BHIVA
UK and Ireland
Liver Transplantation Centres

Consensus Meeting on
Liver Transplantation in
HIV-positive Patients

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The prognosis of HIV has greatly improved in the past ten years. Conditions such as concurrent liver disease from viral hepatitis co-infections and drug-induced hepatotoxicity now pose some of the more significant risks to the health of HIV-positive people. We are at a stage where our confidence in the long-term survival of people with HIV infection is such that liver transplantation is justifiably being considered as a valid option for acute or chronic end-stage liver failure. Indeed, early data from the US on transplanted HIV-positive patients is very encouraging and there has already been some experience of liver transplantation in HIV-positive patients in the UK.

The need to consider transplantation for HIV-positive people has been recognised both by the UK and Ireland Transplant Centres at their Autumn 2003 meeting and the British HIV Association (BHIVA) Executive. Therefore, the time was opportune for a meeting of interested parties to discuss a unified approach to liver transplantation in the setting of HIV infection.
2.0 Introduction

This is a summary of the Consensus Meeting on Liver Transplantation in HIV-positive Patients, which was held on 18 June 2004, supported by Roche, Gilead and BHIVA. Invitees included representatives from all liver transplant centres in the UK and Ireland, HIV physicians from the same hospitals, members of the BHIVA Executive and Hepatitis Subcommittees and others who had a special interest in the subject (see Appendix). The booklet is intended to act as a quick reference to the findings of the meeting.

The format follows the meeting structure, with initial background presentations by Gary Brook, Sanjay Bhagani and John O’Grady (sections 3–5), followed by open group discussions (section 6), which looked at three important issues:

1. the clinical criteria for liver transplantation in HIV-positive patients;
2. dealing with barriers to transplantation in HIV-positive patients; and
3. setting up a national database of patients to be considered for transplantation.

Finally, the way forward is discussed (section 7).
3.0 Setting the scene: HIV treatment and prognosis

*Dr Gary Brook*

**Background**

At the beginning of the 21st century, HIV/AIDS still represents one of the greatest global threat to public health. The incidence is rising steadily throughout the world, but especially in developing countries, and it can present at any age. Since the late 1990s, heterosexually acquired HIV has become the predominant type in the UK, overtaking the early epidemic in gay men. Currently, about two-thirds of the 6000 annual HIV infections in the UK are of heterosexual origin [1] (Figure 1). Nonetheless, the incidence of new infections among gay men remains worryingly high.

![Figure 1: Number of new HIV diagnoses by year of diagnosis and probable route of exposure. Note: numbers, particularly for recent years, will rise as further reports are received.](image-url)
Should they be transplanted?

Let us consider a disease that leads to immune dysregulation and the development of opportunistic infections, ultimately leading to multisystem disease, including liver disease. There are particular concerns about cardiovascular disease and there is a worryingly rising incidence in developing countries. The adult mortality is about 20 per 1000 patient years of follow-up (PYFU). This data applies in fact to diabetes [2,3] but is much the same for HIV [4]. We, therefore, have to ask ourselves, ‘if we can transplant diabetics routinely, why not HIV-positive patients?’

Fall in HIV-associated mortality, but rise in liver-related deaths

The treatment and prognosis of HIV have changed dramatically over the years since its discovery in the 1980s. Although we are still unable to eliminate the infection, mortality rates have been slashed since highly active antiretroviral therapy (HAART) was introduced; for instance, the EuroSIDA study has shown that death rates fell eightfold between 1994 and 2001 [4]. Today, the prognosis for HIV is not necessarily different from that for a number of other chronic diseases, such as type 2 diabetes. For example, the UK adult mortality rate from HIV/AIDS is currently about 27 per 1000 PYFU compared with about 20 for type 2 diabetes. In many ways, the prognosis for HIV infection is actually better than that for type 2 diabetes.

Since life expectancy in HIV-positive people has increased, there is now an increasing gap between the number of new HIV infections and the number of people becoming seriously ill and dying. Moreover, in the early years, deaths were a direct result of the infection, being due to AIDS, but today, AIDS-related deaths have fallen from 93% to 62% while the other 40% die from other diseases, including liver disease [4]. In fact, having fallen between 1994 and 1998, liver-related deaths among HIV-infected people are now rising again, reaching 3.45 per 1000 PYFU in 2001 [4].

In contrast to liver disease, the incidence of other HIV-related complications has fallen. The incidence of central nervous system disease has fallen by 40% per year between 1994 and 2002, from 59 to 5 per 1000 PYFU [5]. Non-Hodgkins’ lymphoma has fallen by sixfold, from 19.9 to 3 per 1000 PYFU over the same period [6]. Moreover, data from the US Centers for Disease Control and Prevention (CDC) show that the incidence of 15 out of 26 AIDS-related illnesses fell during the 1990s [7].

Effects of treatment for HIV

HAART is able to increase the CD4 count, which is strongly correlated with long-term outcome. Other therapies, such as the treatment of HIV-related complications and the use of antibiotic prophylaxis, have also contributed to improvements in the prognosis of HIV-infected patients. For example, the
Concerted Action on SeroConversion to AIDS and Death in Europe (CASCADE), a study of about 7700 HIV seroconverters, has shown an 87% increase in AIDS-free survival and an 84% decrease in mortality rates between 1997 and 2001 [8]. This improvement correlates very strongly with triple antiretroviral therapy.

In 1996, HIV treatment kept people alive, but with quite a few side effects, and large numbers of pills had to be taken several times a day. In 2004, HIV treatment can be taken as three tablets once a day, and has better efficacy, better viral suppression and a better side-effect profile compared with earlier years.

HIV and liver transplantation

Since antiretroviral therapy can now provide long-term survival for HIV-infected patients, liver transplantation can be considered. In this context, it is particularly interesting that two drugs commonly used in liver transplantation, cyclosporin A and mycophenolate mofetil, may have anti-HIV activity. Moreover, there are significant interactions between the antiretroviral class of protease inhibitors (PIs), commonly used to treat HIV, and cyclosporin A, tacrolimus and sirolimus, so dose reductions are required for these immunosuppressives when PIs are used [9].

Conclusions

HIV is a treatable condition with a long-term prognosis that is steadily improving. Patients newly diagnosed with HIV in 2004, as far as we know now, are not going to die of HIV. Many of the problems faced by HIV-infected patients are evident at the beginning of the infection, and if the patient survives the early years well, the long-term outlook is good, whereas for someone with diabetes, the long-term problems steadily accumulate. Thus, for HIV-infected patients, we can now start concentrating on other therapies, such as liver transplantation.

Reference


4.0 Management and prognosis of HIV and hepatitis co-infection

Sanjay Bhagani

Introduction

There are currently over 21 licensed drugs available for the treatment of HIV, from zidovudine, which has been available since 1987, to atazanavir, which was introduced recently, and there are many more on the horizon.

Since the introduction of HAART in the mid-1990s, we have seen a decrease in the incidence of HIV and in AIDS-related deaths. However, the incidence of HIV is again rising in the UK, mainly in heterosexual men and women.

HIV/hepatitis B co-infection

Much of the increase in HIV reported recently in the UK is within the immigrant population, mainly from Africa, especially south-eastern Africa, which includes countries such as Zimbabwe and Botswana. The hepatitis B virus (HBV) affects around 400 million people worldwide, particularly in Africa and south-east Asia. The greatest prevalence of surface antigen-positive hepatitis B (HBsAg) occurs in those areas of Africa from which many UK patients have emigrated. The EuroSIDA study has shown that the rate of HIV/HBV co-infection, in terms of HBsAg, is now around 10% across Europe as a whole (Figure 1). Among HIV-positive people, 60–90% are also positive for HBV core antibody, signifying previous exposure to HBV.

![Figure 1: Prevalence of HIV and S-antigen-positive hepatitis B viral co-infection. RFH, Royal Free Hospital.](image-url)
A study by the CDC of over 16,000 HIV-positive people in the US found the highest rates of acute hepatitis B infection in Blacks, intravenous drug users and people with low vaccination status. The rate of chronic hepatitis B infection was around 8% in unvaccinated subjects. An interesting finding in this group was that lamivudine-containing HAART was associated with a reduction in chronic HBV infection (2.3% versus 7.8%).

**Prognosis: liver-related mortality**

It is clear that HIV-positive patients are more likely to develop chronic hepatitis B than HIV-negative patients. They tend to have higher HBV DNA levels, although liver enzyme levels (aspartate aminotransferase, alanine aminotransferase) may be lower. Thio et al. [1] have shown that being both HIV-positive and HBsAg-positive increases the risk of a liver-related death by 10-fold compared to infection with HIV or HBV alone (Figure 2).

![Figure 2: HIV/HBV co-infection: effect on liver-related mortality. HBsAg−, antigen-negative hepatitis B; HBsAg+, antigen-positive hepatitis B; HIV−, HIV-negative, HIV+, HIV-positive.](image)

**Treatment**

There is a decreased response to interferon in HIV/HBV co-infected patients, particularly when CD4 counts are low; this decrease in response is also seen in HIV-positive patients co-infected with hepatitis C virus (HCV).
Lamivudine has become one of the cornerstones for treating hepatitis B but unfortunately, as in mono-infected patients, there is a high rate of mutation. The emergence of the YMDD mutation is much higher in the HIV-positive population, with almost 100% of patients becoming lamivudine-resistant after 4 years [2].

The other licensed treatment option for HIV/HBV co-infection is adefovir. Data from 4 years of follow-up have shown that 10 mg adefovir once a day can decrease HBV DNA in lamivudine-resistant patients, with little resistance to adefovir. The Gilead 907 study [3] on tenofovir, which is currently only licensed for use in HIV infection, showed that this agent also has excellent anti-HBV activity and acts against the YMDD mutant.

**HIV/HCV co-infection**

**Rate of co-infection**

HCV affects approximately a third of the HIV-positive population. The rate is variable from country to country and cohort to cohort. For example, in the EuroSIDA cohort, 34% of HIV-positive patients were co-infected with HCV. In Germany, the co-infection rate is around 15%, but in countries with a high population of intravenous drug users, such as Italy and Spain, about 50% of HIV-infected patients are co-infected with HCV (Figure 3). While no national data are available from the UK; at both the Royal Free Hospital and the Chelsea and Westminster Hospital, about 8% of patients are HIV/HCV co-infected, whereas in Edinburgh, the number is probably approaching 40–50%. In addition, there is now a well-recognised epidemic of acute HCV in HIV-positive gay men in London.

![Figure 3: Prevalence of HIV and hepatitis C virus co-infection. HIV+, HIV-positive.](image-url)
Liver-related effects of co-infection

HIV/HCV co-infection accelerates the progression of liver disease. Benhamou et al. [4] showed that rates of fibrosis progression were much higher in HIV-positive patients than singly infected patients, and that a number of factors influence this, including CD4 count, age, sex and alcohol consumption. The incidence of cirrhosis in the first 10 years of developing HCV is also greatly increased in HIV-positive patients [5]. The effects on fibrosis and cirrhosis are age-dependent, so that by the age of 40 years, almost 50% of HIV-positive patients co-infected with HCV will have advanced fibrosis. This is certainly a cause for concern as the HIV-positive population ages due to the decrease in AIDS-related mortality.

HIV-related effects of HCV co-infection

There are also problems with HIV disease progression in HIV/HCV co-infected patients. A Swiss cohort study has shown that HCV co-infection accelerates HIV clinical progression [6], although this effect has not been repeated in other cohorts. There is also less of a CD4 response after starting antiretroviral therapy in patients who are HCV-positive [6].

Treatment options

There is some evidence that the adverse effects of HCV co-infection can be reversed to some degree with treatment. Benhamou et al. [7] found that the use of PI-containing HAART slowed the rate of cirrhosis progression in HIV-positive patients compared to therapy without PIs. Using Kaplan–Meier survival analysis, Qurishi et al. [8] showed that the use of HAART reduced liver-related mortality, and thus overall mortality.

Treatment problems

Treatment for HCV in the context of HIV co-infection is far from optimal. Results from the AIDS Pegasis Ribavirin International Co-Infection Trial (APRICOT) and RIBAVIC studies, which investigated the effects of interferon and ribavirin in co-infected patients, show that at best, the response rate is only 60%. Reasons for this may include:

- the use of low doses of ribavirin;
- the presence of HIV-related immunodeficiency;
- the presence of an advanced grade of fibrosis;
- the presence of a higher rate of steatosis;
- unfavourable baseline HCV virological features;
- a high treatment discontinuation rate of nearly 40%, due to side effects;
interactions between ribavirin and nucleoside reverse transcriptase inhibitors (NRTIs) leading, for example, to hepatic decompensation, pancreatitis and lactic acidosis with didanosine;

- high relapse rates; and
- low drug compliance.

Therapeutic protocols can be tailored to meet some of these problems, such as high discontinuation rates, low drug compliance and drug interactions, but therapy for HCV is still suboptimal in the face of HIV co-infection.

**HBV and HCV: effects on mortality**

Over the years, both HBV and HCV have continued to contribute to deaths from liver disease; however, whereas deaths from HBV have remained fairly constant over the last 10 years, HCV mortality has been rising in England and Wales over the same period. Consistent with the results of the EuroSIDA study discussed above, the GERMIVIC Study Group investigating mortality in HIV/HCV co-infected patients in France has shown very clearly that since the mid-1990s, overall mortality and AIDS-related mortality in particular have decreased, but liver-related mortality has risen sharply (Figure 4) [9].

A similar effect can be seen in mortality data from Italy, Spain, France and the US. All show that to variable degrees, mortality due to end-stage liver disease has increased since the use of HAART began in the mid-1990s (Figure 5).
HBV and HCV: drug effects

It is now becoming clear that almost every drug licensed for use in HIV has been associated with hepatitis or hepatotoxicity [10]. This is true for all three major drug classes, including non-nucleoside reverse transcriptase inhibitors (NNRTIs), NRTIs and PIs, and is a particular problem for patients with HBV or HCV co-infection.

HIV and hepatitis co-infection: effect on liver transplantation

Following the recognition of increased mortality due to liver disease in HIV-positive patients, the HIV Organ Sharing and Transplantation (HOST) project was set up in Italy a few years ago. The aim of the study was to assess the incidence of end-stage liver disease, the need for liver transplantation and the outcomes for HIV-positive patients. The results are still being collated, but preliminary data suggest that HIV-positive patients were excluded from the transplant list for various reasons, including CD4 count and viral load values, and thus did not prove too large a burden on the liver transplant service. A similar assessment, however, is needed in the UK.

Conclusions

HIV co-infection with HBV or HCV is common, and although treatments are far from optimal, they are improving. In the era of HAART, end-stage liver disease is a significant contributor to morbidity and mortality in HIV-positive patients.

Figure 5: Mortality due to end-stage disease in the era of HAART.
References

5.0 Liver transplantation in HIV-positive patients: the King’s College Hospital experience

John O’Grady

Background
The prognosis of HIV has dramatically improved in recent years, so that for patients with HIV and liver disease, the dominant and more life-threatening problem is likely to be liver disease rather than HIV. Infection with hepatitis C virus (HCV) occurs in 30% of HIV-positive patients and this co-infection leads to more aggressive liver disease. In fact, liver disease is now the most common non-HIV-related cause of death, accounting for approximately 40% of mortality in hospitals in the US.

Patient characteristics
The HIV orthotopic liver transplantation (OLT) programme ran for approximately 9 years from January 1995 to November 2003 and included 14 patients. The group was predominantly male (12 males, two females), with an age range of 26–59 years and a reasonable distribution in terms of the route of HIV acquisition. Before 1995, no liver transplants had knowingly been performed on anyone who was HIV-positive.

The most common reasons for transplantation in the group were end-stage chronic liver disease (n = 11), particularly hepatopulmonary syndrome, with a score of between 9 and 12 in the Child’s-Pugh classification of the severity of liver cirrhosis. The remaining three patients had acute liver failure.

Half of all the HIV patients (seven out of 14) were also HCV-positive (all genotype I). Of the seven who were not, four had co-existing HBV; all of these were DNA-negative, either naturally or with therapy, at the time of transplantation. Two patients had alcoholic liver disease (ALD), one of whom also had hepatopulmonary syndrome. The final patient had non-A non-B (NANB) hepatitis but was a carrier of HBV.

HIV characteristics
The diagnosis of HIV was made 3–18 years prior to OLT in 11 patients, and in the remaining three, HIV was diagnosed at the time of transplant for acute liver failure.

The mean CD4 count before transplant was 264 cells/µl (range 125–500). It is generally accepted that the CD4 count should be above 200 cells/µl except when there is also severe hypertension; however, there is little hard
evidence to support this notion. The viral load values before transplantation ranged from <50 to 197,000 HIV-1 RNA copies/ml. It is preferable for patients to have low viral load values if possible.

Nine of the patients were on highly active antiretroviral therapy (HAART) before OLT, and all patients were treated with HAART after transplantation.

**Immunosuppression**

Immunosuppression in this group of HIV-positive patients was almost totally with tacrolimus \( (n = 13) \); only one of the early patients was on a cyclosporin-based immunosuppression regimen, but was switched to tacrolimus after 7 months for efficacy reasons. A low-dose corticosteroid (20 mg prednisolone) was given with tacrolimus at the time of OLT, but only for an average duration of 4 months. So it seems clear that HIV disease does not contribute to any therapeutic immunomodulation that affects tolerance of the graft. No interleukin antibodies were used, which is usual for OLT in the general population in the UK.

**Survival data**

**Overall survival**

Using Kaplan–Meier analysis, the overall survival data show that 1-year survival for the 14 patients was 78.6%, 3-year survival was 70.2% and survival at 5 years was 64.3%.

**Effect of HCV**

When survival was divided into the HCV-positive \( (n = 7) \) and HCV-negative \( (n = 7) \) groups, the effect was clearly different. All seven patients who were not co-infected with HCV are still alive; there is 100% survival up to 8 years in that subgroup. However, only two of the seven HCV-positive patients are still alive, and these are the most recent transplant patients in this subgroup. Similar results, indicating that with HCV co-infection, there is more aggressive disease, are also seen in France, and to a lesser extent in Spain and the US. It is still considered worthwhile to perform a liver transplant in these patients but with a couple of modifications to the therapeutic protocol: (1) eliminate corticosteroids, and add mycophenolate mofetil as an alternative immunosuppressive drug; (2) try to get patients onto antiviral therapy as soon as possible after transplantation.

**Rejection data**

These patients showed the same tendency for rejection as standard liver transplant patients. At least one episode of rejection occurred in 35.7% of patients (five of 14); this was at 5–34 days post-OLT. This is very much in line
with standard figures of 35%. Rejection can be assessed in terms of severity using the rejection activity index (RAI). Three patients with an RAI of 3 were treated in the standard way with methyl prednisolone; however, the use of methyl prednisolone in patients co-infected with HCV is now avoided where possible, as it has become clear that this increases the risk for accelerated HCV-related disease. The other two patients (those with ALD) had an RAI of 5. They required two courses of methyl prednisolone in addition to mycophenolate mofetil. There was no chronic rejection in these HIV-positive patients, again in keeping with a 2% incidence of chronic rejection in the general population. The same immunosuppressive regimen was used as for HIV-negative patients, tacrolimus and prednisolone.

Infections

As with rejection, there is no difference in terms of infection rate between these HIV-positive patients and the general population of liver transplant patients. There were eight cases of bacterial infection: five, respiratory tract infections; one, wound infection; two, line-related infections. There was one case of viral infection due to cytomegalovirus and no fungal infections.

HAART-related issues

There have been three patients with quite severe toxicity related to HAART:

- one case of very severe zidovudine-induced rhabdomyolysis was seen 3 weeks after OLT;
- mitochondrial toxicity was observed 5 months after OLT in one of the patients co-infected with HCV; this was attributed to didanosine. A liver biopsy showed 80% steatosis, a decision was made to withdraw HAART and the patient subsequently died after suffering a stroke;
- hyperlactataemia was noted in one patient at the end of the first week after transplant. HAART was withdrawn and normal lactate levels returned. HAART was then resumed with no further sequelae.

Another concern for HIV-positive patients on immunosuppressive drugs is the variability of the tacrolimus regimens. Patients on protease inhibitors very quickly reach a stage where they require a drastically reduced dose of tacrolimus to maintain normal blood levels. For example, two of the patients on 0.5–1.0 mg tacrolimus per month were accumulating it to high levels and this caused some renal dysfunction.

Graft outcomes

Non-HCV co-infected recipients

All seven patients without HCV are alive today; for all, it is more than 2 years since their graft, and for one, it is up to 8 years. There has been no recurrence
of hepatitis B using standard hepatitis B immunoglobulin prophylaxis. All have normal graft function.

**HCV co-infected recipients**

The first five of these patients died an average of 25 months after the transplant (range 95–784 days). Three deaths were attributed to HCV recurrence, sepsis and multiple organ failure. One had a major stroke about 4 months after the transplant. The fifth death was due to allograft failure unrelated to HCV. The other two patients were not given steroids, but were given pre-emptive interferon and ribavirin 2–3 weeks after the transplant; however, they developed histological evidence of HCV recurrence at 130 and 176 days after OLT. One was treated with interferon and ribavirin at the time of histological recurrence, but the interferon was stopped, due to laboratory abnormalities.

**HIV and HCV**

Therefore, there are two patients with both HIV and HCV infection in the ‘new era’. Neither received interferon as planned because of complications; renal dysfunction in one case and cholestasis due to biliary restriction in the other. Both received a steroid-sparing immunosuppression regimen with mycophenolate mofetil. Both are doing very well after 18 months with no histological evidence of severe recurrent HCV disease at biopsy. No antiviral therapy is planned for the moment, but this will be reconsidered if annual biopsies show any change in liver function.

**HIV outcomes**

There are no longer any real problems in terms of HIV outcomes; any early problems of HAART toxicity have been largely eliminated. CD4 counts are very robust, with a median of 437 cells/µl (range 241–754). The latest viral load measurements are low at <50 HIV-1 RNA copies/ml in six of the seven recipients. In addition, there have been no new HIV-related complications.

**Conclusions**

It is clear that HCV co-infection can be a problem for HIV-positive liver transplant patients; however, with better management of current therapeutic protocols this may now be less of an issue. There is significant interaction between the different immunosuppressive drugs and HAART, but there is more understanding of the mechanisms involved and how to modify therapeutic regimens.

Finally, HIV patients present very standard rejection and infection profiles, compared with the general population. Thus, HIV *per se* is not a contra-indication to liver transplantation.
6.0 Small group work and feedback from the groups

6.1 Clinical criteria for liver transplantation in HIV-positive patients

Working group findings

In general terms, the criteria for considering liver transplantation in HIV-positive patients should be the same as if they were HIV-negative.

A patient who has developed fulminant liver disease due to antiretroviral therapy, and suffers multi-system toxicity, might have a greater risk of a poor outcome than those with fulminant liver disease for other reasons, but no data are available to answer this question.

In patients with hepatitis C, problems arise because of the rapid onset of end-stage liver disease, and an early transplant may not give them added years of life. Consistent management criteria for hepatitis C-infected patients are urgently required. Perhaps, just a few centres should concentrate on this group of patients until more experience is gained. At present, previous treatment for hepatitis C should not be a bar to liver transplantation.

HIV physicians should be made more aware about the possibility of liver transplantation, to achieve earlier referrals and to ensure the same standard of liver care for all patients.

Discussion

B Gazzard: Selection criteria must be based on the chances of a successful transplant, since the procedure is expensive and donors are limited. It is a question of who will benefit most. So far, we have just two HIV/HCV-infected people who are alive 18 months after a liver transplant.

The best candidates will be virologically undetectable, have no resistance, have a CD4 count >200 cells/µl and will be on highly active antiretroviral therapy (HAART); I think as many HAART options as possible should be left. They will not have a series of opportunistic infections, or a low CD4 nadir, and will never have been treated with ribavirin/interferon.

I think selection criteria should be exactly the same whether the patient has hepatitis C or not. Patients without hepatitis C who have lactic acidosis could do very well, for example. The same also applies to the small number of patients with hepatitis B.

G Baily: A patient with hepatitis B-related cirrhosis or tuberculosis-related hepatic failure shouldn’t be excluded from transplantation by the CD4 count.
J O’Grady: It is very important that the programme be clinically successful.

A McCormick: If we can achieve an 80% 2-year survival with 10 people, we can be more flexible afterwards.

B Gazzard: Criteria for patients with hepatitis C must be set carefully.

The difficult question is whether to exclude people who have not had hepatitis C treatment. Those who are naive to interferon and ribavirin with a good prognosis because of co-incident treatment, but a poor liver, are the best candidates. People who have failed treatment with ribavirin and interferon are clearly not the best group. There is currently no evidence at all that liver transplantation works for hepatitis C in the context of HIV.

J O’Grady: About 22 or 23 HIV/HCV-infected patients with a liver transplant in the US are doing well. If we do not feel there is a 50% chance of 5-year survival, we cannot legitimately allocate organs. We need the next 20 or 25 patients to come close to the 5-year survival curve for HIV-negative patients.

B Gazzard: How would you counsel a patient co-infected with HIV and hepatitis C on the chances of survival after a liver transplant?

R Gilson: The available data cover only 2 or 3 years of experience. We have no other information.

6.2 Dealing with barriers to transplantation in HIV-positive patients

Working group findings

Eight transplant centres in the UK and Northern Ireland have capability. They should all be provided with information and asked whether they are willing to perform liver transplants in HIV-infected patients or not. They may choose to refer such patients on.

The risk to the surgeon of HIV infection should be clarified in an evidence-based way, and those surgeons willing to do the operation should be identified.

UK Transplant, the National Health Service body that ensures donated organs are matched and allocated in a fair and unbiased way, should be given a document outlining proposals for liver transplantation in HIV-infected patients. The document should also be sent to the Scottish executive.

A document should be provided to HIV clinicans outlining conditions under which it is appropriate to refer patients for consideration for a liver transplant. This should include waiting times and the preferred condition of the patient. Dr O’Grady has agreed to write this, with assistance.
As well as HIV criteria, patients must be selected according to their overall chances of survival. Ischaemic heart disease and renal dysfunction are major co-morbidities that will affect selection. Renal dysfunction is the most important prognostic factor for outcome in liver transplantation. Other factors include drug dependence, for which there are national guidelines.

Discussion

J O’Grady: With a case of acute liver failure, subsequently found to have a high viral load, the same type of prophylactic treatment could be given as for a needlestick injury. Information about this treatment is available on the Health Development Agency website.

Question: Are any data available on patients transplanted for fulminant liver disease who have drug-induced toxicity due to anti-HIV drugs?

J O’Grady: We have three cases, all still alive. About three more were listed for transplantation and did not get it or died. You get no survival benefit for the first 2 years after transplantation. It is only after 3 years and beyond that you get survival benefit. For patients with ambitions to live 20, 30 or 40 years, the issue is about getting the best window of opportunity for a transplant.

J O’Grady: At the moment there is a donor pool that is excluded from use by people at risk of HIV infection, such as all gay men.

G Baily: Is the use of an orally active drug against hepatitis B an issue in transplantation? Also, there is a lot of lamivudine resistance. Should we use tenofovir in cirrhotic patients with hepatitis B?

J O’Grady: This group of patients should be treated for the hepatitis B viral load. It is very important that a patient is negative for hepatitis B DNA at the time of transplantation, otherwise the hepatitis B immunoglobulin regimens will not work. Lamivudine is superb in rendering a patient HBV DNA-negative in a short time frame. Adefovir is very disappointing because the dynamics of change are so slow, so it is not delivering. I know little about tenofovir yet, but it will probably be more like adefovir than lamivudine.

As hepatologists, we need to be tolerant in accepting referrals even if a transplant will not be necessary for 2 or 3 years.

B Gazzard: It is also very important not to generate a patient expectation that cannot be fulfilled, mainly because the patient is unsuitable.

The consensus criteria for referrals can be presented at a BHIVA meeting. I think the consensus document (including both the hepatology criteria and the HIV criteria) should go on the BHIVA website. Publication in *HIV Medicine* is possible.
6.3 Setting up a national database of patients to be considered for transplantation

Working group findings

There is a clear need for a national database of patients to be considered for liver transplant.

Pertinent questions are:

- What is the size of the problem in terms of end-stage liver disease in HIV infected patients?
- How many patients are currently being referred on for transplantation?
- What is the outcome of the referral?
- What is the outcome of listing patients?
- What is the outcome of patients who were not listed and not transplanted?
- Co-ordination between the transplant centres and the referring HIV centres is required.
- There should be a steering group led by the BHIVA and the Liver Advisory Group as a joint venture, so that there would be ownership from both transplant centres and units and the HIV treating centres. Some centres would co-ordinate.
- There would be notification to the co-ordinating centres that a patient has been referred for transplantation. A specific person at the co-ordinating centre would then contact the HIV centre for data, which would be collected every 6 months, both from the transplant centre and from the HIV centre.
- Issues of consent and data protection need to be addressed.
- In the early years, just one research co-ordinator based at one of the transplant units is likely to be needed. This person would be responsible to the steering group.

MR Nelson: Set-up costs would be around £30,000, plus overheads and hardware.

S Bhagani: It may be important to include all cirrhotics on the database, so that if they require transplantation it can be at the right time and they can be in as good a state as possible. However, there will be a lot of variability. Once networks have been established, we could finally include all cirrhotics.

New speaker: This is an opportunity to include all co-infected patients from large centres in the database, but not everyone will have good information about their patients and their liver co-infections.
C Leen: In Scotland, the hepatitis C database and the HIV database have been merged. The data may not be complete because not all HIV-infected patients have a hepatitis C test, but 900 patients are already in that cohort. The Health Protection Agency might be able to look at the same thing for England and Wales.

C Sabin: In addition, each of the centres is gradually developing a co-infection database, but these databases are not yet advanced enough to be usable for our purposes.

J O’Grady: At present, there is a very extensive database on patients who have been transplanted. Two years ago, UK Transplant considered setting up a specific database for HIV-positive transplant recipients, but decided that enough information had already been collected and that the proposal overlapped with European audits.

G Brook: I propose that a preliminary database working party be set up comprising Drs Bhagani, Sabin and Burroughs, who work on the same site and who can call on help from others. Perhaps someone from the BHIVA Executive should be included, and another hepatologist.

C Leen: A Scottish representative would be useful.

A Burroughs: Existing HIV databases can be used in many cases. I am working on hepatitis co-infection data.
7.0 Conclusions and future: the way forward

The following action points were agreed at the meeting:

To form a consensus writing group who will publish a short document outlining the case for increased liver transplantation in HIV-positive patients.

- First draft to be written by John O’Grady and Chris Taylor with additional work by Clifford Leen, Andy Bathgate, Richard Gilson and Gary Brook;
- Gain agreement from the wider group;
- Aim for publication in a peer-reviewed journal but also gain as wide a distribution as possible to ensure that all relevant physicians and patients are aware of the issues;
- UK Transplant and the relevant Scottish and Irish bodies involved in co-ordination of organ donation to be targeted in this education process;

A working group will look at the logistics of setting up a database of HIV-positive patients with cirrhosis or otherwise potentially in need of a liver transplantation;

- Steering group of Caroline Sabin, Andrew Burroughs, Sanjay Bhagani with help from Clifford Leen, Andy Bathgate and Gary Brook. Others to be co-opted as necessary;
- To work closely with the UK and Ireland Transplant Centres group and BHIVA;

As a group we should work in every way possible to educate colleagues about the problem of liver disease in HIV-positive patients and the need to consider transplantation;

- There will be a liver transplantation session at the BHIVA Autumn Conference;

A further meeting of this group may be convened in the future if necessary.
# Appendix

## 8.0 Appendix

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<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
<th>Specialty</th>
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<tbody>
<tr>
<td>Dr Michael Allison</td>
<td>Addenbrooke’s Hospital, Cambridge</td>
<td>Liver</td>
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<td>Dr Guy Baily</td>
<td>Royal London Hospital</td>
<td>HIV</td>
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<tr>
<td>Dr Andy Bathgate</td>
<td>Edinburgh Royal Infirmary</td>
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<td>Dr Sanjay Bhagani</td>
<td>Royal Free Hospital, London</td>
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<td>Dr Gary Brook</td>
<td>Central Middlesex Hospital, London</td>
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<td>Prof Andrew Burroughs</td>
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<td>Prof Brian Gazzard</td>
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<td>Dr Richard Gilson</td>
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<tr>
<td>Dr Geoffrey Haydon</td>
<td>Queen Elizabeth Hospital, Birmingham</td>
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<tr>
<td>Dr Mia Huengsberg</td>
<td>Whittall Street Clinic, Birmingham</td>
<td>HIV</td>
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<td>Dr Ranja Kulasegaram</td>
<td>St Thomas’ Hospital, London</td>
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<td>Dr Clifford Leen</td>
<td>Western General Hospital, Edinburgh</td>
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<td>Dr Aidan McCormick</td>
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<td>Dr Mark Nelson</td>
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<td>Dr John O’Grady</td>
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<tr>
<td>Dr Caroline Sabin</td>
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<td>Dr Gabrielle Scapak</td>
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<td>Dr Christopher Taylor</td>
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<td>Dr Edmund Wilkins</td>
<td>North Manchester General Hospital</td>
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<tr>
<td>Mr Nigel Hughes</td>
<td>Gilead Sciences Limited (Observer)</td>
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<tr>
<td>Dr Shafique Virani</td>
<td>Roche Products Limited (Observer)</td>
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