Kidney Transplantation in HIV-Infected Recipients: Encouraging Outcomes, but Registry Data Are No Longer Enough

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Highly active antiretroviral therapy (ARV) transformed HIV from a rapidly fatal infection into a chronic disease. With improved overall survival, morbidity and mortality from other chronic medical conditions, such as ESRD, are now an important concern in this patient population. ESRD occurs in patients with HIV at a rate of 3.2 times that of age-, race-, and sex-matched uninfected peers, and approximately 1.5% of dialysis-treated patients in the United States are HIV-positive.[1,2] Patients with HIV who require dialysis have a reduced life expectancy compared with both ESRD patients without HIV and HIV patients without ESRD.[3–5]

HIV infection was initially considered a contraindication to transplantation because of concerns about the risk of HIV progression and opportunistic infection with the use of immunosuppressant drugs and uncertainty about allocating a scarce resource to a group in which outcomes and survival benefit were unknown. Early cases series in highly selected patients surprisingly showed that HIV-infected transplant recipients maintained a brisk alloreactive immune response and experienced high acute rejection rates, necessitating the use of more potent immunosuppression.[6] In 2010, the results from a nonrandomized National Institutes of Health (NIH)–sponsored clinical trial demonstrated excellent short-term outcomes, stability of HIV infection, and few HIV-associated complications.[7] However, this trial contained a highly selected group of 150 patients with $CD4^+$ counts $\geq$200 per cubic millimeter and undetectable HIV RNA levels treated with a stable ARV regimen. The study also highlighted important challenges. Rejection rates remained high (31% at 1 year) despite the addition of induction therapy with anti-CD25 antibodies or antithymocyte globulin (ATG). Both acute rejection and use of ATG were associated with an increased risk of allograft failure. ATG-treated patients did not have a lower risk of rejection and had twice as many serious infections.

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The study by Locke and colleagues represents an important update of the experience with kidney transplantation in HIV-positive patients in the United States before the expected increase in HIV transplantation related to the recently approved HIV Organ Policy Equity Act.[8] This act ended the federal ban on transplantation of organs from HIV-infected deceased donors to HIV-infected recipients and is expected to increase the donor pool for candidates with HIV. On the basis of Scientific Registry of Transplant Recipients (SRTR) data, the study provides an understanding of outcomes in the real world. The median duration of follow-up was 3.8 years compared with only 1.7 years in the NIH trial, and the authors were able to provide 5- and 10-year allograft survival estimates and demonstrate that these outcomes were noninferior to those in a matched cohort of HIV-negative recipients (with the important exception of those with hepatitis C virus [HCV] coinfection who had worse outcomes than the HIV-negative/HCV-positive controls).

Despite these encouraging findings, the study was unable to inform many of the important clinical challenges faced when caring for HIV-positive transplant recipients. The ideal immunosuppressant regimen in this patient population remains uncertain. Unlike the NIH trial, detailed information regarding maintenance immunosuppression and drug levels was not available, and the study was unable to provide information on the indications and safety of ATG in this population. The NIH trial suggested that tacrolimus was superior to cyclosporine in preventing rejection.[7] However, cyclosporine, which has *in vitro* activity against HCV and HIV, may be preferred for coinfected patients.[9] The role of sirolimus, which possesses intrinsic antiviral activity in addition to its ability to enhance the activity of other ARVs, also remains uncertain.[10]

The lack of information regarding antiviral treatment precludes insights into the pharmacokinetic interactions between ARVs and immunosuppressant drugs that likely contribute to the high rate of rejection.[11] Protease inhibitors are significant substrates and inhibitors of CYP3A4 and also the p-glycoprotein efflux system.[12] Calcineurin inhibitors are substrates and inhibitors of CYP3A4 and substrates and inhibitors of p-glycoprotein. Not only would the two be predicted to have significant initial drug interactions when given together, but this interaction may actually change over time or vary depending on the exact antiretroviral and immunosuppression regimen used.[12] These bidirectional and time-dependent drug interactions leave patients at risk of under-immunosuppression and rejection or over-immunosuppression and drug toxicity. The most recent Infectious Disease Guidelines from the American Society of Transplantation recommend choosing an ARV regimen to minimize the potential for drug interactions or toxicities.[11] Switching candidates from a protease inhibitor or non-nucleoside reverse transcription inhibitor to an integrase inhibitor (*e.g.*, raltegravir) is one easy way to eliminate these concerns. However, using raltegravir comes at the cost of an increased risk for virologic failure because of a lower barrier to resistance. If alternative ARVs are chosen, the optimal dosing and monitoring protocol for patient outcomes is not yet known.

The inferior outcomes in HIV/HCV coinfected patients brings into question whether coinfection should be considered a relative contraindication to kidney transplantation. Similar to pivotal

changes in HIV treatment in the mid-1990s, HCV is also undergoing a seismic shift in management. Over the last few years, several new drugs have become available for treatment of HCV, and these drugs have driven the success rate of therapy for many patients to >90%.[13] Because the previous barriers of life-threatening side effects or risk of graft rejection have been nearly eliminated, this change includes higher success rates for patients treated after transplantation.[14] Therefore, the poorer outcomes in HCV coinfected recipients represent an opportunity for innovation and improvement rather than a barrier to transplantation.

In sum, Locke and colleagues should be commended for providing a national perspective on the status of HIV transplantation which supports the expanded use of kidney transplantation in this group. The authors' analysis is limited only by the information available in the SRTR registry. Given the anticipated increase in HIV transplantation with the HIV Organ Policy Equity Act and the appropriate expansion of HIV transplant services beyond NIH study centers, it is time to consider new strategies to capture the detailed information necessary to advance the care of this subset of patients in SRTR.

DISCLOSURES

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See related article, "A National Study of Outcomes among HIV-Infected Kidney Transplant Recipients," on pages 2222–2229.

IgA Nephritis with Declining Renal Function: Treatment with Corticosteroids May Be Worthwhile

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Primary IgA nephropathy (IgAN) is an autoimmune GN characterized by the presence of diffuse mesangial deposits of IgA associated with mesangial proliferation and expansion of the mesangial matrix. In patients with IgAN, circulating IgA1 molecules have an aberrant structure of *O*-glycans, and this can provoke the formation of autoantibodies and circulating immune complexes. These immune complexes can localize in the glomerular mesangium, with activation of mesangial cells, proliferation of extracellular matrix, and release of cytokines and chemokines acting to initiate and perpetuate glomerular injury.[1] Genetic factors are likely to influence the pathogenesis of IgAN. Genes at the HLA region may predispose to the development of IgAN.[2] Independent

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