

# Guidelines for liver transplantation in patients with HIV infection (2005)

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## 1.0 Key recommendations

Levels of evidence:

I = Meta-analysis or RCT

II = Other good-quality trial

III = Observational studies/case reports

IV = Expert opinion

- (1) Given the improved prognosis of HIV in recent years, HIV-positive patients should be considered for liver transplantation where necessary [III].
- (2) Indications for transplantation include
  - a. acute liver failure [III];
  - b. decompensated liver disease with ascites, encephalopathy (having excluded HIV-related dementia) or problematic varices and poor synthetic function, e.g. albumin <30 g/l, INR >1.5 and elevated serum bilirubin e.g. >50 µmol/L [III];
  - c. hepatocellular carcinoma (HCC) detected during regular tumour surveillance (recommended at least 6 monthly in all patients with cirrhosis) and meeting the Milan criteria [III].
- (3) Given the lag time between referral for assessment and liver transplantation (currently about 1 year), patients should be referred to a transplantation centre as early as possible [IV].
- (4) Patients with HCC who are being considered for liver transplantation should not have a needle biopsy due to the significant rate of needle-track seeding leading to recurrence post-transplant [III].
- (5) Patients being considered for transplantation should have a prognosis (excluding the liver disease) of 50% survival for 5 years [III].
- (6) HIV-specific parameters that should pertain include [III]:
  - a. CD4 counts >200 cells/µl or >100 cells/µl in the presence of portal hypertension;
  - b. absence of HIV viraemia;
  - c. absence of AIDS-defining illness after immune reconstitution;
  - d. antiretroviral therapeutic options available if the HIV disease reactivates.
- (7) Absolute contraindications to transplantation include [II]:
  - a. alcohol-related liver disease without total abstinence for 6 months;
  - b. currently injecting intravenous drug use;
  - c. cholangiocarcinoma;
  - d. extrahepatic malignancy;
  - e. uncontrolled extrahepatic sepsis, e.g. endocarditis;
  - f. total thrombosis of porto-mesenteric system;
  - g. severe pulmonary hypertension (mean pulmonary pressure >50–55 mmHg).
- (8) A relatively recent diagnosis of non-HIV-related malignancy does not necessarily contraindicate liver transplantation but the duration of recurrence free survival required before transplantation is varied (ranges from 1 to 5 years) and is determined by classifications based on the Penn registry data [IV].
- (9) Relative contraindications to transplantation include malnutrition, cardio-pulmonary disease, chronic renal impairment or poor motivation [II].
- (10) Calcineurin inhibitors interact with drugs in the highly active antiretroviral therapy (HAART) regimens. It is essential that no alterations are made to the HAART therapy without consultation with the host transplant centre [III]. Antiretroviral and immunosuppressive drug levels may need to be monitored.
- (11) Given that donated livers are a scarce resource, the outcome of transplantation needs to be considered carefully before accepting someone on to a waiting list. Currently the outcome for patients transplanted

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for hepatitis C/HIV coinfection is worse than other causes due to accelerated disease. The outcome of liver transplantation in hepatitis B infection and other indications are in line with non-HIV-infected liver transplant recipients over the first 3–5 years [III].

- (12) Patients have significant emotional, psychological and counselling needs that need to be met both before and after transplantation [II].
- (13) There is a need for a national database of patients considered for transplantation to gauge access and outcomes [IV].

## 2.0 Audit standards

- (1) All patients meeting the criteria for liver transplantation as defined in these guidelines should be discussed with and referred to the regional liver transplantation centre and this should be documented in their case notes.
- (2) All patients considered for transplantation should be included on a national database once this is in place.

## 3.0 Background

The prognosis of HIV has greatly improved in the past 10 years such that currently, HIV-positive patients have a similar prognosis to those with type II diabetes [1–3]. Liver disease has emerged as a significant cause of morbidity and mortality in HIV-infected patients in line with the dramatic improvement in survival in the HAART era [3–6]. This is especially important given that the rate of coinfection of HIV and hepatitis B or C is 5–10% in the UK and considerably higher elsewhere [6–8]. In the non-HIV population liver transplantation has become a standard therapy for a wide range of liver diseases, although organ shortage means that only a minority of patients with liver disease ultimately receive transplants [9]. In the UK, it is estimated that about five out of every six patients who die with liver disease are not considered for liver transplantation. Guidelines have been developed to select patients for liver transplantation that reflect the reality of the donor pool and aim to maximize the benefit of the scarce resource [10,11]. However, these guidelines are not set in stone and are undergoing a constant process of refinement. HIV seropositivity is a case in point and was until recently almost universally considered to be an absolute contraindication to transplantation. A limited but significant number of liver transplant programmes no longer consider this to be the case [12–15].

The global experience with liver transplantation in HIV-infected individuals currently numbers in the region of 150–200 cases but is increasing quite rapidly [12–15]. Approximately half of these cases have been described in the world

literature. This experience has established the feasibility of liver transplantation in HIV-infected patients although with a number of important caveats and the need for adjustments to standard protocols [12–17]. Hepatitis C re-infection of the transplanted liver is the issue of most concern to date with broad recognition that accelerated disease is a feature in some patients [15]. However, this scenario is not unique to patients with HIV infection and the precise scale of the problem remains to be defined with more experience. Broadly the outcome of liver transplantation in hepatitis B infection and other indications are in line with non-HIV-infected liver transplant recipients over the first 3–5 years [12–17].

## 4.0 Indications for liver transplantation

The indications for liver transplantation include those directly related to the HIV infection itself or its mode of acquisition as well as diseases occurring incidentally in patients who also have HIV [12–17]. The former category include:

- hepatitis C
- hepatitis B
- drug hepatotoxicity (including acute liver failure).

### 4.1 Chronic liver disease and cirrhosis

In patients with chronic liver disease and cirrhosis the main indications for liver transplantation are [18]:

- decompensated liver disease with ascites, encephalopathy (important to exclude HIV-related dementia) or problematic varices;
- poor synthetic function, e.g. albumin < 30 g/l, INR > 1.5 and elevated serum bilirubin e.g. > 50 µmol/L;
- hepatocellular carcinoma detected during regular tumour surveillance (recommended at least 6 monthly in all patients with cirrhosis).

The guidelines above need to be adjusted for the likely lag time between referral for assessment and the transplant actually taking place. This is increasing quite quickly in the UK at present [9,18,19] and can be up to 1 year or greater. Patient characteristics associated with longer waiting times include blood group O [20] and small stature.

### 4.2 Hepatocellular carcinoma (HCC)

The selection criteria for HCC are normally what are referred to as the Milan criteria [21–24]. These are:

- no more than three tumour nodules
- no nodule greater than 5 cm in diameter
- absence of macroscopic portal vein invasion

- absence of recognizable extrahepatic disease (lymphadenopathy may complicate assessment in patients with HIV).

A few centres are accepting patients for liver transplantation with so-called 'extended criteria' or UCSF criteria [22–24] that accept single tumours of up to 6.5 cm in diameter as long as the cumulative diameters of all tumours do not exceed 8 cm. Patients with hepatocellular carcinoma do not receive any priority in the UK and these patients may need therapy to stabilize the disease while awaiting transplantation, usually with TACE (transarterial chemoembolization) [25,26]. It is important not to biopsy any hepatocellular carcinoma if the patient is still under consideration for liver transplantation as seeding of cells along the track of the biopsy needle has been the only cause of recurrent disease in some patients [27,28].

## 5.0 Contraindications for liver transplantation

Some pertinent specific issues include the following [9–11]:

- There is no specific upper age limit for transplantation but in assessing individual patients the guideline operative in the UK is that the patients should have at least a 50% chance of being alive 5 years after the transplant.
- Patients in whom alcohol is the cause or a co-factor in the cause of the liver disease must abstain from alcohol for at least 6 months before being transplanted and commit themselves to total abstinence afterwards. Some centres allow patients to go on the waiting list before the 6-month period is completed to avoid excessively long waiting times.
- Current intravenous drug use is universally seen as an absolute contraindication to liver transplantation. Patients who are stable on methadone or use cannabis are not absolutely excluded from transplantation.
- A relatively recent diagnosis of non-HIV-related malignancy does not necessarily contraindicate liver transplantation but the duration of recurrence free survival required before transplantation is varied (ranges from 1 to 5 years) and is determined by classifications based on the Penn registry data.

Current absolute contraindications to transplantation include:

- cholangiocarcinoma,
- extra-hepatic malignancy,
- uncontrolled extra-hepatic sepsis, e.g. endocarditis,
- total thrombosis of porto-mesenteric system,

- severe pulmonary hypertension (mean pulmonary pressure > 50–55 mmHg).

Factors that cause concern and may contribute to a decision not to accept a patient on the waiting list include:

- malnutrition,
- cardio-pulmonary disease,
- chronic renal impairment,
- poor motivation.

## 6.0 HIV-specific issues [13–17]

Current practice is targeting liver transplantation at patients with:

- CD4 counts > 200 cells/ $\mu$ l or > 100 cells/ $\mu$ l in the presence of portal hypertension,
- absence of viraemia,
- absence of AIDS-defining illness after immune reconstitution,
- therapeutic options available if HIV disease re-activates.

These criteria are somewhat empirical and may well change with expanded experience.

## 7.0 Post-transplantation

- Standard immunosuppression protocols are applied and there are little data yet that any specific regimens are better or worse in HIV-infected patients than in non-infected recipients.
- Bacterial, viral and fungal sepsis profiles seem to be similar to non-HIV-infected recipients.
- Calcineurin inhibitors interact with drugs in the HAART regimens [29,30]. The most important is effect of protease inhibitors reducing metabolism of calcineurin inhibitors (tacrolimus and cyclosporin) resulting in greatly decreased requirements (some patients require 1–2% of standard dose). It is essential that no alterations be made to the HAART therapy without consultation with the host transplant centre.
- Patients have significant emotional, psychological or counselling needs both pre- and post-transplantation. Preparation and emotional support, together with communication around prognosis, ramifications, future adaptation and quality of life are issues that may need attention. All studies show a marked improvement in quality of life, especially related to physical function, in HIV-negative patients who are successfully transplanted [31,32].

## 8.0 National database of HIV-positive individuals assessed for liver transplantation

- Given the rapidly evolving knowledge base in terms of selection of suitable candidates and outcomes it is important to monitor the situation closely through a nationally coordinated database.
- This would hold information on patients suitable for transplantation, time taken before transplantation is performed and outcomes for those transplanted and those who were not.
- Such a database would be an important measure of access to transplantation.

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### **Appendix: Participants at the Liver Transplantation Consensus Meeting, 18th June 2004, London**

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Edinburgh Royal Infirmary, Dr Sanjay Bhagani, Royal Free Hospital, London, Dr Gary Brook, Central Middlesex Hospital, London, Prof Andrew Burroughs, Royal Free Hospital, London, Prof Brian Gazzard, Chelsea & Westminster Hospital, London, Dr Richard Gilson, Royal Free and UCMS, London, Dr Mia Huengsberg, Whittall Street Clinic, Birmingham, Dr Ranja Kulasegaram, St Thomas' Hospital, London, Dr Clifford Leen, Western General Hospital, Edinburgh, Dr Aidan McCormick, St Vincent's Hospital, Dublin, Dr Geoffrey Haydon, Queen Elizabeth Hospital, Birmingham, Dr Mark Nelson, Chelsea & Westminster Hospital, London, Dr John O'Grady, King's College Hospital, London, Dr Caroline Sabin, Royal Free & UCMS, London, Dr Gabrielle Scapak, Royal Free Hospital, London, Dr Christopher Taylor, King's College Hospital, London, Dr Edmund Wilkins, North Manchester General Hospital, Mr Nigel Hughes, Gilead Sciences Limited (Observer), Dr Shafique Virani, Roche Products Limited (Observer).

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