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## Organ Transplantation in Human Immunodeficiency Virus Infected Patients

The increased survival of HIV infected patients resulting from the administration of highly active antiretroviral therapy has led to an increase in the number of patients with advanced liver or kidney disease. Until recently, such patients were excluded as transplantation candidates owing to their high risk of developing AIDS; however, improvements in their immune and virological conditions have led to this situation being revisited. In recent years, HIV infected patients have been shown to be as amenable to organ transplantation as the general population. Although some questions still remain unanswered, it is no longer justified to exclude them from transplantation programmes.

### Key words:

HIV, transplantation, HAART, liver transplantation, kidney transplantation

### *Organtransplantation bei HIV-infizierten Patienten*

*Das infolge des Einsatzes von hoch aktiven antiretroviralen Therapien verbesserte Überleben von HIV-infizierten Patienten hat zu steigenden Zahlen von Patienten mit fortgeschrittener Leber- oder Nierenerkrankung geführt. Bis vor kurzem wurden solche Patienten als Transplantationskandidaten abgelehnt aufgrund ihres hohen Risikos, AIDS zu entwickeln; nachdem jedoch Verbesserungen in ihrem virologischen und Immunstatus erzielt werden konnten, wird diese Situation derzeit erneut geprüft. In den letzten Jahren hat sich gezeigt, dass HIV-infizierte Patienten ebenso einer Organtransplantation zugeführt werden können wie die Allgemeinbevölkerung. Auch wenn noch einige Fragen offen bleiben, ist es dennoch nicht länger zu rechtfertigen, diese Patienten von Transplantationsprogrammen auszuschließen.*

### *Schlüsselwörter:*

*HIV, Transplantation, HAART, Lebertransplantation, Nierentransplantation*

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## Introduction

Ever since its inception, highly active antiretroviral therapy (HAART) has reduced the morbidity and mortality associated to human immunodeficiency virus (HIV) infection.<sup>1</sup> This has led to the presence of many clinically, immunologically and virologically stable patients with a high risk of developing end-stage liver or kidney disease for whom, similarly to the general population, transplantation is the sole possible therapeutic choice.<sup>2,3</sup>

Although such patients were systematically excluded from transplantation programmes until fairly recently<sup>4,5</sup> and a number of questions remain to be answered in this respect, there is increasing evidence in favour of revising this situation. Thus, the United Network for Organ Sharing (UNOS) currently holds the view that asymptomatic HIV infected patients need not be excluded as transplantation candidates.

The last few years have seen a strong debate and a deep analysis of the ethical, legal and medical issues of organ transplantation in HIV infected patients.<sup>6-12</sup> However, only recently has enough evidence of the effectiveness and safety of transplantation in HIV patients been gathered to consider it a suitable therapeutic choice for those requiring it.

## Liver Transplantation

### 1. End-stage Liver Disease in HIV Infected Patients

Although the origin of end-stage liver disease in HIV infected patients can be as diverse as that in other individuals, coinfection by hepatitis B virus (HBV) or hepatitis C virus (HCV) are especially relevant in the former for various reasons. Thus, because these infections share transmission routes, they exhibit a high incidence in HIV patients. Also, the increased survival provided by HAART has raised the number of patients eventually developing liver cirrhosis, which worsens their quality of life and prognosis.<sup>13</sup>

Infection by human immunodeficiency virus is the primary cause of chronic liver disease in HIV patients.<sup>14</sup> The prevalence of HCV coinfection typically ranges from 23 to 33%,<sup>15</sup> but can

be as high as 88% in some risk groups such as users of parenteral drugs.<sup>16-18</sup>

The mortality associated to liver disease in HCV patients has been found to rise ever since the inception of HAART in the mid-1990s.<sup>19,20</sup> Thus, 50% of deaths in HIV infected patients in 1998 were due to liver disease associated to HCV as opposed to only 11.5% in 1991;<sup>19</sup> worth special note is the fact that 93.8% of the HIV infected patients dying in 1998 were coinfecting with HCV.

HIV infection alters the course of HCV infection, which exhibits faster progression to cirrhosis and higher HCV replication rates than in the general population.<sup>21</sup> Such a rapid progression to cirrhosis can be influenced by the immunodepressive state of the patients. Thus, Benhamou *et al.* have shown a CD4+ lymphocyte count below 200 cells/ $\mu$ l to be a risk factor for the development of accelerated fibrosis in coinfecting patients.<sup>22</sup>

The prevalence of HBV coinfection is 9%;<sup>15</sup> however, vaccination campaigns have lowered its incidence. HIV infection in HBV coinfecting patients seemingly results in faster progression to a chronic state upon acute HBV infection than in other individuals;<sup>23,24</sup> however, the clinical course of chronic hepatitis B, and ALT and HBV-DNA levels, differ little between the two groups.<sup>25</sup>

In HBV and HCV coinfecting patients, liver disease can be complicated not only by an increased progression to cirrhosis, but also by the toxic side-effects of antiretroviral therapy,<sup>26</sup> the development of hepatitis as a result of the immune restoration associated to HAART,<sup>27,28</sup> or the appearance of lamivudine-resistant strains.<sup>28</sup> Liver transplantation may thus be the sole therapeutic choice for these patients, particularly when virological suppression of HIV is to be expected from the post-transplantation institution of HAART.

### 2. Liver Transplantation in the pre-HAART Era

Liver transplantation in HIV infected patients before the inception of HAART was scant and involved individuals who were infected either prior to or during transplantation.<sup>29-35</sup> Such HIV patients exhibited poorer survival than the general population and high rates of progression to AIDS. However, many had been treated with zidovudine

alone or no drug at all. Also, no record of their pre-transplantation immunological or virological condition was available, which precludes extrapolation of their outcome to the present situation.

### 3. Liver Transplantation in the HAART Era

The outcome of liver transplantation in the HAART era provides encouraging prospects as regards patient survival. Thus, Prachalias *et al.*<sup>36</sup> and, more recently, Boyd *et al.*,<sup>37</sup> reported a case series of seven HBV and HCV coinfecting patients with pre-transplantation CD4 lymphocyte counts exceeding 100 cells/ $\mu$ l who were subjected to liver transplantation. None developed HIV-related opportunistic infections. HCV coinfecting patients died 3–25 months post-transplantation through recurrent HCV infection. On the other hand, the HBV coinfecting patients survived 3, 13 and 33 months; they had been given lamivudine and immunoglobulins against HBV, and exhibited good tolerance to HAART, CD4 lymphocyte counts above 200 cells/ $\mu$ l and a viral load lower than 400 copies/mL.

Bonham *et al.*<sup>38</sup> reported on the progress of 6 patients who had been subjected to liver transplantation (5 for HCV end-stage liver disease and 1 for fulminant hepatitis). None met any diagnostic criteria for AIDS and all had pre-transplantation CD lymphocyte counts higher than 100–200 cells/ $\mu$ l. Two of the patients died (one from immediate post-transplantation complications and the other from acute rejection due to tacrolimus underdosing). The other patients have survived with a median follow-up time of 17.5 months and good tolerance of HAART. None of the patients developed any HIV related complications. Neff *et al.*<sup>39</sup> reported on another case series of 6 patients who received liver transplants. Five had HAART prior to transplantation. CD4 lymphocyte counts were above 100 cells/ $\mu$ l and HIV loads lower than 50 copies/mL. Patients survived 10–39 months after transplantation and none acquired opportunistic infections during that period. Only one exhibited progression of the HIV infection, which was controlled after adjusting the HAART. Didier *et al.*<sup>40</sup> reported their results for a case series of 6 HCV coinfecting pa-

tients receiving liver transplants. All exhibited controlled HIV replication prior to transplantation. Also, all continued to receive HAART after transplantation and survived a mean of 9 months without opportunistic infections or increased HIV loads. Schliefer *et al.*<sup>41</sup> reported on an HBV coinfecting patient subjected to liver transplantation who had survived 27 months at the time the paper was published. Finally, Radecke *et al.*<sup>42</sup> reported a case series of 5 transplanted patients with a mean survival of 15.6 months.

Recently, the outcome of liver or kidney transplantation in 49 HIV infected patients was reviewed.<sup>43</sup> The review included the prospective evaluation of patients on a trial currently in progress, as well as the retrospective evaluation of patients transplanted in each of 14 participating centres. Selection criteria included (1) the absence of a clinical history of opportunistic infections; (2) CD lymphocyte counts exceeding 200 and 100 cells/ $\mu$ l for the patients receiving the kidney and liver transplants, respectively; (3) an HIV load lower than 50 copies/mL —or higher for the patients not subjected to HAART who received a liver transplant if virological suppression was expected from the post-transplantation institution of this therapy. Survival one year post-transplantation in these patients was similar to that in non-HIV-infected transplanted patients on the UNOS database. Graft survival was also similar in both groups. Finally, no evidence of virological or immunological progression of the HIV infection was observed. While encouraging, these results are limited by the retrospective and prospective nature of the data collection approach used, the relatively small number of patients examined and the short duration of the follow-up period. Prospective studies spanning longer follow-up periods are therefore needed.

Very recently, preliminary results of three prospective studies<sup>44-46</sup> encompassing a total of 50 transplanted patients (35 with a liver, 14 with a kidney, and 1 with a kidney and a liver) who were monitored for 3, 17 and 18 months, respectively, were reported. The results support the previous assumption that transplantation can be relatively effective and safe in seropositive patients with a low viral load and a fairly high CD4 lymphocyte count before transplantation.

Tab. 1: Selection criteria for transplantation in HIV infected patients

	INCLUSION	EXCLUSION
<b>CD4+ count (cells/<math>\mu</math>l)</b>	Kidney > 200 Liver > 100	
<b>HIV-RNA</b>	Undetectable Detectable, but suppressible <ul style="list-style-type: none"> <li>• Intolerance of ART</li> <li>• No treatment</li> </ul>	
<b>Clinical</b>		AIDS (except EC)
<b>Mental state</b>		Thoroughly assessed

ART antiretroviral treatment, AIDS acquired immunodeficiency syndrome, EC esophageal candidiasis

Adapted from Roland, M. *et al.* 9<sup>th</sup> Conf Retroviruses Opportunistic Infect (Seattle, February 24–28, 2002; Abst 655)

Patients in a good immunological and virological condition prior to transplantation thanks to the institution of HAART should obviously continue to receive this therapy after transplantation. Thus, Ragni *et al.*<sup>47</sup> found early mortality among HIV infected recipients of a liver transplant to be related to the inability to administer HAART post-transplantation —whether because of intolerance or of toxic effects. Other variables such as the pre-transplantation CD4 lymphocyte count, viral load and immunosuppressive approach used were found not to influence mortality in these patients. However, one should bear in mind that the liver toxicity of HAART in non-transplanted patients can also develop in liver grafts; this requires strict monitoring of liver function after HAART is resumed upon transplantation.

## Kidney Transplantation

### 1. End-stage Kidney Disease in HIV Infected Patients

HIV infected patients exhibit a high risk of developing end-stage kidney disease. This is a result of their increased survival being accompanied by an increased prevalence of the causes of chronic renal disease affecting the general population and of an increased prevalence of HIV-related nephropathy, IgA nephropathy, hemolytic-uremic syndrome, amyloidosis, and membranous, focal and segmentary glomerulonephritis among such patients.<sup>9</sup> In addition, HCV coinfection, which is highly frequent in this sub-population, increases the risk of nephropathy and

exhibits a broad spectrum of glomerular processes including membranoproliferative, immune complex-mediated and membranous glomerulonephritis.<sup>48,49</sup>

HIV-related nephropathy accounts for two-thirds of end-stage kidney disease cases among HIV infected patients. Although it has been reported to occur mainly in immunodepressed users of parenteral drugs, there is evidence that it can be acquired via any transmission route and that 20% of cases involve CD4 lymphocyte counts above 200 cells/ $\mu$ l.<sup>50</sup> Also, although its origin is uncertain, there is evidence that a direct action of HIV itself on kidney tissue plays a crucial role in its development, consistent with the fact that progression to end-stage kidney disease is slower in patients receiving HAART than in untreated individuals.<sup>51</sup> According to Schwartz *et al.*,<sup>52</sup> HAART has reduced end-stage kidney disease in HIV infected patients by 23%; also, the treatment has resulted in complete recovery from nephropathies in some cases.<sup>53</sup>

The effectiveness of HAART, however, should not delay the indication of transplantation in these patients as the administration of an antiretroviral treatment to individuals on hemodialysis is confronted with serious problems such as the difficulty of reaching adequate drug concentration levels and an increased risk of side effects; this, together with the low survival rate of HIV patients on hemodialysis,<sup>54</sup> makes kidney transplantation an appealing choice with a view to reducing morbidity and mortality, and the high added costs of hemodialysis in this patient population.

## 2. Outcome of kidney transplantation in HIV infected patients

Available information about kidney transplantation in HIV infected patients continues to be scant. Most reported data correspond to small case series in the pre-HAART era.<sup>25,29,55-58</sup> Although the immunological and virological condition of the patients prior to transplantation was unknown, a high proportion survived a long time. However, a historical cohort study of the pre-HAART era involving 32 recipients of a kidney transplant who had been infected with HIV prior to transplantation revealed HIV infection to be an independent variable of difficult diagnosis associated to increased mortality and graft failure relative to uninfected controls.<sup>59</sup> A subsequent study of 26 kidney transplants in "eligible" HIV infected patients in the HAART era revealed their survival one-year post-transplantation to be on a par with that of patients on the UNOS database; graft survival was also similar and no progression of the HIV infection was observed.<sup>45</sup>

## Other Solid Organ Transplantations

Experience on the transplantation of organs other than the kidney and liver is even more limited. There were reports on a case series of 5 heart transplants<sup>27</sup> and three isolated cases in the pre-HAART era.<sup>60-62</sup> More recently, two successful cases of cardiac transplantation in HIV patients have been reported.<sup>63,64</sup> By contrast, only one case of pancreas transplantation,<sup>29</sup> and seemingly none of lung transplantation, have been reported.

## Criteria for Organ Transplantation in HIV Patients

Available experience with organ transplantation in HIV infected patients allows one to establish selection criteria primarily based on the clinical immunological and virological condition of the HIV infected patient on the one hand, and on the psycho-social features of the candidate recipient on the other. It is therefore important for the Patient Assessment Team to include transplan-

tation, infection and AIDS specialists, as well as experts in alcohol and drug addictions and social workers.

### 1. Clinical Criteria

Most authors hold the view that patients experiencing some event typical of the acquired immunodeficiency syndrome should be excluded as transplantation candidates on the grounds of the increased risk of recurrence of opportunistic infections and tumours during the post-transplantation period. This criterion, however, should be revised as those patients recovering their immune stability with HAART regain their immunospecificity against opportunistic pathogens.

### 2. Immunological Criteria

Because most opportunistic infections in HIV infected patients occur with CD4 lymphocyte counts below 200 cells/ $\mu$ l, this could be used as a threshold for selection of candidates. With liver transplants, however, the lymphopenia associated to portal hypertension results in successful control of viral replication and a good immunological condition in patients with lower CD4 lymphocyte counts. Such patients have exhibited no increased risk of opportunistic infections during the post-transplantation period, even when transplanted with CD4 lymphocyte counts above 100 cells/ $\mu$ l. This count can therefore be used as the lower bound for inclusion in liver transplantation programmes.

### 3. Virological Criteria

Although, formerly, most assessment teams required patients to have an undetectable HIV load upon HAART administration, this is not always feasible, particularly in cirrhotic patients, where the treatment frequently has to be stopped because of decompensated liver disease or the liver toxicity of antiretroviral drugs. The most important requisite for candidates as regards control of their HIV infection is to have therapeutic alternatives for effectively controlling viral replication after transplantation. Correct initial assessment and inclusion on a transplantation list there-

fore relies heavily on having an undetectable HIV load; in patients where this is impossible, a potential resistance to antiretroviral drugs should be excluded, using a resistance test, in order to check for effective alternatives during the post-transplantation period.

### 4. Miscellaneous Criteria

In addition to the previous clinical, immunological and virological requisites, users of parenteral drugs should be required to abstain for at least 2 years, and so should alcoholics for at least 6 months. In addition, candidates should attain stable psychosocial conditions for transplantation to be feasible.

## Post-Transplantation Issues

### 1. Pharmacokinetic Interactions between HAART and the Immunosuppressive Treatment

One of the main problems with which organ transplantation in HIV infected patients is confronted is the interaction between antiretroviral drugs and immunosuppressors. These two drug groups share a narrow therapeutic spectrum and, frequently, identical metabolic pathways; as a result, they can interact mutually. Thus, cyclosporin and tacrolimus, on which the immunosuppressive treatment relies, are metabolized by the enzyme CYP3A4 in cytochrome p450; this is the same enzymatic pathway through which most protease inhibitors are metabolized. The joint administration of these drugs can thus substantially raise cyclosporin and tacrolimus levels. It is therefore very important to strictly monitor these drugs in order to ensure proper dosing with a view to obtaining appropriate levels.<sup>65</sup> Similarly, the immunosuppressor mycophenolate mofetil exhibits synergistic activity *in vitro* with abacavir, didanosine and tenofovir, as well as antagonism to zidovudine and stavudine.<sup>66,67</sup> On the other hand, nucleoside and nucleotide analogues exhibit no relevant pharmacokinetic interactions with immunosuppressors. Available information about the new immunosuppressors is still limited. There is, however, evidence that nelfinavir increased sirolimus levels in a liver transplant recipient.<sup>68</sup>

## 2. Risk of Opportunistic Infections

Although one can assume post-transplantation immunosuppression to reactivate latent infections, experience gathered over the last few years suggests no increased risk of opportunistic infections in these patients thanks to use of prophylactic measures used and HAART. Double-blind trials involving the administration of a placebo, corticoids or cyclosporin A for 2 months in patients with acute or chronic HIV infection revealed no increased risk of opportunistic infections, immune decline or viral replication.<sup>69,70</sup> As with the general population, however, patients should be closely monitored in order to facilitate the early detection of potential opportunistic infections, particularly by herpes virus, fungi (pneumocystis, histoplasma, candida, cryptococcus), mycobacteria and parasites (toxoplasma, cryptosporidium, leishmania), which can affect both HIV infected and transplanted patients.

## 3. Re-infection by HBV and HCV

Prophylactic measures based on immunoglobulins and lamivudine have been found to reduce the post-transplantation incidence of HIV re-infection in HIV patients receiving a liver transplant as a treatment for HBV.<sup>39</sup> However, patients who are administered an antiretroviral treatment including lamivudine prior to transplantation can become resistant to this drug.<sup>71</sup> Lamivudine-resistant HBV strains are responsive to adefovir and tenofovir,<sup>72</sup> which may thus be required by such patients.

Unlike HBV, re-infection with HCV after transplantation is virtually universal<sup>11</sup>—as in the general population. Because the history of HCV infection in grafts in the medium to long term, and the responsiveness to pegylated interferon and ribavirin after transplantation in these patients are unknown, long-term follow-up studies comparing seronegative patients with HCV–HIV coinfecting patients are required in order to identify any differences in recurrence strength and responsiveness to the HCV treatment.

In summary, HIV infection has traditionally been considered an absolute contraindication for transplantation. However, this criterion should not be applied to all patients as HAART has

resulted in an increasing number of individuals possessing the required immunological and virological status for reception of a transplant; such individuals exhibit survival, graft function and opportunistic infection rates similar to those for the general population. Although some questions about HIV infection and organ transplantation still remain unanswered, the need has arisen to revise former attitudes that led to HIV infection as such being held as a contraindication for transplantation in any kind of patient.

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