LIVER TRANSPLANTATION IN HIV-POSITIVE PATIENTS: the position of the Brazilian groups

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ABSTRACT - ***Background*** - Patients infected with the human immunodeficiency virus (HIV) have generally been excluded from consideration for liver transplantation. Recent advances in the management and prognosis of these patients suggest that this policy must be reevaluated. ***Aim*** - To identify the current position of Brazilian transplant centers concerning liver transplantation in asymptomatic HIV-infected patients with end-stage liver disease. ***Methods*** - A structured questionnaire was submitted by e-mail to Brazilian groups who perform liver transplantation and were active in late 2003, according to the Brazilian Association of Organ Transplantation. ***Results*** - Of the 53 active groups, 30 e-mail addresses have been found of professionals working in 41 of these groups. Twenty-one responses (70%) were obtained. Most of the professionals (62%) reported that they do not include HIV-infected patients in waiting lists for transplants, primarily on account of the limited world experience. They also reported, however, that this issue will soon be discussed by the group. Those who accept these patients usually follow the guidelines provided by the literature: patients must fulfill the same inclusion criteria as the other patients with end-stage liver diseases, present low or undetectable HIV viral load, and a CD4 count above 250/mm^3. They reported that there are 10 HIV-infected patients in waiting list and that only one patient has received a liver transplant in the country. ***Conclusion*** - Most centers do not accept in waiting lists for liver transplantation patients with HIV infection, even asymptomatic ones. However, advances in the management of HIV-infected patients suggest that this policy must be reevaluated. In Brazil, there is practically no experience in liver transplantation in HIV-positive patients.

HEADINGS - Liver transplantation. AIDS.

INTRODUCTION

One of the conclusions of the Consensus Conference on the Indications of Liver Transplantation, held in Paris in 1993, was that infection of the recipient with the human immunodeficiency virus (HIV) must be an absolute contraindication to liver transplantation[5]. The main concern was the potential adverse effects of immunosuppressive drugs on HIV disease progression, in a disease characterized by progressive immunocompromise. Indeed, before the introduction of treatments using a combination of antiretrovirals, commonly known as highly active antiretroviral therapy (HAART) in the management of HIV-infected patients, the results of organ transplants in these patients – either infected during the procedure or knowingly carriers of HIV before transplantation – were poor, most of them having progressed to death due to complications associated with the acquired immunodeficiency syndrome (AIDS)[7, 8, 38].

Since the mid 1990s, however, the prognosis of these patients improved significantly. As a result of earlier diagnosis, more effective prophylaxis and treatment of opportunistic infections and, above all, the introduction of highly effective antiretroviral therapy – particularly, non-nucleoside and protease inhibitors – the morbidity and mortality associated with AIDS has been decreasing significantly[12, 24]. In our country, in the 1995-2003 period, the Ministry of Health reported that mortality due to AIDS fell from 9.7 to 6.3/100.000 individuals[19].

Infection with the hepatitis B (HBV) and hepatitis C (HCV) viruses are very common in HIV-infected patients, since these viruses share the same transmission routes[14, 16, 18, 25, 30, 40]. Moreover, the natural history of hepatitis B and C is accelerated in individuals co-infected with HIV, as compared with those without from co-infection[12, 30, 31, 34, 35, 40]. Consequently, hepatitis is currently the leading cause of death and morbidity in patients co-infected with HIV[3, 6, 12, 36].

These observations, together with other indicators, suggest that HIV-positive patients represent a growing population of individuals who are potential liver transplantation candidates. Recent studies showed that,

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in selected individuals, the results of liver transplantation are good, and, most importantly, there is no evidence that the HIV infection is accelerated[10, 21, 29]. In Brazil, the Ministry of Health does not contraindicate or prohibit liver transplantation in these patients[4].

This study was designed to evaluate the present policy and experience of the Brazilian groups active in 2003, as regards the liver transplantation in HIV-infected patients, in the post-HAART era.

METHOD

A survey was conducted using a structured questionnaire, sent by e-mail, to professionals in charge of or working in Brazilian liver transplantation centers, which were active in 2003, assessing these groups' position with regard to liver transplantation in patients infected with HIV.

More specifically, we evaluated: 1. the characteristic of the program (years of activity, type of patients cared for – children and/or adults –, number of transplants performed in 2003; 2. request of anti-HIV testing during pre-transplant evaluation and whether anti-HIV-positive patients are accepted in waiting lists; 3. care, procedures and criteria adopted by the groups before including HIV-positive patients in waiting list; 4. for the centers who accept HIV-infected patients, the number of transplants performed, the results and the number of patients in waiting list; and 5. for the groups who have decide not to include patients with HIV infection, the reasons for this decision.

RESULTS

In December 2003 there were 53 groups accredited to perform liver transplantation in Brazil[1]. The e-mails of 30 medical professionals were identified who, as a group, worked in 41 of the 53 groups. These 41 groups performed 773 transplants in 2003, which comprises 97% of the 792 liver transplants performed in this period.

The questionnaires were sent from July to August 2004. Of the 30 questionnaires sent (encompassing 41 groups), 21 were responded and returned (corresponding to 24 groups). Participants from more than one center chose to respond only once, including data from the centers they work in, instead of filling a questionnaire for each center. The results refer to the views and conducts reported in these 21 questionnaires.

Since some groups did not report the number of liver transplants performed in 2003, we chose to use the data from the 2003 yearbook of the Brazilian Association of Organ Transplantation[1].

General characteristics of the centers which responded to the questionnaire

The participating centers have been active for an average of 8.5 years, more commonly care for both children and adults, accounted for 74% of the 792 procedures performed in Brazil in 2003, and always require HIV antibody testing in the protocol of evaluation for inclusion of patients in the waiting list (Table 1).

TABLE 1 – Information provided by 21 respondents of the questionnaire about liver transplantation in HIV-positive patients

	Characteristic of the centers*
Years of activity (mean)	8.5
Patients cared for	
Adults and children	11
Adults	06
Children	03
Transplants in 2003 (n)	570
HIV antibody testing in pre-transplant evaluation	21

* One center failed to inform the date of beginning of activities and the type of patient cared for

Table 2 presents the characteristics of transplanting centers categorized according to the practice of including or not including HIV-infected patients in waiting lists for liver transplantation.

Note that about two thirds of the responders do not accept HIV-positive patients in waiting lists for liver transplantation, yet the time in activity is similar across the centers. The number of transplants performed in the 12 months preceding the survey varied widely among the centers but the groups that include HIV-positive patients transplanted more patients in 2003.

TABLE 2 – Characteristics of the centers classified according to the decision of including or not HIV-positive patient in waiting list for liver transplantation

	Includes HIV-positive patients	Does not include HIV-positive patients
Centers	8 (38%)	13 (62%)
Years of activity (mean)	8	7.5
Patients cared for		
Adults/children	5	6
Adults	3	3
Children	0	3
Transplants in 2003	322	248
Mean number of transplants in 2003 per center (SD)*	40 (± 31)	19 (±15)

*SD: standard deviation

Groups that do not include HIV-infected patients in waiting lists

The reasons reported by 13 responders not to include HIV-positive patients in waiting lists for liver transplantation are presented in Table 3.

Note that the main reason reported for not including HIV-positive patients was the little international experience on the subject. Nevertheless, a significant number of centers intend to discuss the matter in the near future.

TABLE 3 – Reasons mentioned for not including HIV-positive patient in waiting list for liver transplantation

Justification	Centers (%)*
Awaiting more international experience	7 (54)
Matter not yet discussed but in agenda	6 (46)
Must be a government program rather than one of isolated groups	3 (23)
Unethical	1 (08)

* Some groups presented more than one reason

Groups that accept to include HIV-infected patients in waiting lists

The centers which accept to perform liver transplantation in HIV-positive patients adopted this policy 3 years ago, in average. Most of them (87%) took this decision only by consulting with the clinicians and surgeons directly involved in the process. Some groups (25%) shared the decision with the Infection Control Service, while 12.5% also listened to the views of nurses or anesthesiologists or any agency concerned with the treatment of AIDS patients.

Opportunistic infections

Two centers (25%) accepted to include in waiting lists only those patients with a history of certain opportunistic infections (such as tuberculosis or esophageal candidiasis) and as long as it had occurred years ago. Three groups (37.5%) accept patients with history of opportunistic infection without discriminating between them and not considering when they have occurred, while other three centers do not accept to perform transplantation in patients with any history of any type of opportunistic infection.

CD4 Count

Seven responders informed the CD4 count they considered adequate to accept patients in waiting lists. Most of them (71%) accept patients with CD4 >250/mm^3, while 14.5% accept CD4 >200/mm^3, and 14.5% do not use this parameter in the decision of including the patient in the waiting list. Except for one, which considers only the CD4 count at the moment of inclusion, all the other centers informed that they consider CD4 values of the 6 months preceding the inclusion.

Viral load

Seven centers informed the HIV viral load they consider as safe for inclusion of patients in waiting list. Most of them (57%) include only patients with undetectable viral load. However, patients with <200 copies/mL (14%) and with 300 copies/mL (14%) are also accepted, or even regardless of the viral load (14.5%).

HIV genotyping

Six groups (86%) informed they do not to request HIV genotyping before the transplant, which is requested only by one group (14%). One center did not answer the question.

Number of patients in waiting list and of transplanted patients

At the completion of data collection, there were 10 HIV-positive candidates for liver transplantation in waiting lists. No HIV-positive patient received a transplant in 2003, and only one received a transplant since this subgroup of patients has been accepted in waiting lists.

Results and immunosuppressive regimen

Only one patient infected with HIV received a liver transplant in the country. The patient died 6 months later from fibrosing cholestatic hepatitis (co-infected by HBV and HCV).

The responders did not comment on the immunosuppressive regimen due to lack of experience.

DISCUSSION

Before analyzing the results, it is important to consider that they reflect the views of the groups which performed 72% of the liver transplants carried out in Brazil in 2003.

Most of the Brazilian groups do not include HIV-positive patients in waiting list even if they fulfill the criteria for liver transplantation. Although they present the same time of activity as the groups who include such patients, they transplant less patients yearly.

The main reason stated was the limited experience with liver transplantation in this group of patients. Indeed, the publication of the largest series evaluating the results of the procedure in patients with HIV infection using HAART are recent, the number of cases included is small, and the follow-up time is short[10, 21, 22, 29]. For example, a multicenter study involving major transplanting centers (Pittsburgh, Miami, San Francisco, Minneapolis and London), published in 2003, evaluated 24 patients, with mean follow-up of 17 months[27]. However, occasionally, results of studies with a limited number of patients have a considerable impact and have been used as guides for conduct. It is worth noting that, worldwide, most of the services adopt as criterion for transplantation in patients with hepatocellular carcinoma, conclusions of a study including 48 cases, with mean follow-up of 26 months[17].

Another reason mentioned for not considering HIV-positive patients for liver transplantation was the lack of a government program providing the necessary infra-structure and funding for the care of these patients. It is possible that transplantation in patients infected with HIV will be more expensive than in the other patients, because in addition to the usual costs there will be, among other, those of antiretrovirals and additional tests (for example, the interaction of calcineurine inhibitors and antiretrovirals[5, 37] determines the need for monitoring the serum levels of the former more frequently). Moreover, the management of this group of patients requires the concurrence of specialists – virologists, infectologists, and so on –, which certainly increases the costs. In Brazil, the Brazilian Health System (SUS) covers the expenses of transplants and there is a highly effective public system for the care of AIDS patients. Nevertheless, the value paid for the transplant is one and the same, i.e. regardless of the costs involved. Thus, during hospitalization for the procedure, there are no additional funds for additional expenses when the transplant is done in patients of higher complexity who, usually, use more resources. In France[12, 29] and Italy[39], studies evaluating variables related to the decision of including in list and transplanting in patients infected with HIV are part of a government action.

Another reason presented for not accepting HIV-positive patients on ethical grounds, due to the reduced number of donors and the great number of patients (without the infection) in the waiting list. Certainly the inclusion of HIV-patients in programs of transplantation, besides the clinical aspects, must also consider ethical, deontological and legal aspects, a matter that has recently been reviewed[13, 26, 28]. Nevertheless, it seems clear that, once unquestionably proven that the result of liver transplantation is similar in patients infected or not with HIV,

it will not be ethical to exclude them from the waiting list, and it will be incorrect to favor transplantation in patients whose rights to receive organs have been firmly established longer ago to the disadvantage of those whose rights are being established more recently. In other words, patients with HIV infection are not to blame if medicine only now enables them to undergo transplantation, and thus should compete together with the others in waiting for an organ.

Whatever the reasons mentioned not to accept patients with HIV infection in the waiting list, 46% of the centers plan to discuss this issue soon.

Is there enough evidence supporting liver transplantation in patients infected with HIV? A recent review indicated that, in the HAART era, 51 patients received transplants, the largest experience being in the Pittsburgh University, with 29 cases[11]. In these, the mean follow-up was 18 months and the 1 year survival rate was 76% (considering all patients). In those who did not progress to death in the first 30 days (26 patients), 1 year survival was 89%[10]. In the experience of RAGNI et al.[27] with 24 HIV-positive, the cumulative survival rate in 1, 2 and 3 years was 87.1%, 72.8% and 72.8%, respectively, while in HIV-negative patients it was 86.6%, 81.6% and 77.9%. Long term results are still unknown.

Most of the centers decided to perform transplants in HIV-positive patients only based on the opinion of clinicians and surgeons directly involved in the process. However, it is recommended that the issue must be widely discussed by a multidisciplinary team (hepatologists, surgeons, pathologists, virologists, infectologists, immunologists, etc.[29]), and centers which do not have these resources should no take care of HIV-infected transplant recipients[9]. Another aspect to be discussed by the professionals involved is the risk of needle stick injury, which are more frequent in surgeries of long duration and often performed at night or early morning, as is common in transplants (remember that the risk is present after the procedure). On this account, SAMUEL et al.[29] suggest that the susceptibility of the HIV strain to antiviral therapy must be known in advance, so as to adopt prompt effective prophylaxis in case of accident. This procedure was not adopted by 86% of the responders who reported including HIV-positive patients. However, the knowledge of HIV genotyping seems to be important primarily in patients who failed to respond to conventional therapy[2]. In Brazil, the Ministry of Health provides HIV genotyping exams in the public network for patients who, adherent to treatment, are considered as non-responders (www.aids.gov.br). Currently, in the tests offered by the Ministry of Health, a viral load of ≥5.000 copies/mL is required. Thus, non-responders (patients with high viral load) would not be accepted in waiting list for transplantation, at least at that moment. However, once responding to the treatment, liver transplantation could be considered.

Patients with a history of opportunistic infections are usually excluded from the programs transplanting HIV-positive patients[27, 29, 32, 33]. In this survey, 37.5% of the respondents reported accepting patients with a history of opportunistic infections, 25% include them only when they had particular types of infection (esophageal candidiasis) which occurred in a more distant past. However, HAART increased the survival even in patients with a history of opportunistic infections[20, 24]. Thus, at present this history does not seem to be a good predictor of survival, as long as the patient is stable, considering the CD4 count and the viral load. However, patients with opportunistic infection in the preceding 6-12 months have not been submitted to transplantation[10].

The transplantation of organs in HIV-infected patients is not considered an experimental procedure anymore but it is certainly not routine. Consequently, there are no clear guidelines yet to be followed as to the criteria for inclusion of these patients in waiting lists. However, most of international centers consider that the patient must present: 1. fulfill the same criteria of severe end-stage liver disease used for other patients, 2. present very low or undetectable viral load, 3. a CD4 count above 200/mm^3, and 4. no AIDS-defining conditions[22]. Most of the Brazilian groups reported adopting these parameters, more often including patients with undetectable viral load and CD4 count above 250/mm^3, considering the count of the 6 months preceding inclusion in the list. Since cirrhotic patients with hypersplenism may have a low CD4 count, this may not reflect the clinical state of the patient, and thus the absolute count of neutrophils should be taken into consideration[10]. The criteria of exclusion have been changed as the groups gain more experience. In Pittsburgh, for instance, patients with a history of Kaposi sarcoma are not accepted for liver transplantation (high recurrence rate), neither those infected with the JC virus or those who are not adherent to antiretroviral therapy[10].

As only one patient has received a liver transplant, Brazil has no experience in the post-transplant management of HIV-positive patients. Recently a review has been published on this theme[10].

In conclusion, it has been demonstrated that in Brazil, most of the centers do not accept HIV-positive patients in the waiting lists for liver transplantation. In the groups who accept them, the decision has been taken in isolation a few years ago. There is no government program to evaluate the impact of the decision to perform transplantation in these patients. However, to date only one patient received a transplant. On account of the Brazilian reality, and considering that liver transplantation in HIV-patients is a complex and expensive procedure, it would be all the more convenient that a multicenter approach should be implemented, organized by professionals interested in the subject and sponsored by the federal government.

Participating physicians and their centers

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RESUMO – ***Racional*** - Pacientes infectados com o vírus da imunodeficiência humana (HIV) têm sido comumente excluídos dos programas de transplantes de fígado. Avanços recentes no tratamento e prognóstico desses pacientes sugerem que essa política deva ser reavaliada. ***Objetivo*** - Identificar a orientação atual dos transplantadores brasileiros em relação a transplante de fígado em pacientes infectados com HIV, assintomáticos, com doença hepática terminal. **Métodos** - Envio de questionário estruturado, por correio eletrônico, para grupos que realizam transplante hepático e ativos no final de 2003, segundo Associação Brasileira Transplantes de Órgãos. ***Resultados*** - Dos 53 grupos em atividade, identificou-se o endereço eletrônico de 30 profissionais, que atuam em 41 desses grupos. Foram recebidas 21 respostas (70%). A maioria dos profissionais (62%) informou não incluir pacientes anti-HIV reagentes em lista para transplante, fundamentalmente em razão da pequena experiência mundial. Contudo, relataram que o assunto será discutido brevemente pelo grupo. Profissionais que aceitam esses pacientes adotam, em geral, orientações sugeridas na literatura: devem preencher os critérios de inclusão que os demais pacientes com doenças hepáticas terminais, ter carga viral do HIV baixa ou negativa e contagem de CD4 >250/mm^3. Informaram haver 10 pacientes anti-HIV reagentes em lista e que apenas 1 paciente foi transplantado no país. ***Conclusão*** - A maioria dos profissionais não aceita pacientes anti-HIV reagentes mesmo que assintomáticos, em lista de espera para transplante hepático. Contudo, os avanços no manejo de pacientes com HIV recomenda que essa posição seja reavaliada. Praticamente não há experiência em nosso país, com transplante hepático em pacientes anti-HIV reagentes.

DESCRITORES - Transplante hepático. AIDS.

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