Comprehensive guidelines translate research findings into clinical policy for HIV-infected transplant candidates and recipients

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Introduction

The GESIDA/GESITRA-SEIMC, SPNS and ONT Consensus Document on Solid Organ Transplantation in HIV-Infected Patients in Spain published in this issue of Spanish Journal of Infectious Diseases and Clinical Microbiology represents a rigorous translation of recently acquired clinical research data to the clinical setting. This is the first national policy advocating solid organ transplant for carefully selected patients with HIV infection. Unfortunately, dramatic improvements in HIV-associated mortality and morbidity have come at the cost of frequent complications related to end-organ disease. Several small studies in the era of highly active antiretroviral therapy (HAART) suggest that patient and graft survival rates are similar to those in HIV-uninfected transplant recipients. Understandable fears of rapid HIV disease progression in the setting of post-transplant immunosuppression, reflected by CD4+ T-cell decline and the development of opportunistic infections and cancers, have not been realized. In fact, several immunosuppressive agents have antiretroviral properties. Despite complex interactions between immunosuppressants and antiretroviral agents, HIV viremia has remained successfully suppressed in most recipients.

HIV infection is not considered a contraindication to transplantation by the United Network for Organ Sharing (UNOS), the agency responsible for deceased donor organ allocation policies in the United States. The traditional exclusion of HIV-infected patients at most transplant centers was borne in the early days of the HIV epidemic, when symptomatic HIV infection progressed rapidly and relentlessly. With transplant candidates dying on long waiting lists, the exclusion of a group with an especially poor underlying prognosis made sense on ethical grounds. Had these policies been developed in the current treatment era, however, it is likely that HIV-infected patients would have been assumed to be high risk, as are patients with hepatitis C infection (HCV) or diabetes, but would not have been excluded simply based upon HIV infection status.

While we are strong proponents of solid organ transplantation in selected HIV-infected patients, important questions remain. Encouraging preliminary studies have been small and of relatively short duration. In addition, we have observed an unusually high incidence of rejection among our kidney transplant recipients that remains unexplained. Finally, the outcomes of HCV co-infected liver transplant recipients have been mixed, and several cases of rapid and severe recurrent HCV have been reported. As long as there is uncertainty, some will argue that it is unethical to utilize the deceased donor pool and thus deprive another transplant candidate from the benefit of that organ, or put living donors at risk. The amount of data required to resolve these concerns remains a contentious issue in the United States. We concur with the Spanish Consensus Document that sufficient data exist at this time. In fact, in the absence of data demonstrating poor outcomes, it can be reasonably argued that it is now ethical to withhold this option from patients with HIV infection. To definitively resolve these ethical and clinical dilemmas, it would be optimal for every willing HIV-infected transplant recipient to contribute by participating in a clinical outcomes study. Thus, it is important that coincident with the publication of this Consensus Document, the Spanish AIDS Foundation has provided funds to prospectively collect data related to all liver transplantation in Spain during 2005-07. We would advocate that additional funds be pursued to include all kidney transplant recipients as well.

The challenge now, as undertaken in the Consensus Document, is to develop patient selection and clinical management guidelines while we await definitive data describing predictors of good and poor outcomes. We will review several areas where the Spanish Consensus Document differs from the clinical trial protocol employed in the United States National Institutes of Health (NIH) sponsored 20-center study of liver and kidney transplantation. As noted by the authors of the Spanish Consensus Document, “this field is evolving continuously and the indications for transplant or management of these patients may change as more evidence becomes available. Therefore, this Committee undertakes to provide periodic updates of this document.” We concur that reevaluation of existing data and flexibility are imperative in this rapidly evolving field.

Key Issues in Patient Selection

The goal of patient selection criteria is to offer transplantation to patients who are able to tolerate immunosuppression without significant HIV disease progression. The GESIDA/GESITRA-SEIMC, SPNS and ONT Consensus Document on Solid Organ Transplantation in HIV-Infected Patients in Spain includes a 15-page supplement that outlines the current policies of post-transplant antiretroviral therapy and details a 17-step evaluation process for patients with HIV infection who are being considered for transplantation. It is a comprehensive document that should be a guide for all transplant centers in the United States.

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sion. We believe such criteria should be applied to both de-
cassed donor organs, suggesting that the benefits of living do-
nated organs are not outweighed by the risks to both donor and
recipient may be unacceptably high. In the case of living

donation, the risks and benefits to the potential donor and
recipient must be considered carefully. In the context of
long waiting lists and dialysis-associated morbidity, we
believe that living kidney donation is a necessary option.
The potential risk of accelerated HCV progression in li-
voring donor liver grafts (right lobe) must be weighed
against the benefits of providing liver transplantation
when the recipient is less ill. This is particularly proble-
matic in the United States, where livers are allocated on
the basis of disease severity, represented by the MELD
score. Unfortunately, by the time the co-infected patient
has a high enough MELD score to be allocated a de-
cased donor liver, they are often too sick to tolerate the pro-
cedure. We believe the potential for receiving a liver
transplant prior to significant deterioration outweighs the
unknown increased risk of HCV recurrence in the set-
ting of regeneration following living donor liver trans-
plantation.

Because we often have waiting lists of several years, we
have also utilized deceased organs considered to be at
“high infectious risk,” i.e. those that are serologically ne-
gative for HIV and hepatitis B and C but from a donor who
may have engaged in behavior putting them at risk for
recent acquisition. These donors are frequently turned
down for kidney transplantation into HIV negative recipi-
ents who have the option of remaining on dialysis and
have thus been an important source for kidney transplan-
tation in HIV-infected patients. “High infectious risk” do-
ors have been largely unavailable for liver transplan-
tation into the HIV-infected patient, as these organs are
commonly accepted for all liver transplant candidates.
The issue of high-risk donors stands in contrast to the use
of known HIV-infected donors. We agree with the Con-
sensus Document that such organs carry the risk of su-
per-infection with drug-resistant and/or more virulent
HIV and should not be utilized until a study can be con-
ducted to assess the safety of this approach.

Key Issues in Post-Transplant Clinical Management

Appreciating the diversity of immunosuppressant ma-
agement protocols, the Consensus Document suggest
that post-transplantation immunosuppressant and rejec-
tion therapy should be managed at each transplant cen-
ter according to local protocols. This has been our prac-
tice as well, and it remains unclear what the optimal approa-
ches to immunosuppression and rejection management
are in this population. This question is complicated by
complex drug-interactions, additive drug toxicities (e.g.
hyperlipidemia and cytopenias) and frequent endocrino-
logic comorbidities (e.g. insulin resistance) common in
this population.

Rejection rates, especially among kidney transplant re-
cipients, have been unexpectedly high in our experien-
ce10,11, although less dramatic in a recent report from an-
other transplant center10. The high incidence of rejection
may be related to insufficient immunosuppressant levels
in the context of an activated or dysregulated immune sys-
tem. Calcineurin-inhibitor (CI) pharmacokinetic parame-
ters are altered by the use of protease inhibitors (PIs) and,
to a lesser degree, non-nucleoside reverse transcriptase in-

hbitors (NNRTIs)\textsuperscript{11,12}. Thus, HIV-infected renal transplant recipients may be unable to tolerate "normal" CI trough levels without developing suprathreshold toxicity due to differences in HAART-associated drug exposure kinetics. There are numerous other potential explanations for the higher incidence of rejection which are being explored, but are beyond the scope of this editorial.

The use of IL-2 receptor inhibitor induction therapy has not eliminated early rejection episodes in HIV-infected kidney transplant recipients. There is currently interest in the use of cell-depleting induction therapy, which we cautiously support. Despite our initial near-prohibition of this practice, we have often had to utilize anti-lymphocytope preparations (Thymoglobulin), for the treatment of moderate to severe rejection episodes. Not surprisingly, there have been prolonged declines in CD4+ T-lymphocyte counts in these patients\textsuperscript{9}. While these patients have not developed AIDS-defining opportunistic infections, they have experienced other serious infections, including staphylococcus aureus endocarditis, influenza pneumonia, and pseudomonas sepsis. Thus, when indicated for the treatment of moderate to severe acute rejection we cautiously use these agents. However, we remain concerned about the marked lymphodepletion that persists for up to a year following administration.

Similar to the complexity of immunosuppression management, HAART management must be patient-specific. Some clinicians have interpreted the greater degree of pharmacologic interactions between the CIs and the PIs to mean that NNRTIs should be utilized instead of PIs. This is not necessarily the case, and several issues must be taken into account in making this decision. First, a PI may be indicated based on drug resistance or intolerance to the NNRTIs. Second, the use of nevirapine in a liver transplant recipient with a CD4+ T-cell count of greater than 250 for women or 400 for men should be undertaken with great caution\textsuperscript{9}. Third, efavirenz-induced hepatic metabolism results in increased CI dosing requirements which are not always well-tolerated. Although the interactions between PIs and CIs or sirolimus are very significant, we are learning how to dose these agents together and it can be done safely. Until a center develops expertise with these drug interactions in various patient populations, we encourage active consultations with an experienced center for advice about initial immunosuppressant doses based upon the HAART regimen, the frequency of monitoring, and anticipated changes in immunosuppressant dosing over time as a result of ongoing metabolic and pharmacologic changes.

The critical antiviral choices in hepatitis B- (HBV) infected patients also deserves special mention, as noted in the Consensus Document. Parenthetically, some HIV- HBV co-infected liver transplant candidates with lamivudine-resistant HBV may be found to be under-managed at the time of transplant evaluation. In such cases, the need for transplant may be delayed substantially with the addition of tenofovir or adefovir. Entecavir availability will expand management options further.

The thoughtful management of HAART agents in the post-transplant period is critical. The advice that "HAART must be administered again as soon as the patient begins to receive food orally" is important in the case of the HBV-HIV co-infected transplant recipient in order to minimize the risk of developing HIV resistance to agents that are active against both HIV and HBV. In other cases, it is more important to reintroduce HAART when the patient is likely to tolerate it and not experience interruptions in dosing. We have not experienced bad outcomes as a result of moderately delaying reintroduction of HAART.

Finally, it is critical that any change being considered in the HAART regimen post-transplant be discussed with the member of the transplant team managing the immunosuppressants before the change is made. There have been rejection episodes and even a death that resulted from a PI being discontinued without such communication, resulting in very low immunosuppressant levels. Ideally, all drug changes would be communicated as even some antibiotics and antifungals can have dramatic pharmacokinetic effects. Knowledge about these complex drug interactions evolves rapidly. For example, many potential transplant candidates come to evaluation using the PI atazanavir which cannot be used with a proton-pump inhibitor (PPI). PPIs are used indefinitely in many transplant recipients. Although a database of drug interactions has been provided in the Consensus Document, expert pharmacologic consultation should be utilized both prior to and following transplantation by centers with limited experience.

In addition to standard post-transplant prophylaxis, we recommend institution of HIV-associated prophylaxis against mycobacterium avium complex (MAC) if the CD4+ T-cell count declines below 50. If patients with an OI history are provided with a transplant, then secondary prophylaxis should be reinitiated if the CD4+ T-cell count declines and/or treatment for acute rejection is required. Unfortunately, there are also some opportunistic complications for which we do not have prophylaxis. In the case of HPV, surveillance for cervical and ano-rectal intraepithelial neoplasia and cancer should be performed. Finally, disease caused by HHV8 should be considered in cases of unexplained hepatitis and/or bone marrow suppression.

Prevention of HIV transmission to healthcare workers

The potential for HIV transmission to healthcare workers during surgery (especially with a high-risk procedure like liver transplantation) and in the peri-transplant period is small but not trivial\textsuperscript{16}. Consideration of appropriate regimens for post-exposure prophylaxis (PEP) should be part of the pre-transplant evaluation. If HAART regimens are modified prior to transplant, PEP recommendations should be reevaluated. Availability of PEP medications and consultation about the management of the exposed healthcare worker should be a priority. Concerns about HIV transmission have prevented several American surgeons from embracing liver transplantation in co-infected patients. In order to reduce the risk of transmission alone, it is appropriate to make every attempt to suppress plasma HIV prior to liver transplant if HAART can be tolerated.

Conclusion

As noted in the Consensus Document, the selection of HIV-infected patients for solid organ transplantation and their subsequent care is complex and requires excellent
References


