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Solid organ transplantation in the HIV-infected patient: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

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Abstract

These updated guidelines from the Infectious Diseases Community of Practice of the American Society of Transplantation review the management of transplantation in HIV-infected individuals. Transplantation has become the standard of care for patients with HIV and end-stage kidney or liver disease. Although less data exist for thoracic organ and pancreas transplantation, it is likely that transplantation is also safe and effective for these recipients as well. Despite what is typically a transient decline in $CD4^+$ T lymphocytes, HIV remains well controlled and infection risks are similar to those of HIV-uninfected transplant recipients. The availability of effective directly active antivirals for the treatment of Hepatitis C is likely to improve outcomes in HIV and HCV co-infected individuals, a population previously noted to have decreased survival. Drug interactions remain an important consideration, and integrase inhibitor-based regimens are preferred due to the absence of interactions with calcineurin and mTOR inhibitors. Additionally, despite the use of more potent immunosuppression, rejection rates exceed those found in HIV-uninfected recipients. Ongoing research evaluating HIV-positive organ donors may provide support for utilizing these donors for HIV-positive patients in need of transplantation.

KEYWORDS
acquired immunodeficiency syndrome, human immunodeficiency virus

1 | EPIDEMIOLOGY

With the advent of combined antiretroviral therapy (cART) in the mid-1990s, morbidity and mortality in patients with human immunodeficiency virus (HIV) is less frequently attributed to HIV-related causes; cirrhosis and cardiovascular complications have been increasingly implicated.[1] Despite a decline in HIV-associated nephropathy, individuals with HIV remain at increased risk for end-stage kidney disease.[2,3] Consequently, organ transplantation has become increasingly common in persons living with HIV, offering a survival advantage over dialysis and becoming a standard of care for individuals with end-stage liver disease.[4-6]

Currently, the vast majority of transplant recipients with HIV are known to have HIV infection prior to transplant. Donor-derived HIV infection has occurred rarely 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.[7-10] In an unknown number of cases, HIV has been acquired following transplantation; outcomes may be worse in those individuals with post-transplant acquisition.[11]

Liver and kidney transplants are the most common transplant procedures performed in patients with HIV, reflecting the common occurrence of end-stage kidney disease and liver cirrhosis in this patient population and increasing familiarity with these procedures. HIV-associated nephropathy is an important, although declining, cause of end-stage kidney 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.[2,3] Due to common infection pathways, HIV often co-exists with both hepatitis C virus (HCV) and hepatitis B virus (HBV), both of which appear to have accelerated progression to cirrhosis in co-infected individuals. Historically, HIV-infected individuals had diminished responses and intolerance to therapy; however, therapy with directly active antivirals has improved outcomes with HCV and likely will lead to a decrease in liver transplantation for end-stage liver disease due to HCV.[12,13] Cardiovascular disease has become an increasingly common cause of death in HIV-infected patients, and experience with heart transplantation in this population is limited but increasing.[1,14-16] Reports of lung transplantation and pancreas transplantation are also uncommon but increasing.[17,18]

Outcomes of liver and kidney transplant in HIV-infected individuals have been consistent with those in HIV-uninfected people, especially in the absence of HCV coinfection.[22-30] Moreover, HIV-infected patients with end-stage kidney disease experience superior survival when compared with maintenance on dialysis.[5] Results in liver transplantation vary based on the underlying disease. Prior to the availability of oral direct-acting antiviral agents (DAAs), HIV-infected individuals transplanted for chronic hepatitis C were found to have decreased survival when compared with HIV-infected counterparts transplanted for other indications, whose survival may be comparable to non-HIV-infected liver transplant recipients.[23,28,29] 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.[14-20] Large-scale, multi-center prospective data are lacking in these populations; consequently, recommendations for cardiac, lung, and pancreas transplant recipients have been extrapolated from the kidney and liver experience. Data available on outcomes in combined liver and kidney transplants are not yet available in the era of DAAs. We anticipate that the poor outcomes previously seen in patients co-infected with HIV and HCV will be abrogated with use of DAAs.[9]

2 | RISK FACTORS

In order to limit the potential impact of HIV on transplant outcomes, most centers have required patients to have well-controlled HIV infection prior to transplantation. Suggested criteria for transplantation in HIV-infected individuals are noted in Table 1 and mirror those utilized for the NIH-sponsored collaborative trial of transplantation in HIV-infected individuals.[24,30] 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 cART. In those cases, cART should be resumed as soon as possible following transplant to control viral infection. There are no data that establish a time period for which individuals need to demonstrate evidence of controlled HIV infection prior to transplantation; it is possible that longer periods of control may decrease immune activation potentially decreasing the risk of rejection, but this has not been definitively established.[31]

Whether prolonged waiting times may affect outcomes following liver transplantation is debatable. Early reports suggested that pre-transplant survival for liver candidates was diminished in HIV-infected individuals when compared with others awaiting liver transplantation despite equivalent MELD scores.[32] Subsequent studies have not confirmed these results, instead demonstrating that MELD was an accurate predictor of wait list mortality in HIV-infected patients, similar to its use in HIV-uninfected candidates.[33] Another survey suggests that HIV-infected hemophiliacs may be at increased risk for death due to accelerated MELD.[34]

Following kidney transplantation, diminished patient and allograft survival have been noted in older recipients, those with diabetes mellitus and pre-transplant dialysis, recipients of older donor organs and organs with prolonged ischemic time as well as those with delayed graft function and rejection.[24,27,35] There have been conflicting data regarding the use of thymoglobulin with the original NIH study suggesting that thymoglobulin might be associated with decreased patient and allograft survival and subsequent analysis of registry data noting decreased rejection rates with thymoglobulin induction.[24,29,36,37]

Historically, HCV has been associated with worse outcomes in both kidney and liver recipients.[22-24,27] Live kidney donor organs were associated with better outcomes.[24,27] In liver transplant recipients, HCV-positive recipients had reduced survival compared with HBV-infected recipients.[23,28,29] Factors associated with reduced patient and graft survival in HIV and HCV co-infected kidney recipients included use of an HCV-infected donor.[27] In co-infected liver recipients, older donor age, higher donor risk index, combined liver and kidney transplant, higher MELD at transplant, HCV genotype 1, and BMI <21 kg/m^2 have all been associated with reduced survival.[28,30,38] Patients whose HCV and HIV are undetectable at the time of transplant appear to have improved survival compared to those with detectable virus.[38,39] In the current era of DAA therapy, it is possible that HCV in either donor or recipient will not portend the same poor prognosis; consequently, observations regarding outcomes of HCV in HIV-infected recipients of and candidates for solid organ transplantation are expected to change.

Reduced survival on the wait list has been noted in HIV-negative liver candidates with increased frailty as measured by the use of

standard frailty indices.[40] Preliminary data suggest that frailty may also be an important predictor of outcomes in HIV-infected liver recipients in whom it has been associated with reduced patient and allograft survival.[41]

Significantly increased rejection rates (2-3 fold) have been noted throughout the post-transplant period in both kidney and liver recipients, and case series also suggest increased rejection rates in cardiac and pancreas transplant recipients.[15,19,24,26,27,36,38] The etiology of the higher rejection rates remains unclear; innate immune system dysregulation in the HIV-infected recipient, choice of immunosuppressive agents, and inadequate exposure to immunosuppressive agents secondary to pharmacokinetic interactions with cART have all been considered to be contributory.[42]

Opportunistic infections and other AIDS-defining conditions have been uncommonly reported following transplantation. Instead, HIV-infected recipients more commonly experience bacterial infections typically found in HIV-uninfected patients.[7,24,26,39,43,44] Patients typically experience transient declines in the CD4+ T-cell counts following transplantation, but these transient declines do not appear to have an impact on long-term infection risk; although short-term CD4 counts <200 cells/mm^3 may be associated with early infections following transplant.[24,44,45] Moreover, T-cell responses

TABLE 1 Suggested criteria for transplantation in HIV-infected Individuals[a,24]

	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/μL (without history of OI)	NR[b]	X[c]	NR	NR	NR
CD4 count >200 cells/μL during 3 mo prior to transplantation	X	X	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[d]	X	X	X	X	X
Absence of chronic wasting or severe malnutrition	X	X[e]	X	X	X
History of hepatitis B or C with lack of evidence of advanced fibrosis or cirrhosis	[f]	NA	[f]	[f]	[f]
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

NR, not recommended; NA, not applicable.

[a]All recommendations are strong, moderate for kidney and liver transplantation but strong, low for all others given the more limited experience with these populations.

[b]There are currently insufficient data upon which to base recommendations regarding transplantation of non-liver recipients with lower CD4 counts but no history of OIs.

[c]With no history of AIDs defining illness such as opportunistic infection or malignancy.

[d]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 original HIV-TR study. Patients with hepatocellular cancer can be considered for liver transplantation if they meet center-specific criteria. Data on the safety of transplantation in patients with HPV-related anal carcinoma in situ are insufficient to determine definitive guidance for patients with this malignancy.

[e]BMI > 21 kg/m^2 (weak, low)

[f]Absence of data in current era of DAAs and in setting of non-liver HBV co-infected recipients. Patients with controlled hepatitis B on therapy may be considered. Caution for hepatitis C-infected patients, in whom DAA therapy has not been initiated.

following transplantation both directed at HIV and at herpesviruses have been shown to be stable or expanded, reflecting an increase in immune reactivity.[46] A major exception to this both in vitro and clinically has been related to the administration of thymoglobulin 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.[47] HIV viremia is generally well controlled with occasional transient episodes of viremia and less frequent persistent HIV viremia.[24,38]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.[24,48] 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-uninfected recipients.[30,49,50] It is unclear whether there is an increased risk of vascular thrombosis; single center reports noted an increased incidence of vascular complications post-liver transplant and pancreas transplants involving arterial and venous systems.[19,20,51]

- HIV-infected patients should be on a stable cART regimen with no evidence of viremia and a CD4 count ≥200 cells/mm^3 for all except liver candidates in whom a CD4 count ≥100 cells/mm^3 can be considered (strong, moderate).
- HIV-infected liver candidates who cannot tolerate cART due to advance liver disease can be considered for transplantation if they have evidence of an easily controllable HIV infection based on genotypic and/or phenotypic assessment (weak, low).
- HIV-infected candidates who are co-infected with HCV can be considered for transplantation assuming there is a plan for treatment of HCV either prior to transplant or in the early post-transplant period (strong, low).

3 | DIAGNOSTIC STRATEGIES POST-TRANSPLANT 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), liver enzymes (liver transplant recipients), or amylase, lipase, or blood glucose (pancreas transplant recipients). Use of "for cause" or surveillance biopsies in the setting of heart and/or lung transplant should follow center-specific standards of care.

Assays using cell-free DNA to aid in diagnosis of allograft injury were recently approved for use in heart and kidney transplant recipients.[52] Limited data exist on the use of these assays in HIV-infected transplant recipients. It is unknown how HIV may adversely impact the interpretation of these assays; therefore, caution is recommended in use of cell-free DNA assays in the HIV-infected transplant population until more data are available.

Since liver enzymes may not reflect the degree of damage in kidney transplant candidates co-infected with hepatitis B or C, all candidates for kidney transplantation with hepatitis co-infection should undergo assessment of liver disease with either transient elastography or liver biopsy prior to listing. Patients with cirrhosis should be carefully evaluated for hepatic decompensation and potentially excluded from kidney transplantation unless they could be considered for combined liver and kidney transplant.

In order 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 in order to determine the need for anti-infective prophylaxis. If patients have persistent HIV viremia, resistance testing should be performed (genotypic and phenotypic) to determine treatment options. Use of new archival resistance testing techniques which interrogate the viral archive using next-generation sequencing (NGS) may be beneficial in determining resistance in the setting of suppressed or low HIV viral loads and the desire to modify the cART regimen due to concern for drug-drug interactions (DDIs) or drug intolerance.[53,54]

- All candidates for kidney transplantation with hepatitis co-infection should undergo assessment of liver disease with either transient elastography or liver biopsy prior to listing and patients with cirrhosis should be carefully evaluated for hepatic decompensation and potentially excluded from kidney transplantation unless they could be considered for combined liver and kidney transplantation (strong, low).
- Biopsy should remain the gold standard in assessing graft dysfunction in HIV-infected individuals (strong, moderate).
- HIV RNA and CD4+ T-cell counts should be monitored 1-month post-transplant and then every 2-3 months post-transplant to insure control of HIV (strong, low).
- Individuals with persistent HIV viremia should undergo genotypic and phenotypic testing for resistance (strong, moderate).
- Use of archival resistance testing should be considered prior to modifying cART regimens due to drug intolerance or interactions when HIV VL is suppressed (weak, very low).

4 | TREATMENT CONSIDERATIONS IN THE HIV-POSITIVE TRANSPLANT RECIPIENT

One of the most intriguing outcomes, seen consistently across almost all HIV-positive transplant studies, is the surprisingly high rejection rates, which are in excess of 30% in kidney recipients and nearly twice those of HIV-uninfected liver recipients.[24,26,27,36,38]

Consequently, polyclonal depleting antibodies especially anti-thymocyte globulin (rabbit) (rATG) have been considered for use in HIV-infected kidney transplant recipients and are commonly used in many kidney transplant programs. Unfortunately, data regarding the long-term safety and efficacy of such use are conflicting. Large-scale registry data have suggested a benefit with use of rATG induction whereas more granular prospective data have demonstrated an increased risk of graft loss and significant infectious complications seen when used at higher doses for rejection.[24,29,36,37] 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 HIV-uninfected population.[24,55] Based on these results, induction therapy with either lymphocyte depletion or interleukin 2 receptor antagonist may be appropriate. Consideration can be given to use more potent lymphocyte-depleting induction in high immunologic risk candidates (African American, presence of donor specific antibodies, prior transplant). Monitoring for infection risks including measurement of CD4 counts should be performed every 2-3 months to assess infection risk.

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 in addition to that from various single center experiences and the large UK HIV transplant study suggest that tacrolimus is the optimal CNI due to its superior ability to prevent rejection.[24,56] Mycophenolate mofetil is the more potent antiproliferative agent (compared to azathioprine) and may therefore be more effective in preventing rejection in this high-risk population. A possible benefit of mycophenolate is its potential to suppress HIV replication, especially in combination with nucleoside reverse transcriptase inhibitors such as abacavir.[57] Sirolimus, an mTOR inhibitor, has also been shown to possibly enhance in vitro the antiviral activity of cART including enfuvirtide, efavirenz, and the CCR5 inhibitors.[58] Sirolimus may also play a role in modulating the progression of HIV-associated nephropathy (HIVAN) by altering HIV gene expression in the kidney and may reduce HIV persistence following transplantation.[59,60] The lack of potential for drug-drug interactions (DDIs) and nephrotoxicity in addition to the potential for additive antiviral activity against HIV make use of belatacept an intriguing alternative to CNIs and mTOR inhibitors post-transplant, and there has been a report of successful conversion to belatacept in an HIV-infected kidney recipient with subsequent kidney recovery.[61] Experience comparing belatacept with cyclosporine in HIV-uninfected individuals reported higher than expected rates of early rejection, which may explain the reluctance for many to use this agent in the HIV-infected transplant population.[62] Caution should be advised given the limited data with use of this agent at this time.

The desire to avoid the long-term steroid-associated metabolic adverse effects should be carefully weighed against known risks of steroid avoidance protocols, including the increased risk of rejection. Given the already increased risk of rejection in the HIV-infected transplant population, most centers include prednisone as part of their long-term maintenance immunosuppression regimens. In one single center study employing induction treatment followed by early steroid withdrawal, rates of rejection were low.[63] However, an Italian cohort of 13 HIV-infected patients receiving basiliximab induction followed by CNI and half dose mycophenolate sodium experienced 1-year rejection rates approaching sixty percent.[64] Given the limited data on successful steroid withdrawal protocols in HIV-infected transplant recipients, this approach should be avoided.

One of the most challenging aspects of managing the HIV-infected transplant recipient has been managing the numerous drug interactions associated with cART and immunosuppressive agents.[65] Prior to transplantation, HIV-infected individuals should be on a stable treatment regimen, which ideally does not contain a protease inhibitor or pharmacokinetic enhancer such as cobicistat. The use of once daily single tablet combination regimens in the HIV-infected transplant population should be used with caution as many of these combination regimens do not allow for easy renal dose adjustment and many contain the pharmacokinetic booster cobicistat. Cobicistat is a structural analog of ritonavir and has been demonstrated in in-vitro studies to inhibit CYP3A to a similar degree. Two case reports illustrating the clinical significance of this DDI and the consequences of inadequate CNI dose adjustments were recently published.[66,67] If it is identified that patients are receiving one of these products, the patients' infectious disease providers should work together to determine whether the patient has a history of cART resistance that would preclude a change in therapy. If this information is unavailable, and the patient has a suppressed or low HIV viral load, use of archival testing may be beneficial to determine whether the cART regimen can be altered to minimize the impact of detrimental interactions in the post-transplant setting. If a patient's cART regimen is not able to be modified to remove the protease inhibitor or cobicistat, significant dose adjustments of both CNI and mTOR inhibitors will be necessary.[68]

Tacrolimus should be initiated in patients remaining on PIs or cobicistat through the peri-transplant period with a mini-load of 1-2 mg. Daily tacrolimus levels should be monitored and tacrolimus 0.5 mg should be given 3-5 days later when the tacrolimus level plateaus in the therapeutic range consistent with organ specific targets. Patients receiving boosted PIs or cobicistat typically require 0.25-0.5 mg of tacrolimus once or twice a week to maintain therapeutic targets.[65] A similar degree of adjustment is necessary when boosted PIs are used with sirolimus. A sirolimus dose adjustment down to 0.5-1 mg once weekly has been reported.[68] No data currently exist on everolimus dose adjustments with use of PI or cobicistat-based regimens. Everolimus has a long half-life similar to sirolimus (38 hour vs 67 hour), therefore, one may assume a similar adjustment to that seen with sirolimus where small doses are given once or twice a week would be necessary. Use of cyclosporine in combination with boosted PIs is somewhat easier because available formulations allow for administration of the substantially lower daily doses required when PIs are used. In order to maintain therapeutic targets, patients receiving PI or cobicistat containing regimens generally require modified cyclosporine doses in the range of 15-25 mg

twice daily.[65] 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 potentially resulting in lower than expected overall drug exposure.[69,70] Data have begun to emerge suggesting that use of PI-based cART regimens may increase the risk of allograft loss and patient death within the first-year post-transplant.[71]

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 appear to have as significant of an effect on CNI clearance.[65] 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[65] reported that patients receiving efavirenz required twice the dose of cyclosporine to achieve therapeutic levels. Consequently, close monitoring of immunosuppressive levels is critical in all patients with HIV and should begin on the first-day post-transplantation with daily follow-up until levels have stabilized. Additionally, it would be prudent to increase the frequency of therapeutic drug monitoring any time an NNRTI is removed from a patients cART regimen.

The choice of antiretrovirals should take into account the potential for increased toxicity when combined with common immunosuppressants following transplantation. Table 2 outlines the potential pharmacokinetic and pharmcodynamic interactions that may result in additive toxicity when various cART classes are combined with available immunosuppressants. A number of significant concerns are outlined in this table. Use of the integrase inhibitors raltegravir, bictegravir, and dolutegravir offers the advantage of having no drug interactions and minimal toxicity. This class has become the favored backbone of cART regimens post-transplant.[72] Dolutegravir has a higher barrier to resistance than raltegravir and comes with the advantage of once daily dosing. Serum creatinine levels may increase after initiation of dolutegravir as this agent can inhibit tubular secretion of creatinine in a similar manner to that of trimethoprim, rilpivirine, and cobicistat without reducing glomerular filtration.[73] A recent case of dolutegravir use post-transplant speculated that the increase in serum creatinine post-kidney transplant may be more profound than anticipated due to the presence of only one functional kidney.[74] The recent approval of a single tablet co-formulated product consisting of bictegravir, emtricitabine, and tenofovir alafenamide allows for the opportunity to decrease pill burden using cART with a favorable side effect and DDI profile; experience using this in HIV-infected transplant recipients is limited thus far. There is limited experience using maraviroc but theoretic interest in its use due to the potential for reduction of rejection; a clinical trial of its uses is ongoing.

Treatment of HBV prior to and following transplantation is essential in HIV-infected transplant recipients who are co-infected with HBV.[75] The most recent guideline on use of antiretrovirals suggests that all HBV and HIV co-infected patients receive antiretroviral therapy that includes two drugs with activity against HBV: specifically, tenofovir (Tenofovir alafenamide or Tenofovir disoproxil fumarate) plus lamivudine or emtricitabine.[54] Use of tenofovir alafenamide is preferred to tenofovir disoproxil fumerate because of its improved safety profile. The lower incidence of nephrotoxicity and bone disease is particularly important in the co-infected HBV and HIV transplant recipient because of the potential for synergistic toxicity with long-term prednisone and CNI use. Standard management of co-infected liver transplant recipients 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).[29] Lamivudine resistance in HBV B has been common in patients co-infected with HBV and HIV as a result of prolonged utilization of lamivudine as a component of cART therapy.[54] Termination of anti-hepatitis B therapy should be avoided as it may result in a hepatitis flare.

Treatment of HCV infection in the co-infected transplant recipient has evolved tremendously with the emergence of the new direct-acting antiviral agents (DAAs). The guideline on hepatitis viruses (see Hepatitis section of the 4th edition of the AST ID Guidelines) will provide the details necessary to understand the treatment guidelines as well as navigate the complex DDIs that exist with various combinations of cART and DAAs. In HIV-infected recipients, it is unknown if it is preferable to treat patients prior to or following transplant. Consideration for pre-transplant treatment in the non-liver candidate should include the severity of liver disease, the increased likelihood of earlier transplant with receipt of an HCV-positive donor organ, and the availability of treatment. If treatment is delayed until after transplant, genotype appropriate treatment should be instituted in the early post-transplant period to minimize rapid hepatic deterioration.

- Induction therapy with either lymphocyte depletion or interleukin 2 receptor antagonist should be used (strong, moderate). Lymphocyte-depleting induction is recommended for high immunologic risk candidates (African American, presence of donor specific antibodies, prior transplant) (strong, moderate).
- Maintenance immunosuppression regimens for kidney recipients should include tacrolimus, a mycophenolate analog, and long-term corticosteroids (strong, moderate). Steroid avoidance regimens should not be used given the increased risk of rejection (strong, very low).
- Protease inhibitor-based regimens and cobiscistat should be avoided (strong, moderate). Regimens avoiding these medications should be implemented prior to transplant, unless there are no alternative options based on genotypic and phenotypic testing (strong, moderate).
- If use of a protease inhibitor or pharmacokinetic enhancer such as cobicistat is necessary, significant dose reductions of calcineurin and mTOR inhibitors are necessary; daily monitoring of levels is required to determine optimal dosing (strong, moderate).
- Use of an integrase inhibitor-based cART regimen is preferred due to the favorable safety profile and lack of DDIs (strong, moderate).
- Transplant recipients co-infected with HBV and HIV should receive cART that includes two drugs with activity against HBV

(strong, high). Tenofovir alafenamide is preferred to tenofovir disoproxil fumerate because of its improved safety profile (strong, weak).

- All patients co-infected with HIV and HCV should be treated with DAAs for HCV (strong, high). The timing of HCV treatment in non-liver recipients should be determined based on the degree of liver disease, the likelihood of earlier transplant with an HCV-positive organ, and the availability of DAA therapy; treatment can be

TABLE 2 Potential pharmacokinetic (PK) and pharmacodynamic (PD) drug interactions between antiretrovirals and immunosuppressants[54,64,65]

	Glucocorticoids	Calcineurin inhibitors	mTOR inhibitors	Antimetabolites
NNRTI's				
PK	↓	↓	↓	NI
PD		RPV, EFV: QTc prolongation		
	EFV: ↑ TG, LDL, HDL Psychiatric AE's—depression, psychosis, suicidal ideation	RPV: ↑ Scr (no change in GFR)		
NRTI's				
PK	NE	NI	NE	NI
PD	TDF > TAF: Loss of BMD	TDF > TAF: Renal dysfunction, proteinuria, ↓phos		ZDV: Anemia and neutropenia 3TC, ABC—↑ lactic acidosis and mitochondrial toxicity ZDV/D4T—avoid with MMF—antagonistic
	d4T > ZDV > ABC: ↑ TG and LDL TAF:↑ TG, LDL, HDL			
Unboosted protease inhibitors (PI)[a]				
PK	↑↑	↑↑	↑↑	NI
PD		SQV/r: QTc prolongation ATV and LPV/r: ↑ risk CKD		Gi intolerance
Boosted protease inhibitors (PIs)[a]				
PK	↑↑	↑↑↑	↑↑↑	NI
PD	DRV, FPV,IDV, LPV/r: Increased risk CV events IDV, LPV/r: Increase risk of diabetes COBI and r boosted PIs: ↑ TG, LDL, HDL			
Integrase inhibitors[b]				
PK	NE	NI	NI	NE
PD		RAL,DTG: ↑CPK and rhabdo DTG: ↑ Scr (no change in GFR)		
Pharmacokinetic boosters (cobicistat)				
PK	↑↑	↑↑↑	↑↑↑	NI
PD		COBI: ↑ Scr (no change in GFR)		
CCR5-antagonists				
PK	NE	NE	NE	NE
PD				
Fusion inhibitors				
PK	NE	NE	NE	NE
PD	NE	NE	NE	NE

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

Drug name abbreviations: 3TC Lamivudine; ABC Abacavir; ATV Atazanavir; COBI Cobicistat'; D4T Stavudine; DDI Didanosine; DRV Darunavir; DTG Dolutegravir; EFV Efavirenz; FPV Fosamprenavir; IDV Indinavir; LPV Lopinavir; r Ritonavir; RAL Raltegravir; RPV Rilpivirine; SQV Saquinavir; TAF Tenofovir alafenamide; TDF Tenofovir disoproxil fumarate; ZDV Zidovudine.

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

[b]Integrase inhibitors combined with pharmacokinetic boosters such as cobicistat will result in increased exposure of glucocorticoids, calcineurin inhibitors, and mTOR inhibitors.

deferred to the early post-transplant period in stable patients in whom HCV-positive organs are readily available (strong, moderate).

5 | PREVENTATIVE MEASURES IN THE HIV+TRANSPLANT POPULATION

Despite their potential history of opportunistic infections prior to transplant, HIV-infected patients undergoing transplantation have a similar risk of developing opportunistic infections to that of their HIV-uninfected counterparts. Similar to HIV-uninfected recipients, prophylactic regimens for prevention of opportunistic infections have been recommended which also incorporate current prophylaxis recommendations for HIV-infected individuals who have not undergone transplant.[76] Recommendations for opportunistic infection prophylaxis in the HIV-infected transplant population are outlined in Table 3 and reflect the most recent guidelines for HIV-infected individuals. Notably, the HIV-TR protocol called for lifelong *Pneumocystis jirovecii* prophylaxis. Whether HIV-infected transplant recipients require this more aggressive prophylactic approach is not known; most studies report low incidences of opportunistic infections in recipients using this extended prophylaxis protocol.

Similar to HIV-uninfected transplant candidates, vaccination status should be assessed prior to transplantation and vaccines updated as per regular schedules.[76,77]Vaccination recommendations for HIV-infected transplant recipients are outlined in Table 4. Additionally, all candidates should be screened for latent tuberculosis prior to transplantation using either tuberculin skin testing or interferon gamma release assay.[76,77]

- All HIV-infected transplant recipients should receive standard institution-based prophylaxis for against *Pneumocystis*, cytomegalovirus, and fungal pathogens (strong, moderate).
- The need for extended *Pneumocystis* prophylaxis beyond 1 year should be weighed against therapy-related adverse effects that may warrant early discontinuation (weak, low).
- Primary and secondary prophylaxis against opportunistic pathogens in HIV-infected transplant recipients should be initiated in accordance with national HIV guidelines (moderate, moderate).
- Vaccine recommendations for HIV-infected transplant candidates and recipients should mirror those of HIV-uninfected transplant candidates and recipients (strong, moderate).
- Live vaccines should be avoided in most cases (see Vaccine section of 4th edition of AST ID Guidelines) (strong, moderate).

6 | HIV TO HIV TRANSPLANTATION

Wait list mortality is higher in transplant candidates infected with HIV; therefore, there is a pressing need to identify an alternative source of donors for this population.[5] The safety of transplanting HIV-infected donors into HIV-infected transplant candidates was first evaluated in South Africa, where HIV-infected patients with ESRD were historically not considered transplant or dialysis candidates. This initial experience of HIV to HIV transplantation illustrated that the use of kidneys from HIV-infected donors did not adversely impact patient and graft survival or acute rejection rates.[79] This experience from South Africa provided the preliminary data needed to move the HIV Organ Policy Equity (HOPE) Act forward in the United States. With approval of the HOPE act in 2013, the law banning use of HIV-positive donors was revised allowing for use of these organs under specific research protocols.[80] The Health and Human Services (HHS) Secretary set forth specific criteria in six categories that must be met by participating centers. The six categories include donor eligibility, recipient eligibility, Transplant Hospital Criteria, Organ Procurement Organization (OPO) responsibilities, prevention of inadvertent transmission of HIV, and study design/required outcome measures. All donors must be free of invasive opportunistic complications of HIV and undergo a pre-implantation biopsy. Living donors with HIV must have well-controlled HIV defined as a CD4 count ≥500 cells/mm^3 for the 6-month period prior to donation and an HIV-1 RNA <50 copies/mL, whereas deceased donors must have a history of HIV that can be treated with a cART regimen that the study team deems will be safe, tolerable, and effective. Details surrounding the other requirements can be found in the HOPE Act Safeguards and Research Criteria Document published by the Department of Health and Human Services.[81] Currently, there are multiple US transplant centers participating in an NIH trial evaluating the safety of this practice and additional centers internationally performing kidney and liver transplants using HIV-infected donors.

It is anticipated that the HOPE Act will expand the donor pool for HIV-infected transplant candidates although the ultimate impact on the pool of donors for HIV-infected individuals and the downstream effects on HIV-uninfected candidates is not yet known. An unexpected benefit of the HOPE act has been the increased use of organs that would have been discarded due to false-positive HIV tests; a recent report identified an opportunity to use 10 suspected false-positive donors (with organs for 21 HIV+ recipients) over a period of 2 years with excellent outcomes.[82] The authors estimated that the use of false-positive donors may result in the opportunity to increase the donor pool by 50-100 donors per year. Use of HIV-infected organs through implementation of the HOPE Act may also pose a number of challenges and risks. Given that this is relatively unchartered territory, there is much that remains unknown. There is an inherent risk of HIV superinfection and potential for transfer of resistant virus to recipients with well-controlled HIV. There is potential for inadvertent transplantation of an HIV-infected organ into a HIV-uninfected individual, and risk of HIV transmission to members of the healthcare team procuring and transplanting these organs. Finally, it is unknown how the use of HIV-infected organs may impact the risk of rejection in a population that already is at a higher risk than the general transplant population.[83]

- With approval of the HOPE Act, transplantation of HIV-infected organs into HIV-infected recipients may be performed under specific research criteria (moderate, moderate).

TABLE 3 Preventative measures in HIV+ transplant recipients—Opportunistic infection prophylaxis[24,76]

Opportunistic infection	Primary prophylaxis (patients with no prior history of infection)	Regimen	Additional comments
Pneumocystis jirovecii pneumonia (PJP)	Indicated for a minimum of 1-y post transplant (Strong, moderate)	Sulfamethoxazole/trimethoprim (TMP-SMX)1 double strength (800/160) (Strong, High) or single strength (400/80)PO daily (Strong, High) Alternatives: TMP-SMXDS three times weekly (Strong, moderate), dapsone 100 mg PO daily (Strong, moderate), (contraindicated if G6PD deficient) or atovaquone 1500 mg PO daily (Strong, moderate). If above agents not tolerated or unavailable can consider aerosolized pentamidine 300 mg via nebulizer monthly (weak, moderate)	Optimal duration of PJP prophylaxis is unknown; limited data exist on the need for lifelong TMP-SMX. Risks and benefits of continuation beyond 1 y should be made on an individual basis. Consider monitoring CD4 counts and could consider discontinuation if CD4> 200 for >3 mo after 1-y post-transplant (Weak, low) Double strength may be preferred in the setting of donor or recipient also having positive Toxoplasmosis IgG (Strong, moderate) Patients treated with dapsone should be monitored for methemoglobinemia and anemia. Dapsone and aerosolized pentamidine monotherapy do not prevent toxoplasmosis or bacterial infections
Toxoplasma gondii Infection	ToxoplasmosisIgG+ recipients with CD4+ T-cell count <100 or any recipient of an organ from a toxoplasmosis seropositive donor (weak, high) Indicated for a minimum of 1-y post-transplant when used as both PJP and Toxoplasmosis prophylaxis (strong, low) May discontinue in those receiving ART when CD4 >200 for >3 mo (strong, low)	Preferred primary px: TMP-SMX DS PO daily (strong, high) Alternatives: TMP-SMX SS 1 tab PO daily (high, low), TMP-SMX DS three times a week (weak, low) or dapsone 100 mg PO daily + pyrimethamine 50 mg PO daily + leucovorin 25 mg PO daily (strong, high) or atovaquone 1500 mg PO daily (weak, moderate) or Atovaquone 1500 mg PO daily + pyrimethamine 50 mg PO daily + leucovorin 25 mg PO daily (weak, low)	Sulfa desensitization should be attempted in those with a history of sulfa allergy (strong, moderate)
Mycobacterium avium Complex (MAC)	Indicated when CD4+ T-cell count ≤50 active infection excluded (1A). Discontinue when CD4 count is >100 cells/μL for 36 mo	Primary px: Preferred: azithromycin 1200 mg PO once weekly (weak, moderate) Alternative: clarithromycin 500 mg PO BID (weak, moderate), azithromycin 600 mg po twice weekly (weak, moderate) or rifabutin 300 mg PO QD (weak, moderate)	Significant drug interactions exist with clarithromycin and rifabutin, monitor immunosuppression levels closely. Rifabutin must be administered at one-half the usual daily dose (ie, reduce from 300 mg to 150 mg PO QD) if coadministered with protease inhibitors. (weak, moderate) Use of MAC prophylaxis could be considered in all transplant recipients receiving induction therapy with polyclonal depleting antibodies (weak, low)
Mycobacterium tuberculosis infection (TB) (treatment of latent TB or LTBI)	(+) screening test for LTBI with no evidence of active TB, and no prior history of treatment for active or latent TB (strong, high) Close contact with person with infectious pulmonary TB, no evidence of active TB, regardless of screening result (strong, moderate) Donor with untreated latent TB (strong, moderate)	Preferred: Isoniazid (INH) 300 mg po daily plus pyridoxine 25-50 mg po daily for 9 mo (strong, moderate) or 900 mg po twice weekly (by DOT) plus pyridoxine 25-50 mg po daily for 9 mo (weak, moderate) Alternatives: rifampin (RIF) 600 mg po daily orrifabutin (RFB) (dose adjusted based on concomitant ART) for 4 mo (weak, low)or rifapentine (RPT) (weigh-based, 900 mg max) + INH 15 mg/kg (900 mg max) + pyridoxine 50 mg weekly × 12 wk in those receiving EFV or RAL-based ART) (weak, low)	If possible, treatment of LTBI should be completed prior to transplantation, especially if using a rifamycin containing regimen. Significant drug interactions exist with the rifamycin class of antibiotics, monitor immunosuppression levels closely. Adjustments in ART regimens may also be necessary to avoid significant drug interactions and loss of efficacy. Limited data exist with use of rifapentine in HIV-positive transplant recipients though this agent may be preferred due to less potent interactions with immunosuppressants

(Continues)

TABLE 3 (Continued)

Opportunistic infection	Primary prophylaxis (patients with no prior history of infection)	Regimen	Additional comments
Cytomegalovirus (CMV)	Indicated if either donor or recipient is CMV IgG+ to be given for a minimum of 3 mo (strong, moderate)	Preferred: valganciclovir 900 mg PO QD (strong, high) Alternative: intravenous ganciclovir 5 mg/kg daily (strong, moderate)	Although no data specific to HIV-infected recipients, prophylaxis is preferred to pre-emptive therapy for highest risk individuals. Longer durations of prophylaxis (eg, 6 mo) are recommended for CMV seronegative recipients of CMV seropositive organ donors in the absence of HIV and should be therefore also be considered, especially for HIV-positive kidney and thoracic recipients (strong, moderate)
Histoplasma capsulatum infection	CD4 count <150 and at high risk because of occupational exposure or residing in an endemic area (strong, moderate) May discontinue when CD4 count >150 for 6 mo on ART (weak, low)	Preferred: itraconazole tablets or capsules 200 mg PO daily taken with food (strong, low)	Significant drug interactions exist with itraconazole, monitor immunosuppression levels closely
Coccidioidomycosis	IgG or IgM (+) in a patient from an endemic area for a minimum of 6-12 mo post-transplant (longer for those with history of more advanced disease, possibly lifelong) (strong, moderate) Lifelong for recipient of organ from donor with history of coccidioidomycosis (strong, low)	Fluconazole 400 mg po daily (weak, low) Alternatives: Voriconazole 200 mg po BID after appropriate load or posaconazole DR tablet 300 mg po daily after appropriate load with therapeutic dose monitoring(weak, low)	Significant drug interactions exist with fluconazole, voriconazole, and posaconazole, monitor immunosuppression levels closely. Given increased risk of non-melanoma skin cancer, voriconazole is not preferred for lifelong prophylaxis

1. At least the first-month post-transplant
2. During treatment of rejection and for 1 mo following acute rejection therapy
3. When CD4 count falls below pre-specified cutoff 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* infection, and Coccidioidomycosis (strong, moderate).

[a]Secondary prophylaxis for the above mentioned infections and for Cryptococcus in patients with a prior history of symptomatic infection could be considered in the following circumstances based on the NIH HIV-TR protocol (strong, low)

TABLE 4 Preventative vaccinations in the HIV+ transplant recipient[54,74,75]

Vaccine	Population	Vaccination schedule	Recommended product	Additional concerns
Influenza A and B	All HIV+ transplant candidates and recipients	Annually (strong, moderate)	Inactivated influenza vaccine 0.5 mL IM	Avoid use of live intranasal vaccine
Streptococcus pneumoniae infection	All HIV+ transplant candidates and recipients	Every 3-5 y (weak, low)	For first pneumococcal vaccination: Pneumococcal conjugate vaccine (PCV13) 0.5 mL IM × 1 (strong, moderate) Pneumococcal polysaccharide vaccine (PPV23) 0.5 mL IM at least 8 wk after the PCV13 vaccine (strong, moderate) PPV23 can be offered at least 8 wk after receiving PCV13 (weak, low) or can wait until CD4 count increased to ≥200 cells/μL (weak, low). Previous PPV23: One dose of PCV13 should be given at least 1 y after the last receipt of PPV23 (strong, moderate)	
Varicella virus (VZV) infection	*Pre-transplant pre-exposure prevention*—CD4 count ≥200 who have not been vaccinated, have no history of varicella or herpes zoster, or who are seronegative for VZV *Post-exposure*—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 of vaccine series with 3 mo between 2 doses of varicella vaccine doses	*Pre-exposure prevention for pre-transplant candidates only*—Primary varicella vaccination (Varivax™®) 2 doses (0.5 mL SQ) administered 3 mo apart (weak, low) *Post-exposure therapy* Varicella-zoster immune globulin (VariZIG™®) 125 IU per 10 kg (maximum of 625 IU) IM, administered as soon as possible and within 10 d of exposure. In the US, VariZIG™® can be obtained only under a treatment investigational new drug application from the Food and Drug Administration (strong, low) Alternative Valacyclovir or acyclovir for 7 d beginning 7-10 d post exposure (weak, low) or intravenous immune globulin (IVIG)[84] (weak, low)	ProQuad™® (Measles, Mumps, Rubella, and Varicella Virus Vaccine Live) and live attenuated zoster vaccine (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 (weak, low)
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 (AII). May delay vaccination until CD4+ count>200.	One time administration of vaccine series unless patient is considered a non-responder	Hepatitis A vaccine 1 mL IM (Havrix™®, Vaqta™®) × 2 doses at 0 and 6-12 mo OR Combined HAV and HBV vaccine (Twinrix™) 1 mL IM as a 3-dose series (at 0, 1, and 6 mo) or as a 4-dose series (at days 0, 7, 21-30, and 12 mo) (AII)	IgG antibody response should be assessed 1 mo after final vaccination; non-responders should be revaccinated

(Continues)

TABLE 4 (Continued)

Vaccine	Population	Vaccination schedule	Recommended product	Additional concerns
Hepatitis B virus (HBV) infection	All HBV seronegative patients. (AII). Patients with with isolated anti-HBc: vaccinate (BII)	One time administration of vaccine series unless patient is considered a non-responder	Hepatitis B vaccine IM (Engerix-B™ 20 μg/mL or Recombivax HB™ 10 μg/mL) at 0, 1, and 6 mo (AII) or HBV vaccine IM (Engerix-B™ 40 μg/mL or Recombivax HB™ 20 μg/mL) at 0, 1, 2 and 6 mo. Some experts recommend vaccinating with 40 μg doses of either vaccine (Engerix-B™ or Recombivax) (strong, moderate) or Combined HAV and HBV vaccine (Twinrix™) 1 mL IM as a 3-dose series (at 0, 1, and 6 mo) or as a 4-dose series (at days 0, 7, 21-30, and 12 mo) (strong, moderate)	Hepatitis B surface antibody (HBs) should be obtained 1 mo after completion of vaccine series. If patient is a non-responder (anti-Hbs < 10 IU/mL), they should be revaccinated with a second series (weak, low). If the first series was given with low CD4 count consideration should be given to wait for a sustained increase in CD4 count and repeat the series For patients with isolated HBV core antibody positivity, administer 1 standard dose of HBV vaccine, check anti-HBs1-2 mo after, if >100 IU, no further vaccination needed. If titer is <100 IU, vaccinate with full series (weak, low)
Human Papillomavirus (HPV) infection	Males and females aged 9-45	One time administration of three vaccines over 6 mo	HPV recombinant vaccine 9 valent (Types 6.11.16, 18, 31, 33, 45, 52, 58) 0.5 mL IM at 0, 1-2, and 6 mo (weak, low)	Consideration can be given to providing an additional vaccination with recombinant 9-valent vaccine to those who have completed a vaccination series with the recombinant bivalent or quadrivalent vaccine, there is however no data to define who might benefit or how cost effective this approach might be (weak, low)
Meningococcus	All adults and adolescents	2 doses separated by at least 2 mo with single dose booster every 5 y	MEN ACWY for all recipients(strong, moderate); MEN B should also be given to those age 16-23	

[a]Whenever possible vaccines should be administered prior to transplantation.

7 | FUTURE RESEARCH

Patients with HIV are appropriate candidates for transplantation. Due to the significant drug interactions and increased risk of rejection, management of these patients can be complex. Development of novel highly potent antivirals for both HIV and HCV has resulted in single pill treatment options allowing for simplification and improved tolerability of treatment regimens. Emerging data in the non-transplant literature have suggested that two drug regimens may be safe for use in cART-naive patients without baseline resistance mutations and those with sustained viral suppression. It is unknown if use of two drug regimens can be safely used in the setting of concomitant immunosuppression. Introduction of novel DAAs into treatment algorithms for HIV/HCV co-infected transplant recipients has the potential to negate the

previously seen negative impact of HCV coinfection and use of HCV-positive donors on transplant outcomes. The optimal timing of HCV treatment in HIV-infected candidates and recipients is unknown, and it is also unknown if the use of new DAAs will expand the opportunity for use of HCV-positive organs to HCV negative HIV-infected transplant recipients. We await the results of this novel strategy in the non-HIV-infected population coupled with additional data on the impact of DAAs in the HIV-infected population.

Additional research focusing on strategies to decrease the incidence of post-transplant rejection is still needed. Center specific data providing granular detail on the impact of depleting antibodies on rejection and infection risk will be helpful to supplement the data gathered from registry studies. Center specific opportunistic infection data can provide guidance on the need for lifelong PJP prophylaxis as well as the need for supplemental OI prophylaxis when depleting antibodies are used. Published data thus far have been heavily focused on outcomes in adult kidney and liver transplant recipients; there remains a need for additional data on outcomes in heart, lung, pancreas, vascular composite allograft, and pediatric populations to determine whether differences exist. Finally, we await data from US and other international clinical trials using HIV-positive donors to determine whether this is a viable option to expand the donor pool. Ultimately given the challenging issues related to patient selection and post-transplant management, an integrated multidisciplinary approach involving diverse healthcare providers experienced in the care of these patients is recommended for optimal long-term outcomes.

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CONFLICT OF INTERESTS

Emily A. Blumberg, Research support: Shire and Merck (both unrelated research), Data Safety Monitoring Board: Bristol Myers Squibb, Glaxo Smith Kline (both unrelated), Scientific Advisory Committee: Merck (unrelated). Christin C Rogers, No conflicts.

REFERENCES

1. Smith CJ, Ryom L, Weber R, et al. Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration. *Lancet*. 2014;384:241-248.
2. Abraham AG, Althoff KN, Jing Y, et al. End-stage renal disease among HIV-infected adults in North America. *Clin Infect Disease*. 2015;60:941-949.
3. Cohen SD, Kopp JB, Kimmel PL. Kidney diseases associated with human immunodeficiency virus infection. *New Engl J Med*. 2018;377:2363-2374.
4. Locke JE, Reed RD, Mehta SG, et al. Center-level experience and kidney transplant outcomes in HIV-infected recipients. *Am J Transplant*. 2015;15:2096-2104.
5. Locke JE, Gustafson S, Mehta S, et al. Survival benefit of kidney transplantation in HIV- infected patients. *Ann Surg*. 2017;265:604-608.
6. Terrault NA, McCaughan GW, Curry MP, et al. International Liver Transplantation Society consensus statement on Hepatitis C management in liver transplant candidates. *Transplantation*. 2017;101:945-955.
7. Simonds RJ, Holmberg SD, Hurwitz RL, et al. Transmission of human immunodeficiency virus type 1 from a seronegative organ and tissue donor. *N Eng J Med*. 1992;326:726-732.
8. Ison MG, Llata E, Conover CS, et al. Transmission of human immunodeficiency virus and hepatitis C virus from an organ donor to four transplant recipients. *Am J Transplant*. 2011;11:1218-1225.
9. Villa E, Nanni CA. HIV-positive organs used for transplant in Italy due to human error. *Euro Surveill*. 2007;12(E070308):1.
10. CDC. HIV transmitted from a living organ donor–New York City, 2009. *MMWR Morb Mortal Wkly Rep*. 2011;60:297-301.
11. Cristelli M, Mazolin MA, Manzardo M, et al. Sexual acquisition of HIV-Infection after kidney transplantation: late presentation and potentially fatal complications. *Transplant Inf Dis*. 2018;20(4):e12894.
12. Sherman KE, Thomas DL, Chung RT. Human immunodeficiency virus and liver disease forum 2010: conference proceedings. *Hepatology*. 2011;54:2245-2253.
13. Schlabe S, Rockstroh JK. Advances in the treatment of HIV/HCV coinfection in adults. *Expert Opin Pharmacother*. 2018;19:49-64.
14. Agüero F, Castel Ma, Cocchi S, et al. An update on heart transplantation in Human Immunodeficiency Virus-infected patients. *Am J Transplant*. 2016;16:21-28.
15. Uriel N, Jorde UP, Cotarlan V, et al. Heart transplantation in human immunodeficiency virus-positive patients. *J Heart Lung Transplant*. 2009;28:667-669.
16. Castel MA, Perez-Villa F, Miro JM. Heart transplantation in HIV-infected patients: more cases in Europe. *J Heart Lung Transplant*. 2011;30:1418.
17. Kern RM, Seethamraju H, Blanc PD, et al. The feasibility of lung transplantation in HIV-seropositive patients. *Ann Am Thorac Soc*. 2014;11:882-889.
18. Morabito V, Grossi P, Lombardini L, et al. Solid organ transplantation in HIV+ recipients: Italian experience. *Transplant Proc*. 2016;48:424-430.
19. Grossi Pa, Righi E, Gasperina DD, et al. Report of four simultaneous pancreas-kidney transplants in HIV-positive recipients with favorable outcomes. *Am J Transplant*. 2012;12:1039-1045.
20. Miro Jm, Ricart Mj, Trullas Jc, et al. Simultaneous pancreas-kidney transplantation in HIV-infected patients: a case report and literature review. *Transplant Proc*. 2010;42:3887-3891.
21. Akhtar Mz, Patel N, Devaney A, et al. Simultaneous pancreas kidney transplantation in the HIV-positive patient. *Transpl Proc*. 2011;43:3903-3904.
22. Locke Je, Mehta S, Reed Rd, et al. A national study of outcomes among HIV-infected kidney transplant recipients. *J Am Soc Nephrol*. 2015;26:2222-2229.
23. Locke JE, Durand C, Reed RD, et al. Long term outcomes after liver transplantation among Human Immunodeficiency Virus infected recipients. *Transplantation*. 2016;100:141-146.
24. Stock PG, Barin B, Murphy B, et al. Outcomes of kidney transplantation in HIV-infected recipients. *N Engl J Med*. 2010;363:2004-2014.
25. Roland ME, Barin B, Huprikar S, et al. Survival in HIV-positive transplant recipients compared with transplant candidates and HIV-negative controls. *AIDS*. 2016;20:435-444.
26. Mazuecos A, Fernandez A, Andres A, et al. HIV infection and renal transplantation. *Nephrol Dial Transplant*. 2011;26:1401-1407.

27. Sawinski D, Forde KA, Eddinger K, et al. Superior outcomes in HIV-positive kidney transplant patients compared to HCV-infected or HIV/HCV-coinfected recipients. *Kidney Int*. 2015;88:341-349.
28. Sawinski D, Goldberg DS, Blumberg E, Abt PL, Bloom RD, Forde KA. Beyond the NIH multicenter HIV transplant trial experience: outcomes of HIV+ liver transplant recipients compared to HCV+ or HIV+/HCV+ coinfected recipients in the United States. *Clin Infect Dis*. 2015;61:1054-1621.
29. Coffin CS, Stock PG, Dove LM, et al. Virologic and clinical outcomes of hepatitis B virus infection in HIV-HBV coinfected transplant recipients. *Am J Transplant*. 2010;10:1268-1275.
30. Terrault NA, Roland ME, Schiano T, et al. Outcomes of liver transplant recipients with hepatitis C and human immunodeficiency virus coinfection. *Liver Transplant*. 2012;18:716-726.
31. Husson J, Stafford K, Bromberg J, et al. Association between duration of Human Immunodeficiency Virus (HIV)–1 viral suppression prior to renal transplantation and acute cellular rejection. *Am J Transplant*. 2017;17:551-556.
32. Ragni MV, Eghtesad B, Schlesinger KW, Dvorchik I, Fung JJ. Pretransplant survival is shorter in HIV-positive than HIV-negative subjects with end-stage liver disease. *Liver Transplant*. 2005;11:1425-1430.
33. Subramanian A, Sulkowski M, Barin B, et al. MELD score is an important predictor of pretransplantation mortality in HIV-infected liver transplant candidates. *Gastroenterology*. 2010;138:159-164.
34. Ragni MV, De Vera ME, Roland ME, et al. Liver transplant outcomes in HIV(+) haemophilic men. *Hemophilia*. 2013;19:134-140.
35. Locke JE, Montgomery RA, Warren DS, Subramanian A, Segev DL. Renal transplant in HIV-positive patients. Long-term outcomes and risk factors for graft loss. *Arch Surg*. 2009;144:83-86.
36. Locke JE, James NT, Mannon RB, et al. Immunosuppression regimen and the risk of acute rejection in HIV-infected kidney transplant recipients. *Transplantation*. 2014;97:446-450.
37. Roland ME, Barin B, Huprikar S, et al. Survival in HIV-positive transplant recipients compared with transplant candidates and HIV-negative controls. *AIDS*. 2016;30:435-444.
38. Miro Jm, Montejo M, Castells L, et al. Outcome of HCV/HIV coinfected liver transplant recipients: a prospective and multicenter cohort study. *Am J Transplant*. 2012;12:1866-1876.
39. Cooper C, Kanters S, Klein M, et al. Liver transplant outcomes in HIV infected patients: a systematic review and meta analysis with synthetic cohort. *AIDS*. 2011;25:777-786.
40. Lai JC, Feng S, Terrault NA, Lizaola B, Hayssen H, Covinsky K. Frailty predicts waitlist mortality in liver transplant candidates. *Am J Transplant*. 2014;14:1870-1879.
41. Guaraldi G, Dolci G, Zona S, et al. A frailty index predicts post-liver transplant morbidity and mortality in HIV-positive patients. *AIDS Res Ther*. 2017;14:37.
42. Degnan KO, Blumberg EA. Human Immunodeficiency Virus in kidney transplantation. *Semin Nephrol*. 2016;36:405-416.
43. Moreno A, Cervera C, Fortún J, et al. Epidemiology and outcome of infections in human immunodeficiency virus/hepatitis C virus-coinfected liver transplant recipients: a FIPSE/GESIDA prospective cohort study. *Liver Transpl*. 2012;18:70-81.
44. Miro JM, Agüero F, Duclos-Valle J-C, et al. Infections in solid organ transplant HIV-infected patients. *Clin Microbiol Infect*. 2014;20(Suppl. 7):119-130.
45. Suarez JF, Rosa R, Lorio MA, et al. Pre-transplant CD4 count influences immune reconstitution and risk of infectious complications in HIV+ kidney allograft recipients. *Am J Transplant*. 2016;16:2463-2472.
46. Gasser O, Bihl F, Sanghavi S, et al. Treatment-dependent loss of polyfunctional CD8+ T-cell responses in HIV-infected kidney transplant recipients is associated with herpesvirus reactivation. *Am J Transplant*. 2009;9:794-803.
47. Carter JT, Melcher ML, Carlson LL, Roland ME, Stock PG. Thymoglobulin-associated Cd4+ T-cell depletion and infection risk in HIV-infected renal transplant recipients. *Am J Transplant*. 2006;6:753-760.
48. Nissen NN, Barin B, Stock PG. Malignancy in the HIV-infected patients undergoing liver and kidney transplantation. *Curr Opin Oncol*. 2012;24:517-521.
49. Vibert E, Duclos-Vallée J-C, Ghigna M-R, et al. Liver transplantation for hepatocellular carcinoma: the impact of human immunodeficiency virus infection. *Hepatology*. 2011;53:475-482.
50. Agüero F, Forner A, Manzardo C, et al. Human immunodeficiency virus infection does not worsen prognosis of liver transplantation for hepatocellular cancer. *Hepatology*. 2016;63:488-498.
51. Cherian PT, Alrabih W, Douiri A, et al. Liver transplantation in human immunodeficiency virus-infected patients: procoagulant, but is antithrombotic prophylaxis required? *Liver Transplant*. 2012;18:82-88.
52. Bloom RD, Bromberg JS, Poggio E, et al. Cell-free DNA and active rejection in kidney allografts. *J Am Soc Nephrol*. 2017;28:2221-2232.
53. Derache A, Shin HS, Balamane M, et al. HIV drug resistance mutation in proviral DNA from a community treatment program. *PLoS ONE*. 2015;10:e0117430.
54. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Department of Health and Human Services. http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed July 28, 2018.
55. Esposito L, Kamar N, Tkaczuk J, Abbal M, Durand D, Rostaing L. Long-term evolution of lymphocytes subsets after induction therapy based on continuous versus discontinuous administration of anti-thymocyte globulins in renal-transplant patients. *Transpl Proc*. 2005;37:785-787.
56. Gathogo E, Harber M, Bhagani S, et al. Impact of tacrolimus compared with cyclosporin on the incidence of acute allograft rejection in human immunodeficiency virus-positive kidney transplant recipients. *Transplantation*. 2016;100:871-878.
57. Margolis DM, Kewn S, Coull JJ, et al. The addition of mycophenolate mofetil to antiretroviral therapy including abacavir is associated with depletion of intracellular deoxyguanosine triphosphate and a decrease in plasma HIV-1 RNA. *J Acquir Immune Defic Syndr*. 2002;31:45-49.
58. Donia M, McCubrey JA, Bendtzen K, Nicoletti F. Potential use of rapamycin in HIV infection. *Br J Clin Pharmacol*. 2010;70:784-793.
59. Rai P, Plagov A, Kumar D, et al. Rapamycin-induce modulation of HIV gene transcription attenuates progression of HIVAN. *Exp Mol Pathol*. 2013;94:255-261.
60. Stock Pg, Barin B, Hatano H, et al. Reduction of HIV persistence following transplantation in HIV infected kidney transplant recipients. *Am J Transplant*. 2014;14:1136-1141.
61. Ebcioglu Z, Liu C, Shapiro R, et al. Belatacept conversion in an HIV-positive kidney transplant recipient with prolonged delayed graft function. *Am J Transplant*. 2016;16:3278-3281.
62. Vincenti F, Charpentier B, Vanrenterghem Y, et al. A phase III study of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT study). *Am J Transplant*. 2010;10:535-546.
63. Muthukumar T, Afaneh C, Ding R, et al. HIV-infected kidney graft recipients managed with an early corticosteroid withdrawal protocol: clinical outcomes and messenger RNA profiles. *Transplantation*. 2013;95:711-720.
64. Bossini N, Sandrini S, Casari S, et al. Kidney transplantation in HIV-positive patients treated with a steroid-free immunosuppressive regimen. *Transplant Int*. 2014;27:1050-1059.
65. Frassetto La, Browne M, Cheng A, et al. Immunosuppressant pharmacokinetics and dosing modifications in HIV-1 infected liver and kidney transplant recipients. *Am J Transplant*. 2007;7:2816-2820.

66. Patel SJ, Kuten SA, Musick ML, Gaber AO, Monsour HP, Knight RJ. Combination drug products for HIV-a word of caution for the transplant clinician. *Am J Transplant*. 2016;16:2479-2482.
67. Han Z, Kane BM, Petty LA, Josephson MA, Sutor J, Pursell KJ. Cobicistat significantly increases tacrolimus serum concentrations in a renal transplant recipient with Human Immunodeficiency Virus infection. *Pharmacotherapy*. 2016;36(6):e50-e53.
68. Barau C, Blouin P, Creput C, Taburet AM, Durrbach A, Furlan V. Effect of coadministered HIV-protease inhibitors on tacrolimus and sirolimus blood concentrations in a kidney transplant recipient. *Fundam Clin Pharmacol*. 2009;23:423-425.
69. van Maarseveen EM, Crommelin HA, Mudrikova T, van den Broek M, van Zuilen AD. Pretransplantaiton pharmacokinetic curves of tacrolimus in HIV-infected patients on ritonavir-containing cART: a pilot study. *Transplantation*. 2013;95:397-402.
70. Vogel M, Voigt E, Michaelis H-C, et al. Management of drug-to-drug interactions between cyclosporine A and the protease-inhibitor lopinavir/ritonavir in liver-transplanted HIV-infected patients. *Liver Transplant*. 2004;10:939-944.
71. Sawinski D, Shelton B, Mehta S, et al. Impact of protease inhibitor-based anti-retroviral therapy on outcomes for HIV kidney transplant recipients. *Am J Transpl*. 2017;17(12):3114-3122.
72. Tricot L, Teicher E, Peytavin G, et al. Safety and efficacy of raltegravir in HIV-infected transplant patients cotreated with immunosuppressive drugs. *Am J Transplant*. 2009;9:1946-1952.
73. Andreev E, Koopman M, Arisz L. A rise in plasma creatinine that is not a sign of renal failure: which drugs can be responsible? *J Intern Med*. 1999;246:247-252.
74. Lee DH, Malat GE, Bias TE, Harhay MN, Ranqanna K, Doyle AM. Serum creatinine elevation after switch to dolutegravir in a human immunodeficiency virus-positive kidney transplant recipient. *Transpl Infect Dis*. 2016;18:625-627.
75. Terrault NA, Carter JT, Carlson L, Roland ME, Stock PG. Outcome of patients with hepatitis B virus and human immunodeficiency virus infections referred for liver transplantation. *Liver Transplant*. 2006;12:801-807.
76. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of health, and the HIV Medicine Association of the Infectious Diseases Society of America. http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Accessed July 30, 2018.
77. Kim DK, Riley LE, Hunter P. Advisory Committee on immunization practices recommended immunization schedule for adults aged 19 years or older – United States, 2018. *MMWR Morb Mortal Wkly Rep*. 2018;67:158-160.
78. Schillie S, Harris A, Link-Gelles R, Romero J, Ward J, Nelson N. Recommendations of the Advisory Committee on immunization practices for use of a hepatitis b vaccine with a novel adjuvant. *MMWR Morb Mortal Wkly Rep*. 2018;67(15):455-458.
79. Muller E, Barday Z, Mendelson M, Kahn D. HIV-positive-to-HIV-positive kidney transplantation – results at 3–5 years. *N Engl J Med*. 2015;372:613-620.
80. Health Resources and Services Administration (HRSA); Department of Health and Human Services (HHS). Organ procurement and transplantation: implementation of the HIV Organ Policy Equity Act. Final rule. *Fed Regist*. 2015;80(89):26464-26467.
81. Health Resources and Services Administration; Department of Health and Human Services. Final Human Immunodeficiency Virus Organ Policy Equity (HOPE) Act safeguards and research criteria for transplantation of organs infected with HIV. *Fed Reg*. 2015;80:34912-34921.
82. Durand CM, Halpern SE, Bowring MG, et al. Organs from deceased donors with false-positive HIV screening tests: an unexpected benefit of the HOPE act. *Am J Transplant*. 2018;18:27.
83. Durand CM, Segev D, Sugarman J. Realizing HOPE: the ethics of organ transplantation from HIV infected donors. *Ann Intern Med*. 2016;165(2):138-142.
84. Center for Disease Control and Prevention. *CDC Yellow Book 2018: Health Information for International Travel*. New York, NY: Oxford University Press; 2017.

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