

# Kidney Transplantation in Patients with HIV

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## Abstract

**Individuals with HIV are at increased risk for ESKD. Kidney transplantation is the best treatment for ESKD in the HIV+ population. Despite reduced access to transplantation, patients who are HIV+ have excellent outcomes and clearly benefit from receiving one. Common post-transplant complications and management concerns, including the optimal antiretroviral regimen, immunosuppression protocols, infectious prophylaxis, hepatitis C coinfection, metabolic complications, and malignancy are all discussed.**

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## HIV and ESKD

Despite advances in HIV care, HIV infection remains associated with an increased risk of ESKD, especially among black individuals. The North American AIDS Cohort Collaboration on Research and Design (1) demonstrated that the standardized incidence ratio for ESKD among black patients was 4.5 (95% CI, 3.9 to 5.2) and 1.5 (95% CI, 1.0 to 2.2) for white patients. Historically, survival on dialysis for individuals with HIV was poor, but has improved with antiretroviral therapy (ART). In analysis of United States Renal Data Systems data spanning 1985–1999, Ahuja *et al.* (2) demonstrated steady improvement in 1-year dialysis survival for patients with HIV, from 56% in 1990 to 74% in 1999; however, overall outcomes were inferior to a matched HIV– cohort. More recently, a contemporary analysis (3) of patients with HIV+ on dialysis (2004–2013) examined the effect of race and hepatitis C virus (HCV) coinfection on dialysis survival. In multivariable models, HIV mono-infection was not associated with an increased risk of mortality among white patients (adjusted hazard ratio [aHR], 1.03; 95% CI, 0.91 to 1.16), but HIV/HCV coinfection was (aHR, 1.48; 95% CI, 1.18 to 1.87); likewise, both HIV infection (aHR, 1.44; 95% CI, 1.37 to 1.52) and HIV/HCV coinfection (aHR, 1.71; 95% CI, 1.60 to 1.84) were associated with an increased risk of death among nonwhite patients. Thus ESKD is a frequent complication of HIV infection, disproportionately affecting black patients, and is associated with persistent racial differences in survival. Before the direct-acting antiviral (DAA) era, patients coinfecting with HCV had diminished dialysis survival and the effect of treating HCV on dialysis survival remains an open question.

## Summary

- ESKD is a common complication of HIV infection.
- Black patients are disproportionately affected.
- Survival on dialysis has improved with ART but racial disparities persist.

## Access to Kidney Transplantation

Kidney transplantation is the ideal form of RRT, yet individuals with HIV face clear barriers to accessing kidney transplantation. A single-center study (4) from New York City demonstrated that from 2000 to 2007 only 20% of the patients with HIV who were evaluated for transplant were listed, whereas 73% of patients who were HIV– achieved listing during the same time period. Black race, a history of substance abuse, and uncontrolled HIV infection (CD4 count <200 cells/m<sup>3</sup> or detectable viral load [VL]) were independently associated with failure to achieve wait-listing. A similar study (5) from Philadelphia largely confirmed these findings: although wait-listing rates had improved, the evaluation process was longer for candidates who were HIV+ and they spent more time inactive on the list. In their cohort of patients evaluated in 2011–2015, incomplete workup, substance abuse, and uncontrolled HIV infection remained the top three reasons patients were not listed. The authors identified integrated HIV care as a contributor to their improved wait-listing rates and clearly comprehensive care benefits complex patients such as those with HIV infection.

## Patient Selection

Patient selection criteria (6) for candidates with HIV mirror those established for patients who are HIV–: they must meet all of a center's general medical and psychosocial criteria in addition to HIV-specific metrics. Patients must have an undetectable VL, a CD4 count >200, and—with the exception of elite controllers—be on a stable ART regimen. They cannot have active opportunistic infections. All candidates who are HIV+ should be evaluated by a transplant infectious disease specialist to review HIV and ART history, vaccinations, and tuberculosis risk factors. Due to shared modes of transmission, many individuals with HIV are coinfecting with HCV or hepatitis B virus (HBV); coinfecting kidney transplant candidates also require an evaluation by hepatology and assessment of degree of liver fibrosis, often *via* transient elastography

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or biopsy as indicated. The more lengthy and complex evaluation process can create additional barriers to wait-listing for transplant candidates with HIV. Thus, preemp-tive referral for patients with HIV who have CKD stage 4 is essential. Transplant centers should be sensitive to the complexities of navigating the evaluation process for individuals who are HIV+ and centralized care that involves coordination with subspecialists whenever possible helps overcome barriers for these patients.

### Summary

- Individuals with HIV face significant barriers in accessing the kidney transplant waiting list.
- Integrated multispecialty care can facilitate wait-list access.
- Individuals with HIV must demonstrate adequate HIV control in addition to meeting general medical listing criteria.

### Wait-List Outcomes

Because of data collection practices by the Organ Procurement and Transplantation Network (OPTN), where HIV and HCV serostatus information is not recorded as part of the transplant candidate registration form, it has been difficult to ascertain the number of individuals with HIV who are wait-listed for transplantation. To overcome this limitation, Locke *et al.* (7) linked detailed pharmacy fill data to transplant registry data, identifying 1636 candidates with HIV wait-listed for a kidney from 2001 to 2012. Like the HIV+ dialysis population, they were predominantly young, male, and black. Although wait-list mortality was similar to candidates who were HIV-, candidates with HIV were significantly less likely to receive a living donor kidney transplant (aHR, 0.53; 95% CI, 0.44 to 0.64) or a transplant at all (aHR, 0.72; 95% CI, 0.64 to 0.82). Data from Europe confirms this trend: in a report of 255 HIV+ dialysis patients from the Renal Epidemiology and Information Network registry (8), candidates with HIV were 32% less likely to be wait-listed and 25% less likely to be transplanted. Challenges remain even among those who are able to be wait-listed: candidates with HIV are 12% less likely (aHR, 0.88; 95% CI, 0.79 to 0.99) to receive a first position organ offer (9). Clearly, multiple barriers in access to transplantation for individuals with HIV exist and registry on the wait-list does not guarantee transplantation.

### Kidney Transplant Outcomes

Kidney transplantation is the best method of RRT, and has been associated with a survival benefit over remaining on dialysis. The benefit associated with transplantation has been demonstrated in many high-risk patient populations and holds true for candidates with HIV as well. Using Scientific Registry of Transplant Recipient (SRTR) data linked to pharmacy fill records, Locke *et al.* (10) showed that patients with HIV achieved a survival benefit with transplantation after 194 days; for those coinfecting with HCV, the time to equivalent survival was a little longer at 392 days. This study underscores the importance of

referring all patients who are HIV+ with advanced CKD or ESKD for transplant evaluation.

Contemporary outcomes are excellent for patients with HIV who are transplanted on ART. An analysis of OPTN data (11) that encompassed HIV+ and HIV/HCV+ first kidney recipients transplanted from 1996 to 2013 demonstrated excellent patient (aHR, 0.90; 95% CI, 0.66 to 1.24) and allograft survival (aHR, 0.60; 95% CI, 0.40 to 0.88) among those monoinfected with HIV, whereas outcomes were notably inferior among those coinfecting with HCV (mortality aHR, 2.26; 95% CI, 1.45 to 3.52; graft loss aHR, 2.59; 95% CI, 1.60 to 4.19). Similar findings were reported in analyses employing SRTR data (12) or matched sampling strategies (13).

### Summary

- Individuals with HIV are less likely to be transplanted than individuals who are HIV-.
- Kidney transplantation confers a significant survival benefit in patients with HIV.
- Patient and allograft outcomes are excellent among recipients who are HIV monoinfected.

### Unique Transplant Opportunities: HIV+ to HIV+ Kidney Transplantation

The most extensive experience in the use of HIV+ kidney donors comes from South Africa. To date they have transplanted 51 recipients of HIV+ donor kidneys (14); outcomes have been comparable to those observed in HIV+ recipients of HIV- donor organs, with 1-year patient survival of 87% and 1-year death-censored allograft survival of 96%. Of note, the South African experience is somewhat unique: the vast majority of donors with HIV are young trauma victims and most are either not on ART or only first-line therapy. One concern with the use of HIV+ donor organs is the transmission of other HIV strains to the recipient, including potentially ART-resistant ones. They performed viral deep sequencing on 25 patients and could only detect donor-derived virus in one recipient, which was transient. There have been no virologic failures reported in the South African cohort.

In response to the profound organ shortage in the United States, there has been interest in exploring the use of donors who are HIV+ in the United States; this was previously illegal due to provisions in the National Organ Transplantation Act but overturned by passage of the HIV Organ Policy Equity (HOPE) Act in 2013, which permits research in the area of HIV+ to HIV+ transplantation. The true number of potential donors who are HIV+ is unknown. Estimates from Boyarsky *et al.* (15)—generated using data from the Nationwide Inpatient Sample, HIV Research Network, and the OPTN—were as high as 500 potential donors with HIV per year. A study (16) that explored the possibilities among individuals with HIV “in care” in Philadelphia generated a much more modest estimate of 13 potential donors over a 5-year period; the authors noted that most had comorbidities such as diabetes, hypertension, or HCV coinfection that would result in them being labeled as high kidney donor profile index organs and therefore less likely to be used for transplantation. The truth may actually be somewhere in

between: in the nearly 2 years since the inception of a multicenter trial of HIV+ to HIV+ transplantation, there were 27 HIV+ donors utilized (17). Although HIV+ donor utilization may have failed to achieve initial projections, research in this area has helped to reduce the stigma around HIV in transplantation and increase public awareness of transplantation as a treatment option for individuals living with HIV and end-organ failure.

Limited outcome data (18) suggest that short-term outcomes for recipients of HIV+ organs are similar to those observed in recipients of HIV– organs, but acute rejection rates are very high (43%), especially among those who did not receive antibody-depleting induction. Loss of HIV viral control was only observed in one study participant and was attributed to nonadherence. These data are encouraging, but longer-term follow-up is clearly needed.

The HOPE Act also contains provisions allowing for living donors who are HIV+. In light of the association between HIV infection and CKD/ESKD, there has been significant concern in the transplant community regarding the suitability of individuals with HIV to serve as living kidney donors. Although one study (19) suggested that the risk of ESKD among potential living donors with HIV was low, there were many limitations to this work, which did not include any actual donors who were HIV+, had short follow-up, missing data, and included individuals in the cohort who would not meet most transplant center standards for donation. To date, only two individuals in the United States have served as an HIV+ living kidney donor and the true risks associated with the practice remain largely unknown.

## Summary

- Transplantation with HIV+ donor kidneys is possible but remains limited to the research setting in the United States.

- Available data do not suggest clinically significant transmission of donor virus.
- The true number of HIV+ organ donors in the United States is unknown.

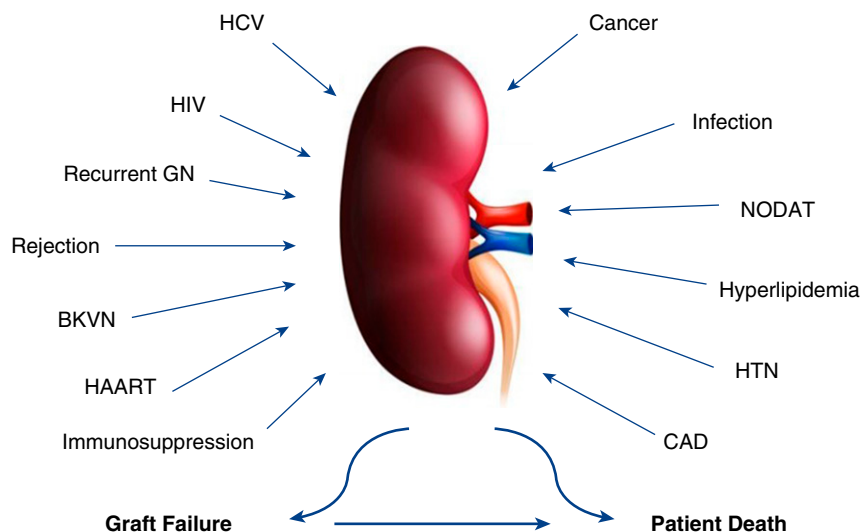
## Post-transplant Management

Kidney transplant recipients who are HIV+ face many of the same long-term challenges to transplant success as their HIV– counterparts (Figure 1). Post-transplant monitoring and risk factor modification is in many ways the same.

## Virologic Monitoring and Control

In addition to routine post-transplant laboratory testing, recipients who are HIV+ should have their CD4 count and HIV VL checked at 1 month post-transplant and every 2–3 months thereafter (20). Individuals with a CD4 count <200 cells/m<sup>3</sup> will require reinstitution of opportunistic infection prophylaxis; those with detectable VL will require adherence assessment and potentially viral resistance testing. This testing and any changes in ART regimen should be coordinated with the patient's infectious disease provider.

Available data clearly suggest that integrase inhibitor-based ART, rather than protease inhibitor (PI)- or non-nucleoside reverse transcriptase inhibitor-based regimens, is preferred for kidney transplant recipients who are HIV+. Protease inhibitors are among the most profound inhibitors of the CYP3A4 metabolic pathway for calcineurin inhibitors (CNIs); concomitant use of PIs and CNIs requires significant CNI dose reductions (21), often irregular dosing schedules, and provides a lower area under the curve of CNI exposure at similar trough levels (22). Together, these can contribute to the increased rates of acute rejection observed in recipients with HIV. Additionally, use of PI-based regimens has been associated with an increased risk of patient mortality (aHR, 1.91; 95% CI, 1.02 to 3.59) and diminished allograft



**Figure 1.** | The long-term threats to patient and allograft survival are similar between HIV+ and HIV– recipients. The challenges faced by kidney transplant recipients who are HIV+ are largely shared by the transplant population who are HIV–. BKVN, BK virus nephropathy; CAD, coronary artery disease; HAART, highly active antiretroviral therapy; HCV, hepatitis C virus; HTN, hypertension; NODAT, new-onset diabetes after transplantation.

survival (aHR, 1.84; 95% CI, 1.22 to 2.77) (23). Non-nucleoside reverse transcriptase inhibitors have a more variable effect on CYP3A4 enzymes. When selecting an integrase inhibitor, it bears noting that dolutegravir inhibits tubular secretion of creatinine, which can falsely elevate serum creatinine levels, and elvitegravir requires cobicistat boosting, which also induces CYP3A4. Therefore, many transplant recipients are on a raltegravir-based regimen.

Patients who are coinfecting with HBV require two drugs with anti-HBV activity. For many, this means a tenofovir-containing regimen. Although tenofovir can be nephrotoxic, one small study (24) did not find a difference in post-transplant graft survival on the basis of tenofovir use; however, the rate of graft loss at 3 years was high in both cohorts. More recently, a less nephrotoxic version of tenofovir, tenofovir alafenamide, became available and this is the preferred agent for use in this population.

### Addressing HCV Coinfection

In the general transplant population, treatment of HCV infection has been associated with improved patient and allograft survival (25). One small study from Miami (26) suggests that the same is true among transplant recipients coinfecting with HIV/HCV. In a cohort of 13 patients with HIV/HCV who were transplanted from 2007 to 2017, patient (100% versus 83%) and allograft (100% versus 67%) survival were significantly better in those treated with DAAs and cured of their HCV infection. Post-transplant treatment—although rendered complex by consideration of drug-drug interactions between immunosuppression, ART, and DAAs—is essential. Data suggest (27) that for many patients, especially those with less severe fibrosis (Metavir stage F0–F1), transplantation with an HCV+ donor followed by post-transplant treatment is more cost-effective than pretransplant treatment; however, for individuals with advanced liver disease, who are at risk of decompensation, or who are listed at centers that do not use HCV+ organs, pretransplant treatment may be preferred.

### Immune Control and Immunosuppression

The HIV-TR Multisite trial (6) clearly demonstrated that, despite relative immunodeficiency, HIV+ kidney transplant recipients are at increased risk of acute rejection; in that study, the 1-year cumulative risk of acute rejection was 30%, compared with 10%–15% nationally among patients who were HIV–. There are aspects of this risk that are modifiable by clinical circumstances. Duration of viral control contributes: patients with undetectable VL for <2 years pretransplant were 2.2-fold more likely to have rejection than those with longer periods of viral control (28). Immunosuppression choices are also relevant. Induction with rabbit anti-thymocyte globulin (rATG) has been associated with a 61% reduction in acute rejection (adjusted risk ratio, 0.39; 95% CI, 0.18 to 0.87) (29) and induction improves death-censored graft loss (30). Use of tacrolimus-based maintenance immunosuppression reduces the risk of rejection, compared with cyclosporine-based regimens (31). Rapamycin, despite reducing the latent proviral reservoir (32), is associated with a more than twofold risk of rejection (29) and is generally to be avoided; likewise “steroid-free” immunosuppression

protocols are associated with unacceptably high rates of rejection (33). Thus, for many patients, rATG induction is preferred, along with tacrolimus-based, triple immunosuppression that includes steroids.

Interestingly, despite the increased risk of acute rejection observed in the HIV+ transplant population, current data do not suggest an increased frequency of *de novo* donor-specific antibodies (34). Some centers perform protocol biopsies in this patient cohort, however, this is not universal practice.

### Summary

- Integrase inhibitor-based regimens are preferred in transplant recipients who are HIV+.
- Individuals coinfecting with HCV benefit from DAA therapy to cure their HCV infection.
- rATG induction and tacrolimus-based triple immunosuppression are associated with reduced rates of acute rejection.

### Infections

Infection is a frequent post-transplant complication among recipients who are HIV+. In the HIV-TR Multisite trial (6), 38% of recipients had an infection necessitating hospitalization and more infections overall were observed in the group induced with rATG as well as in patients coinfecting with HCV. Of these infections, the vast majority were bacterial (69%), with genitourinary (26%), respiratory (20%), and bloodstream (19%) sources being the most common. Importantly, opportunistic infections were rare.

Excess infectious risk has been one of the concerns regarding the use of rATG induction in recipients who are HIV+. Patients with HIV induced with rATG have a more profound and longer-lasting reduction in their CD4 count than those induced with anti-IL2 receptor antibodies (6); however, this CD4 depletion mirrors what is observed in patients who are HIV– who receive rATG (35). There are some data to suggest that individuals with starting CD4 counts <350 cells/mm<sup>3</sup> are more greatly affected than those with higher CD4 counts at time of induction (36). Registry data (30) suggest that, on a national level, use of depleting induction is not associated with an increased risk of common post-transplant infections but does lead to lower delayed graft function rates, shorter hospital stays, and reduced death-censored graft loss.

Similar to recipients who are HIV–, kidney transplant patients with HIV require prophylaxis for common post-transplant infections, including *Pneumocystis jirovecii* pneumonia (PJP) and cytomegalovirus. Consensus guidelines (20) suggest at least 1 year of PJP prophylaxis, with some centers administering it life-long; trimethoprim-sulfamethoxazole is the preferred agent and also provides coverage for toxoplasma. Cytomegalovirus prophylaxis approaches vary, with some centers employing the same approach as in patients who are HIV–, whereas others use high-dose valganciclovir (900 mg daily, dosed for renal function) for 3–6 months, depending on donor and recipient serostatus. Recipients require coverage for histoplasma and coccidioidomycosis if they live in endemic areas. All recipients should be screened for latent tuberculosis as part of

their transplant evaluation and those with known exposure require isoniazid treatment if not completed pretransplant.

BK virus is a frequent complication of kidney transplantation in general and thought to, in part, reflect a patient's overall state of immunosuppression. Interestingly, although kidney transplant patients with HIV can be viewed as more immunocompromised than patients who are HIV<sup>-</sup>, no increase in BK viremia has been observed in this population (34). Post-transplant screening for BK in recipients with HIV should follow general guidelines for kidney transplant recipient screening (37).

### Summary

- Post-transplant infections are common, especially among individuals coinfecting with HIV/HCV.
- Opportunistic infection prophylaxis strategies are similar to that used in individuals who are HIV<sup>-</sup>, but PJP prophylaxis is often extended.

### Metabolic Complications

Cardiovascular disease is an important contributor to post-transplant mortality and HIV infection should be considered a coronary artery disease risk equivalent (38). Attention should be paid to hypertension as a modifiable risk factor and it is reasonable to extrapolate general targets for BP control to this population (39). Dihydropyridine calcium channel blockers are preferred in transplant recipients due to a lack of drug-drug interactions with CNIs; they are also a reasonable first choice for patients with HIV. Post-transplant diabetes is another target for intervention. Individuals with HIV are at increased risk for diabetes and there are multiple mechanisms by which HIV infection and its treatment contributes to this risk (40); a fasting plasma glucose >125 mg/dl or oral glucose tolerance test can make the diagnosis. When initiating treatment, it is important to consider drug-drug interactions between ART and diabetes medications: dolutegravir increases metformin levels; PIs increase dipeptidyl peptidase-4, glitazone, and meglitinide levels, and patients on treatment require close monitoring. Dyslipidemia is common in both the transplant and HIV+ populations. Although a randomized trial (41) failed to show a benefit of statins in the transplant population, meta-analytic data (42) suggest there is a trend toward benefit and most transplant physicians recommend their use. Among people living with HIV, statins are clearly beneficial and one meta-analysis (43) found a 33% reduction in all-cause mortality associated with their use. Drug interactions are a consideration with statins and ART: lovastatin and simvastatin are contraindicated for use with PIs or integrase inhibitors, and all patients with HIV who are on a statin should be closely monitored for side effects.

### Malignancy

Both transplant recipients and individuals with HIV are at increased risk of cancer. Among transplant recipients, virally mediated cancers such as Kaposi sarcoma, liver, and anogenital cancers, are all significantly increased and many "common" cancers such as lung, kidney, colon, skin, and pancreas are also more prevalent (44). Among people living

with HIV, AIDS-defining malignancies are on the decline but a compensatory rise has been noted in other malignancies (45); smoking is a major contributor to malignancy risk, dwarfing other factors such as HIV viral control or hepatitis (46). A meta-analytic comparison (47) of published reports of cancers in both the transplant and HIV+ populations noted that infection-related cancers were increased in both cohorts, whereas epithelial cancers—such as breast, ovarian, and prostate cancers—were not. Lung cancer was increased in both transplant recipients and individuals with HIV. There are no cancer screening guidelines that specifically address HIV+ transplant recipients, but in light of the available data it seems reasonable to suggest regular screening for human papilloma virus-related malignancies (anal and cervical cancers) as well as lung cancer screening among those with significant cigarette exposure. Additionally, any individuals who are currently smoking should be strongly encouraged to quit.

### Bone and Mineral Disease

Bone disease after kidney transplantation is complex; it can encompass low turnover states as well as osteopenia/osteoporosis; use of steroids, CNIs, and hyperparathyroidism all contribute to risk (48). Transplant recipients at increased fracture risk benefit from dual energy x-ray absorptiometry screening, and pharmacotherapy should be considered after contributing factors (such as hypovitaminosis D and hypophosphatemia) have been corrected. Individuals with HIV are at increased risk for osteoporosis and fracture; it has been estimated that almost 30% have osteoporosis and as many as 50% have osteopenia (49). HIV infection contributes to bone loss in several ways. The inflammatory state increases osteoclast activity and promotes osteoblast apoptosis, whereas elevated TNF $\alpha$  levels increase bone resorption by osteoclasts (50). Initiation of tenofovir-containing regimens has been associated with a loss of bone mineral density of 2%–6% (50). Dual energy x-ray absorptiometry should be considered in all individuals with HIV who are over age 50 and pharmacotherapy should be considered for those with T-scores <2.5, a history of fracture, or low bone mass with increased fracture risk; bisphosphonates are considered first-line therapy in this population. All patients benefit from weight-bearing exercise and smoking cessation; consideration should be given to switching ART to regimens that do not contain tenofovir if possible.

### Summary

- Transplant recipients with HIV should be screened for new-onset diabetes after transplant.
- Statin therapy should be considered in all kidney transplant recipients who are HIV+.
- Smoking cessation is important to reduce both post-transplant malignancy and post-transplant bone loss in this patient population.

### Summary

ESKD remains a common complication of HIV infection and people living with HIV clearly benefit from kidney transplantation. Perceived medical complexity should not

be a barrier and comprehensive, multidisciplinary care can help patients achieve transplantation. Post-transplant outcomes are generally similar to those observed in individuals who are HIV<sup>-</sup>. HIV<sup>+</sup> donor organs remain limited to the research domain. For most patients, rATG induction with tacrolimus-based maintenance immunosuppression provides the best protection from rejection. Individuals who are coinfecting benefit from prompt post-transplant treatment of HCV. Post-transplant care is largely similar to that of recipients who are HIV<sup>-</sup>, and includes infectious prophylaxis, laboratory monitoring, and cardiovascular disease risk modification. Aggressive screening for post-transplant malignancy is reasonable, although guidelines specific for this population do not exist.

#### Author Contributions

D. Sawinski wrote the original draft and reviewed and edited the manuscript.

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