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Chapter 12

The Role of Liver Transplantation in HIV Positive Patients

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1. Introduction

1.1. Burden of liver disease

In developed countries, the management and treatment of HIV-1 infection was revolutionised after the introduction of combined anti-viral therapy (cART) in 1996. The major outcome was the reduction of AIDS and AIDS-related deaths (1). Such was the success of cART, that now more than 50% of deaths in HIV positive patients on cART are not directly related to HIV infection or AIDS (1-3). The D:A:D (data collection on adverse events of anti-HIV drugs) study demonstrated that liver disease had become the commonest cause of a non-AIDS related death overtaking cardiovascular disease (2). Given the similar transmission routes, unsurprisingly nearly two-thirds of deaths were secondary to chronic hepatitis C virus (HCV) infection, 17% secondary to chronic hepatitis B virus (HBV) infection and 3% due drug-induced liver injury related to cART (2). Other liver-related aetiologies amongst HIV positive individuals include alcohol, non-alcohol related liver disease (NAFLD), hepatocellular carcinoma (HCC) (Table 1). HIV positive patients present with the same clinical sequelae of chronic liver disease as their HIV negative counterparts but tend to present at a younger age but with a markedly reduced survival rate after the first episode of decompensation (4). In HIV-positive patients with compensated cirrhosis an increased mortality rate is associated with age > 50 years, MELD score > 11 and poor control of HIV disease (5).

1.2. Viral aetiologies

One third of patients with HIV infection are co-infected with chronic HCV, and the majority of deaths in HIV-positive patients with ESLD can be attributable to HCV infection(6). HCV is transmitted via contaminated blood or blood products. At-risk groups include

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intravenous drug users, patients with haemophilia who were exposed to contaminated infusions of plasma derived factor VIII or X concentrate, men who have sex with men (MSM) and individuals who have sex with IVDUs (7). Vertical transmission is also possible and is more likely if the mother is HIV-positive. A more recent trend is the increase in the number of new cases of acute HCV in MSM who are HIV-positive acquired via sexual transmission (8, 9).

HIV infection clearly affects HCV-related liver disease. The combination of HIV/HCV co-infection is associated with a reduced rate of spontaneous HCV RNA clearance and therefore an increased likelihood of developing chronic HCV infection (10). Once HCV infection is established then a more rapid fibrosis progression rate is evident (11). The development of cirrhosis tends to occur on average 15 years earlier than in HCV mono-infected individuals (12). Predictors of fibrosis progression include detectable HIV viraemia, low CD4+ counts, baseline necro-inflammatory activity on liver biopsy and increased alcohol consumption (>50g per day) (13, 14). HIV/HCV co-infected patients have a poorer survival following the first episode of decompensation; median estimated survival of only 13 months (4). Mechanisms for this accelerated fibrosis rate appear to be multi-factorial and include a weaker adaptive immune response of CD8+ cells, the increased number of the pro-fibrogenic CD8+ cells and relative reduction in CD4+ cells, the presence of insulin resistance and reduction of interleukin – 10 expression(15-19, 19, 20). The HIV virus cannot enter hepatocytes directly but it can upregulate pro-fibrotic pathways e.g. transforming growth factor B-1 which further activates hepatic stellate cells (10).

Treatment of HCV in patients with HIV is more difficult compared to HCV-monoinfected patients and is associated with an increased side-effect profile. At present pegylated interferon and ribavirin are the only licensed medications for the treatment of HCV in HIV/HCV co-infected patients. Compared to HCV mono-infected patients, end-of-treatment (29-62%) and sustained virological response rates (SVR) are inferior (17-35%) (21-26). The use of the newer protease inhibitors in the treatment of HCV in HIV-positive patients has only been limited to the trial arena. Preliminary data from the 110 Phase 2 study demonstrate similar outcomes to monoinfection with 74% SVR 12 in telaprevir triple therapy group (n=38) vs 45% standard of care (n=22); with no breakthrough in HIV RNA and similar side effect profile to monoinfection treated with telaprevir.

HIV-positive patients commonly exhibit evidence of previous HBV infection, whereas 10% of the HIV-positive population have evidence of chronic HBV infection (27). Vertical transmission of HBV remains the most common route of infection worlwide, whilst sexual transmission and percutaneous transmission is more likely in Europe and North America (28, 29). HIV-positive patients that contract HBV infection are less likely to clear the virus, a quarter of patients will develop chronic HBV infection, especially those with low CD4+ cell counts (30). HIV/HBV co-infected patients also have increased HBV DNA viral loads compared to HBV mono-infected patients, which also translates into an increased risk of developing HCC (31).

HIV/HBV co-infection related – morbidity is considerably less when compared to HIV/HCV co-infected patients. This is due to the use of nucleoside and nucleotide reverse-transcriptase inhibitors (lamivudine, emtricitabine and tenofovir) that are used in cART regimens and have both anti-HIV and anti-HBV activity.

Given that co-infection with HBV and HCV are the leading causes of liver disease amongst HIV-positive patients, the incidence of hepatocellular carcinoma (HCC) is expected to rise and the MORTAVIC and French Mortalite studies have both demonstrated an increasing number of deaths attributable to HCC (6, 32). HIV-positive patients presenting with HCC are younger at presentation (52 versus 64 years, $p<0.0001$), are more likely to be symptomatic at presentation, have multiple tumours at presentation, and have advanced disease compared to HIV-negative patients (31, 33).

1.3. Non-viral aetiologies

Awareness of drug-induced liver injury or cART-induced hepatotoxicity is increasing. Deciding on the culprit drug is often difficult because of the use of combination therapies. Recognised patterns of liver injury include hypersensitivity, idiosyncratic hepatotoxicity, mitochondrial toxicity, an immune reconstitution syndrome and hepato-steatosis (34-38). Acute liver failure resulting from cART is uncommon. The development of non-cirrhotic portal hypertension (NCPH) secondary to cART in particular to didanosine is an emerging disease entity (39). The pathogenesis of NCPH appears to be linked to a pro-thrombotic state, an acquired protein S deficiency. The spectrum of histological findings include nodular regenerative hyperplasia, hepatoportal sclerosis, peri-portal fibrosis and sclerosing portal venopathy (40-42).

The D:A:D study also highlighted that the prevalence of the metabolic syndrome has increased over the last decade from 19% in 2000-2001 to 42% in2006-2007 (43). This is likely to result in an increase in the prevalence of NAFLD, given that NAFLD is the hepatic manifestation of the metabolic syndrome. There is limited data available on the risk factors for NAFLD in HIV-positive patients but attention has focused on the role of cART because of its negative effects of insulin resistance, glucose metabolism and lipid metabolism. Central adiposity, male sex, low serum high-density lipoprotein levels, raised triglycerides levels and an increased ratio of alanine aminotransferase to aspartate aminotransferase have been suggested as risk factors for the development of NAFLD (44).

1.4. Selection criteria for liver transplantation

Irrespective of liver aetiology, HIV-positive patients with liver disease need to be managed in a multi-disciplinary environment by an experienced HIV physician and Hepatologist. Given their rapid disease kinetic, HIV-positive patients with end stage liver disease (ESLD) need to be identified early. Specific guidelines for LT in HIV-positive patients evolved as our understanding of the specific issues faced by this cohort improves. Current US National

Institutes of Health multi-center trial guidelines for LT in HIV positive patients with chronic liver disease are listed in Table 2. UK guidelines have similar requirements.

The Model for End-Stage Liver Disease (MELD) score has been adopted by transplant centers across Europe and North America to ensure the appropriate allocation of organs to those at the highest risk of death (45). Although MELD has been well validated in the HIV-negative patients, there have been mixed reports on its sensitivity in HIV-positive patients with ESLD (46). One prospective study reported similar MELD scores at the initial LT assessment for HIV-positive and HIV negative patients despite those with HIV having a significantly shorter cumulative survival time (880 versus 1427 days, p=0.04) (47). Another observation made by the same study was that the MELD score did not differentiate between survivors and non-survivors (13 versus 15, p = 0.6). Two more recent studies, both prospective, however have suggested that the MELD score may actually be a sensitive predictor of patient outcome (47, 48). Multivariate analysis of predictive factors of mortality demonstrated that the MELD score was independently associated with death (HR per 5-U increase 1.53, p<0.001). The MELD score also remained predictive of death on subgroup analysis of HIV/HCV patients (without HCC) and on comparison with HIV negative historical controls, the mortality rates were significantly higher for HIV-positive patients in each MELD category (48). In the second study, which matched 167 HIV-positive patients with 792 HIV-negative patients the baseline MELD score was the only significant predictor of pre-LT mortality in HIV-positive patients after controlling for $CD4^+$ counts and HIV RNA levels (47).

Optimal control of HIV disease is an important prerequisite for HIV-positive patients undergoing consideration for LT. In patients with portal hypertension, splenic sequestration of T lymphocytes can lead to a fall in the CD4+ T cell count. In such cases a CD4+ cell count > 100 cells/uL is acceptable. A fall in the $CD4^+$ cell count can also be precipitated by the use of pegylated interferon. In our opinion, CD4+ T cell percentages may represent a more sensitive indicator of immune reconstitution in HIV-positive patients with portal hypertension. HIV-positive patients undergoing evaluation for LT also require an undetectable HIV viral load (< 50 copies/mL) except for those that presently acutely. The inability to achieve an undetectable HIV RNA viral load before LT has been associated with an increased mortality rate (HR 3.5, p<0001)(48). In addition to good therapeutic options available in the pre-transplant period, HIV-positive patients require future cART options based upon their previous regimens and HIV phenol- genotype resistance testing. It is not inconceivable that certain HIV-positive patients may not be able to tolerate cART medications pre-LT due to brittle liver synthetic function. This group should not be automatically excluded from LT as long as HIV control is deemed possible post LT by the multidisciplinary team. cART intolerance post-LT, however has been identified as an important predictor of survival (49).

A thorough knowledge of past opportunistic infections is required. A distant history of an opportunistic infection in a patient that was not taking cART is not a contraindication to LT unless there is no effective treatment available for possible recurrence post-LT. Absolute

contra-indications include multidrug resistant HIV, resistant fungal infections, chronic intestinal cryptosporidiosis, progressive multi-focal leukoencephalopathy and central nervous system lymphoma.

2. Post liver transplantation

Standard surgical techniques with conventional arterial, venous and biliary anastomosis are recommended. One concern highlighted is the possible risk of transmission of HIV to the surgical team. The risk of HIV however is low and is substantially lower than the risk of transmission of HBV and HCV (50). In the event of HIV exposure, current regimens provide effective prophylaxis (51). As HIV infection is associated with a pro-thrombotic state, concerns have been raised regarding an increased risk of vascular complications post transplantation (52). Recent data from our Institution demonstrated an increased an increased incidence of hepatic artery thrombosis compared to HIV negative patients (12% vs. 3.2%, p=0.016) (53). Given the increased pro-thrombotic risk, the introduction of prophylactic subcutaneous heparin (5000 units every 8 hours) is recommended once the international normalised ration (INR) is below 1.5 and the platelet count is greater than 50 x 10^9 cells/L.

Immunosuppression should be tailored to the individual taking into account aetiology of liver disease, renal function, risk factors for the metabolic syndrome and specifically to HIV patients the possible interactions with combined anti-viral therapy (cART) medications. Dual immunosuppression with calcineurin inhibitors (CNIs) and cortico-steroids is recommended post-LT. Target trough levels in the first 3 months should be the same as HIV negative patients (cyclosporin, 100-250 ng/ml; tacrolimus, 8-10ng/ml). Utilising data from HCV mono-infected patients post-LT, rapid withdrawal of cortico-steroids should be avoided due to the association of a more severe recurrence of HCV (54). We therefore recommend that prednisolone, which is usually commenced at 20mg daily, be withdrawn by a slow taper at 3 months. Anti-fungal prophylaxis (fluconazole 50mg daily) should be given for a minimum of 3 months post-LT. Episodes of acute cellular rejection (ACR) should also be managed as one would in HIV negative patients namely moderate-severe episodes be treated with a 3-day course of intravenous methylprednisolone (1g daily). Consideration of the introduction of mycophenalate mofetil (MMF) after the 2nd episode of ACR is recommended.

Both tacrolimus and cyclosporin are metabolised via the P450 cytochrome. In addition, non-nucleoside reverse-transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs), which are commonly part of cART regimens, are also metabolised by the same pathway, therefore increasing the risk of drug – drug interactions. NNRTIs (e.g. efavirenz) decrease serum CNI concentrations by induction of the P450 cytochrome whilst PIs (e.g. ritonavir and lopinavir) are inducers resulting in increased CNI concentrations (55). We have used tacrolimus doses as low as 1mg per week in certain individuals. Raltegravir, a novel HIV-1 integrase inhibitor, is not metabolised via the P450 cytochrome and has been used successfully post transplantation in combination with nucleoside reverse-transcriptase inhibitors and

standard CNI doses (56). Meticulous monitoring and surveillance is required to reduce the possibility drug-drug interactions and toxicity.

2.1. Outcomes post liver transplantation

Initial case series of HIV positive patients undergoing liver transplantation were associated with poor outcomes (57, 58). It is important to note that this was before the introduction of cART regimens. Retrospective data since has however demonstrated an increasing understanding of the complexities faced by this unique patient cohort. To date, the largest study analysed data provided by the US United Network for Organ Sharing LT database (1997-2006) and identified 138 HIV-positive patients (59). Overall survival rates were inferior in the HIV positive cohort compared to a comparative HIV negative cohort (n = 30.520) at 2- and 3-years post transplant (70% and 60% vs 81% and 77%, $p < 0.047$). Considerable data however was missing from the HIV cohort raising the possibility that HIV infection may not have been optimally treated prior to LT.

2.2. Hepatitis C co-infection

The present literature clearly demonstrates that outcomes in HIV/HCV co-infected patients is suboptimal when compared to other aetiologies. Studies to date have only described small numbers from single centres. Survival rates have ranged between 64-88% at 1 year and 33-51% at 5 years (49, 60-62). The only prospective cohort study of 89 HIV/HCV co-infected patients and 235 HCV mono-infected controls performed at 17 US centers which was recently published, warrants further analysis (63). The authors evaluated the 2 cohorts for a median 2.7 years and 2.4 years respectively (ref). Compared to HCV controls, HIV/HCV co-infected patients were younger (49 vs. 54 years, $p<0.0001$), had lower BMI at listing (25 vs. 28 kg/m^2, $p<0.0001$), more HBV co-infection (6% vs. 1%, $p=0.02$), were more likely to receive a non-heart beating graft (17% vs. 4%, $p = 0.0002$), longer median warm ischaemia time (41 vs. 21 minutes, $p =0.001$) and less use of tacrolimus-based (versus cyclosporine) initial immunosuppression (58% vs. 80%, $p<0.0001$). 1- and 3-year patient survival rates were 76% and 60% in HIV/HCV cohort compared to 92% and 79% in the HCV cohort ($p<0.001$). Graft loss was also significantly higher in the HIV/HCV cohort ($p<0.001$). Multivariate analysis identified HIV infection as the only baseline factor associated with increased risk of death (HR 2.3, $p = 0.002$) and graft loss (HR 1.9, $p = 0.01$). Analysis of the HIV/HCV co-infected cohort only identified that receipt of a combined kidney-liver transplant (HR 3.8, $p=0.003$), BMI<21 kg/m^2 at enrolment (HR = 3.2, $p=0.01$), receipt of an anti-HCV positive donor (HR 2.5, $p=0.03$), and older donor age (HR 1.3 per decade, $p=0.04$) were significant predictors of reduced graft survival. A previous study identified a MELD score > 20, intolerance of cART post transplantation and high post-transplant HCV viral loads as predictors of mortality post-LT (49). The cumulative incidence of acute cellular rejection (ACR) requiring treatment was significantly higher in HIV/HCV patients compared to HCV-mono-infected patients (39% vs. 24% at year 3, HR 2.1, $p=0.01$)(63). 50% of the cases of ACR occurred within the first 21 days following LT.

Recurrence of HCV post-LT is universal but an accelerated disease course is well recognised in HIV/HCV co-infected patients (62, 64). HCV recurrence, especially the aggressive severe fibrosing cholestatic variant of recurrent hepatitis C (FCH) and sepsis are the leading causes of death post-LT amongst HIV/HCV co-infected patients (61, 62, 65-68). Although no reliable markers are available to identify patients who will develop FCH, higher HCV viral loads immediately after LT at week 1 and week 2 may be an indicator for those at risk (69). A French study highlighted the rapid fibrosis progression rates in HIV/HCV co-infected patients (2.4 versus 1.4 score, p=0.01) at 24 months post-LT (62). The likelihood of progression to a fibrosis score ≥ 2 was also significantly higher in HIV/HCV co-infected patients ($p<0.0001$).

Re-treatment of HCV recurrence post-LT is associated with an increased side-effect profile and poorer treatment outcomes compared to HCV patient's pre-LT. Pegylated interferon and ribavirin remain the 'standard of care' for a minimum of 48 weeks irrespective of viral genotype. Treatment for recurrent HCV post-LT in our institution is instigated when histological disease is demonstrable ($F\geq2$) although some groups have commenced treatment within 90 days of LT (70, 71). The concurrent use of didanosine and ribavirin is not recommended due to increased risk of mitochondrial toxicity (72). cART regimens that contain abacavir should also be avoided due to the impairment of ribavirin phosphorylation (73).

2.3. Hepatitis B co-infection and non-viral aetiologies

Patients co-infected with HBV and non-viral aetiologies including those that present with acute liver failure, have excellent short and long-term outcomes post LT. Reported median survival at 1 year ranges between 75-100% and 100% at 5 years (74)(75). The largest prospective study to date in HIV/HBV co-infected patients was conducted in 21 patients for a median of 42 months with no patient suffering graft loss (76).

The key difference between HIV/HBV and HIV/HCV co-infected patients is the presence of highly potent anti-viral agents against HBV in the therapeutic armamentarium. Patients co-infected with HBV and receiving cART will undoubtedly be receiving an oral nucleoside/nucleotide analogue that will have anti-viral actions against both HIV and HBV. Tenofovir in conjunction with emtricitabine (Truvada) is recommended (76, 77). The use of these highly efficacious, potent oral agents results in the majority of patients undergoing LT with an undetectable HBV viral load. Immuno-prophylaxis with Hepatitis B Immunoglobulin (HBIg) is also recommended in the post LT period indefinitely. Reported data on the use of HBIg and oral anti-viral agents has demonstrated that this combination is highly effective at preventing HBV recurrence even in those who have a detectable HBV viral load at the time of LT (78). Data on patients with HIV and non-viral liver disease undergoing LT is limited. Our experience suggests that these patients have similar survival rates as HIV negative patients (74).

2.4. Hepatocellular carcinoma

Studies specifically evaluating outcomes of LT in HIV positive patients with HCC have been limited. One such study compared 21 HIV positive patients with 65 HIV negative patients (79). The authors demonstrated a trend towards a higher drop-out rate on the waiting-list amongst HIV positive patients (23% vs 10%, p = 0.08) with 16 HIV positive and 58 HIV negative patients eventually undergoing LT. HIV positive patients were younger at the time of LT (50 versus 58 years, p<0.002) and following LT, observed survival was comparable at 1 and 3 years (81% and 74% versus 93% and 85%, p=0.07). HCC recurred in 5 HIV positive patients (31%) and in 9 HIV negative patients (15%) at a median time of 11 and 18 months respectively. Predictive factors for HCC recurrence before LT included Child Pugh C (p=0.003), being outside the Milan criteria radiologically (p=0.0008) and AFP progression > 15 ug/L per month on the waiting list (p=0.005). Factors predictive of HCC recurrence post LT which took into account pathological factors included those outside the Milan criteria (p=0.01), those outside the UCSF criteria (p=0.03) and those with evidence of satellite nodules (p=0.03) and microscopic (p=0.005) or macroscopic vascular invasion (p=0.001). Further studies are required to evaluate the influence of HIV infection on the impact of HCC post-LT but this indication in the HIV population will become more relevant.

2.5. HIV disease post transplant

At present no standardised cART regimen is utilised, but instead is tailored to the individual patient reflecting known resistance and mutations. The re-introduction of cART post-LT also varies between individual centers, with some continuing cART throughout the transplant period whilst others re-introduce the medication between 4-14 days. We recommend that cART medication should be re-introduced once liver graft function has normalised thereby avoiding the possibility of confusion with the other causes of graft dysfunction immediately post-LT.

In a recent study of HIV/HCV patients bacterial infections were identified as the principal aetiological agents of post-LT infections and viral infections were secondary to uncomplicated herpes simplex virus (HSV) infections (80). Risk factors associated with severe infections included a pre-LT MELD score of > 15 (HR 3.5, 95% CI 1.7-7.1, p = 0.001), history of category C AIDS-defining events (HR4.0, 1.9-8.6, p<0.001) and non-tacrolimus based immunosuppression (HR 2.5, 1.3-4.8, p=0.006). The same study also suggested that opportunistic infections namely CMV disease, disseminated HSV, invasive fungal infections and tuberculosis were increased in HIV positive patients, affecting 11% of their cohort. It is important to note these 'opportunistic' infections however can occur in HIV negative patients post LT. This study also did not have a HIV negative comparative group therefore not allowing the authors to be able to demonstrate that these deemed opportunistic infections were due to HIV infection only. Reassuringly reported data from other studies fails to demonstrate a higher incidence of opportunistic infections in comparison to HIV negative patients (81).

- **Viral:**
  Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis D, Hepatitis E
  CMV
  HSV

- **Non-viral:**
  Alcohol
  cART induced liver injury (e.g. NNRTI, NRTI, PI)
  Immune reconstitution
  Non-alcohol related fatty liver disease
  Non-cirrhotic portal hypertension
  Opportunistic infections

cART, combined anti-retroviral therapy; CMV, cytomegalovirus; HSV, herpes simplex virus; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor

Table 1. Causes of liver disease in HIV-positive individuals

- **The criteria for liver transplantation are met**
- **$CD4^+$ cell count > 100 cells/uL (> 200 cells/uL with a previous history of opportunistic complications).**
- **HIV viral load < 50 copies/mL (using ultrasensitive Amplicor Monitor PCR assay)**
- **Absence of AIDS-defining illness**
- **Absence progressive multi-focal leukoencephalopathy, chronic intestinal cryptosporidiosis (> 1 month) or primary CNS lymphoma**

Table 2. Criteria for Liver Transplantation in HIV-positive individuals

3. Conclusion

HIV-positive patients established on cART are expected to have good long-term outcomes. Given the success of cART, more patients are likely to present with the long-term sequelae of ESLD. In an era of organ/donor shortage, more of these patients are likely to present as potential candidates for liver transplantation. Our understanding of the issues faced by this patient cohort both pre- and post-liver transplantation continues to improve but challenges remain in the management of HIV-HCV coinfection. The data discussed in this article certainly represents a learning curve of the experience of this patient cohort. Liver transplantation in HIV-positive patients is a viable option and should be considered for carefully selected patients in transplant units with multi-disciplinary expertise.

Abbreviations

AIDS – Acquired immunodeficiency syndrome
cART – Combined anti-retroviral therapy
DILI – Drug induced liver injury
HBV – Hepatitis B virus
HCV – Hepatitis C virus
HCC – Hepatocellular carcinoma
HIV – Human immunodeficiency virus
LT – Liver transplantation
NAFLD – Non-alcohol related fatty liver disease

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