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

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Introduction

The GEITAL/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.[1-5] 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 immunosuppressants and antiretroviral agents have antiretroviral properties.[5-9] 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 transplant 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.[4,10] 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.[11,12] 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.[6,7] In fact, in the absence of data demonstrating poor outcomes, it can be reasonably argued that it is no longer 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 expected to tolerate immunosuppression without significant HIV disease progression.
sion. We believe such criteria should be applied to both de-
ceased and living donor transplants. In this regard, we
agree with the CD4+ T-cell count guidelines. We have
seen no evidence of significant HIV disease progression at
these CD4+ T-cell counts.

Control of HIV replication with HAART has resulted in
dramatic improvement in immune function and survival.
Thus, we agree that transplant candidates should be able
to suppress HIV viremia whenever possible. Predicting the
likelihood of complete HIV suppression with a new
HAART regimen, however, can be challenging. Resistance
testing at the time of evaluation to determine if there is a
likely effective HAART regimen may be limited if the pa-
tient has discontinued HAART secondary to hepatitis
city. Even on HAART, such tests may not detect mutations
that are present in minority quasispecies due to remote an-
tiretroviral use. Thus, the expert assessment of the poten-
tial for full virologic suppression must also take into ac-
count all prior resistance test results and any resistance
predicted by past antiretroviral use in the context of on-
going viral replication.

We agree that it is unknown if antiretroviral therapy is
necessary in the context of immunosuppression in patients
who do not otherwise meet criteria to initiate HAART. We
require HAART initiation in all patients except those who
never had a detectable HIV RNA level because of concerns
about potential enhanced viral replication post-transplant.
It will be important to closely monitor patients who do not
use HAART post-transplant for increases in HIV viremia
and declines in CD4+ T-cell count as some immunosup-
pressive regimens may enable these patients to control
their virus while others may exacerbate viral replication.
We excluded patients with any opportunistic infection or
neoplasm history in our pilot study until 2002. Finding
good preliminary outcomes, the protocol was modified to
allow most opportunistic infections (OIs) with continued
exclusive of progressive multifocal leukoencephalopathy
(PML), chronic cryptosporidiosis, and visceral Kaposi’s
sarcoma (KS). We exclude PML because of 2 recent cases
of KS and living donor transplants. In this regard, we
agree with the Consensus Document exclusion of many AIDS-defining disea-
ses based on the possibility of a greater risk of reactivation
may be more conservative than necessary.

Key Issues in Utilization of Donors

The Consensus Document emphasizes the use of decea-
sed donor organs, suggesting that the benefits of living do-
ners are not at a price and that the risks to both donor and
recipient may be unacceptable 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, the right lobe of a decea-
sed 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 of OIs remains
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 reci-
pients 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-
 nors have been largely unavailable for liver transplantation
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-
nagement 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 practice
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 endocrinolo-
getic co-morbidities (e.g. insulin resistance) common in
this population.

Rejection rates, especially among kidney transplant re-
cipients, have been unexpectedly high in our experien-
ces11-13, although less dramatic in a recent report from anot-
er transplant center36. The high incidence of rejection
may be related to insufficient immunosuppressive 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-

hibitors (NNRTIs). Thus, HIV-infected renal transplant recipients may be unable to tolerate “normal” CI trough levels without developing nephrotoxicity 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-lymphocyte 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. 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 lymphopenia 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 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 re instituted 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 the peri-transplant period is small but not trivial. 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 embarking on 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 coordination between transplant surgeons, infectious disease specialists, and HIV/AIDS clinicians.
communication among all members of a truly multidisci-
plinary team. The need for such communication extends to
the patient and their primary care provider as well, as
many patients will receive the bulk of their medical care
close to home rather than at the transplant center. The
multidisciplinary nature of the authors of this Consensus
Document, as well as the early successes with transplan-
tation in Spain, bode well for the Spanish patient seeking
transplantation. We look forward to learning from the
continuing experience of our Spanish colleagues in the
coming years.

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