inhibitors.
Cytomegalovirus (CMV)	Indicated in CMV IgG + donors or recipients for a minimum of 3 months (III)	Preferred: valganciclovir 900 mg PO QD Alternative: ganciclovir 1 gram PO TID if available, intravenous ganciclovir 5 mg/kg daily	Although no data specific to HIV infected recipients, prophylaxis may be preferred to pre-emptive therapy for highest risk individuals
Histoplasma capsulatum infection	CD4 count < 150 and at high risk because of occupational exposure or residing in an endemic area (III)	Preferred: itraconazole 200 mg PO Daily taken with food Alternative: fluconazole 400 mg PO QD	Significant drug interactions exist with fluconazole and itraconazole, monitor immunosuppression levels closely.
Mycobacterium tuberculosis infection (TB) (treatment of latent TB or LTBI)	(+)diagnostic test for LTBI, no evidence of active TB, and no prior history of treatment for active or latent TB (I) (−)diagnostic test for LTBI but close contact with person with infectious pulmonary TB (III) A history of untreated or inadequately treated healed TB (II-2)	Preferred: Isoniazid (INH) 300 mg po daily or 900 mg po BIW for 9 months – both plus pyridoxine 50 mg po daily Alternatives: Rifampin (RIF) 600 mg po daily x 4 months or Rifabutin (RFB) dose adjusted assuming no contraindication based on concomitant HAART) x 4 months	Significant drug interactions exist with rifampin and rifabutin, monitor immunosuppression levels closely
Coccidioidomycosis	IgG or IgM (+) in a patient from an endemic area and a CD4 count < 250 (I) Lifelong for recipient of organ from donor with history of coccidioides (II-3)	Fluconazole 400 mg po daily or Itraconazole 200 mg po BID	Significant drug interactions exist with fluconazole and itraconazole, monitor immunosuppression levels closely.

[1]Secondary prophylaxis in patients with a prior history of symptomatic infection could be considered in the following circumstances based on the NIH HIV-TR protocol (III):

1. During the first month posttransplant.
2. During treatment of rejection and for 1 month after acute rejection therapy.
3. When CD4 count falls below prespecified cut-off for specific OI:
   (a) CD4 cutoffs – Toxo (200), MAC (75), CMV (100).

Lifelong secondary prophylaxis should be considered for patients with a prior history of *Pneumocystis* pneumonia, *Histoplasma capsulatum* and coccidioidomycosis.

Table 4: Preventative measures in HIV+ transplant recipients—Vaccination in the HIV+ transplant recipient

Vaccine	Population	Vaccination schedule	Recommended product	Additional concerns
Influenza A and B	All HIV+ transplant recipients	Annually (II-2)	Inactivated influenza vaccine 0.5 mL IM	Avoid use of live intranasal vaccine
Streptococcus pneumonia infection	All HIV+ transplant recipients	Every 3-5 years (III)	Pneumococcal vaccine–naive adults: 13–valent pneumococcal conjugate vaccine (PCV13) 0.5 mL IM followed by 23–valent pneumococcal polysaccharide vaccine (PPSV23) $\geq$ 8 weeks later. Adults previously vaccinated with PPSV23: 1 dose of PCV13 $\geq$ 1 year after the last PPSV23 dose. Pediatrics PCV13	
Varicella-zoster virus (VZV) infection	Pretransplant pre-exposure prevention – CD4 count $\geq$200 who have not been vaccinated, have no history of varicella or herpes zoster, or who are seronegative for VZV Postexposure – close contact with a person who has active varicella or herpes zoster with no history of vaccination or infection with varicella or herpes zoster, or who are seronegative for VZV	One time administration with 3 months between Varivax® doses (I)	Pre-exposure prevention – Primary varicella vaccination (Varivax®) 2 doses (0.5 mL SQ) administered 3 months apart (I) Postexposure therapy Varicella-zoster immune globulin (VariZIG®) 125 IU per 10 kg (maximum of 625 IU) IM, administered within 96 hours after exposure (II-1) Alternative: Post exposure varicella vaccination (Varivax®) 2 doses (0.5 mL SQ) administered 3 months apart if CD4 count > 200 (III) Valacyclovir or acyclovir for 7 days beginning 3–10 days postexposure (III)	ProQuad® (Measles, Mumps, Rubella and Varicella Virus Vaccine Live) and Zostavax® both contain live virus and should not be administered to HIV+ transplant recipients. If vaccination with Varivax results in disease this may be treated with acyclovir VZV susceptible household contacts should be vaccinated to prevent transmission to HIV infected contact. If contacts develop a rash due to vaccine, transplant recipient should avoid contact with vaccine recipient until rash resolved (II-3)
Hepatitis A virus (HAV) infection	HAV-susceptible patients with chronic liver disease, or who are injection drug users, or men who have sex with men. May delay vaccination until CD4+ count > 200	One time administration unless patient is considered a non-responder (I)	Hepatitis A vaccine 1 mL IM $\times$ 2 doses at 0 and 6–12 months	IgG antibody response should be assessed 1 month after vaccination; non-responders should be revaccinated
Hepatitis B virus (HBV) infection	All HBV seronegative patients	One time administration unless patient is considered a nonresponder (I)	Hepatitis B vaccine IM (Engerix-B® 20 μg/mL or Recombivax HB® 10 μg/mL) at 0, 1 and 6 months Some experts recommend vaccinating with 40 μg doses of either vaccine	Anti-HBs should be obtained 1 month after completion of vaccine series. If patient is a nonresponder (anti-HBs < 10 IU/mL) they should be revaccinated with a second series. If the first series was given with low CD4 count consideration should be given to wait for a sustained increase in CD4 count
Human Papil-lomavirus (HPV) infection	Men and women aged 9–26	One time administration of three vaccines over 6 months (I)	HPV quadravalent vaccine 0.5 mL IM at months 0, 2 and 6	

Whenever possible vaccines should be administered before transplantation.

vaccines updated as per regular schedules (55). Vaccination recommendations for HIV infected transplant recipients are outlined in Table 4. In addition, all candidates should be screened for latent tuberculosis using either tuberculin skin testing or interferon gamma release assay (55).

Future research

Patients with HIV can be appropriate candidates for transplantation. Because of the significant drug interactions and high risk of rejection and recurrent disease (especially hepatitis C), management of these patients can be complex. Future research will need to focus on strategies to decrease the incidence of posttransplant rejection and reduce the impact of HCV co-infection on patient outcomes. Studies to date have focused on adult populations. Whether there may be differences in the management of adult and pediatric patients is an area that will require future study. Finally recent reports from South Africa using HIV infected kidney donors have suggested that select HIV infected donors may be appropriate for some HIV infected candidates (64). Whether this approach can successfully expand the donor pool is unknown and should be considered for future study. Ultimately given the challenging issues related to patient selection and posttransplant management, an integrated multidisciplinary approach involving diverse health care providers experienced in the care of these patients is recommended for optimal long-term outcomes.

Acknowledgment

This manuscript was modified from a previous guideline written by Emily A. Blumberg and Peter Stock published in the *American Journal of Transplantation* 2009; 9(Suppl 4): S131–S135, and endorsed by the American Society of Transplantation/Canadian Society of Transplantation.

Disclosure

The authors of this manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation.* Dr. Rogers is a consultant for Pfizer.

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