Liver transplantation for liver disease caused by hepatitis C virus infection

Hepatitis C is an important problem that often requires liver transplantation. However, outcomes have not improved in line with liver transplants for other indications. This article explores the issues surrounding this difficult area of transplant hepatology.

Hepatitis C virus (HCV), an infection discovered as recently as 1989, is set to be the leading cause of liver-related morbidity and mortality in the western world. There is probably a large pool of individuals unaware of their diagnosis as infection is usually silent and liver disease, when it occurs, has an insidious onset. Only a proportion of infected patients (5–20%) develop significant liver disease manifest as cirrhosis, chronic liver failure and primary liver cancer. However, chronic HCV infection is a common cause of morbidity; complaints of malaise and fatigue predate the onset of hepatic dysfunction. Treatment is available but is no panacea; it is costly, hindered by uncomfortable side effects and often ineffective.

Patients may be asymptomatic in the early stages of the disorder and may present with advanced liver disease or hepatocellular carcinoma when treatment is least effective and most hazardous. Patients with cirrhosis have an annual risk of developing hepatocellular carcinoma of between 1 and 4%. Those with end-stage liver disease face a bleak future; liver transplantation is often the only therapeutic option. Even then, HCV infects the grafted liver in most cases and can re-ignite the cycle of liver damage and liver failure.

The existence of HCV had first been postulated in the 1950s. The discovery of hepatitis A and B viruses did not account for all cases of infective hepatitis, triggering a 30-year hunt for the cause of non-A, non-B hepatitis. It was in the late 1980s that genomic techniques allowed Choo and colleagues (1989) working for the Chiron Corporation to make the critical breakthrough. HCV and the clinical consequences have been well documented since, with more than 6500 citations.

Liver transplantation remains the best and often only treatment for liver failure or for smaller hepatocellular carcinoma arising as a consequence of HCV infection. HCV with or without hepatocellular carcinoma is now the leading indication for liver transplantation in Europe and the United States and is likely to remain so in the immediate future, although continued increases in alcohol consumption and a global epidemic of obesity, associated with non-alcohol-related fatty liver disease, remain important causes of cirrhosis and hepatocellular carcinoma.

A decade ago hepatitis B virus infection was considered a relative contraindication to liver transplantation with a prohibitive mortality because of the risk of graft infection and the high probability of subsequent graft damage and loss. That scenario was transformed by effective antiviral agents. The current situation with HCV is reminiscent of that with hepatitis B virus in the early 1990s. HCV also causes graft infection in most cases and can lead to fibrosis and eventually graft failure in many. Those at highest risk of HCV-related graft loss can now be identified more readily, but strategies to minimize graft infection are needed desperately, while attempts at reducing graft injury are at an early stage. Re-transplantation for graft loss after HCV infection remains contentious, particularly in an era of donor scarcity.

This article explores current issues surrounding transplantation for HCV-related disorders, the natural history of the disease in liver transplant recipients and current approaches to treatment and immune suppression as well as the critical issue of re-transplantation for graft failure.

Natural history of HCV infection following liver transplantation

HCV infection in the grafted liver is a very different disease to that in immune competent patients pre-transplant. HCV infects the graft in most cases, but the subsequent clinical course is variable. A proportion, up to 10%, develops a remorseless, rapidly progressive course, a proportion progresses more steadily to cirrhosis and liver failure after 5–10 years, while some, perhaps 30%, pursue a more indolent course.

Progressive fibrosis

Following transplantation, fibrosis is more common than before liver transplantation and is progressive more frequently. Analysis of fibrosis is based on histological scoring systems (such as the Ishak score, where 0 is no fibrosis and 4 equates with cirrhosis). Although numerical scores are used, these do not represent linear progression but a histological definition (it might have been preferable if the scores were A to E, to describe non-lin-

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ear progression). A more useful measure is the time to achieve a certain fibrosis stage.

A study of European and US patients (Berenguer et al, 2000) analysed 284 cases transplanted for HCV-related liver disease in California and Valencia. There was a significant difference in progression rates between the US and European cohorts (P<0.001). The proportion of patients achieving Ishak stage 4 fibrosis (corresponding to cirrhosis) was 0%, 3%, 7%, 7% and 10% at 1, 2, 3, 4 and 5 years in the US cohort and 1%, 6%, 12%, 26% and 31% at the same intervals in the European cohort. The expected time to graft cirrhosis worsened markedly in both cohorts over a period of 6 years; for those transplanted 1990–1, the median time was 9.8–13 years, in 1992–3 it was 6.8–7.5 years and in 1994–5 it was 3.5–3.9 years. This led the authors to hypothesize that changes in patient management over that period were responsible for the change; the use of more borderline organs was the most likely explanation.

A German series (Neumann, 2004) published a retrospective analysis of 183 patients who received a liver transplant for HCV and had survived at least until a 1-year follow-up biopsy could be performed. Of these 16.4% (n=30) developed stage 4 fibrosis (cirrhosis) after a median duration of 1045 days after transplantation.

An American study prospectively followed up 227 patients transplanted for HCV-related liver disease. Biopsies were performed at 6 months and then at 6–24-month intervals. Advanced fibrosis, defined as bridging fibrosis or cirrhosis, developed in 1%, 11%, 25% and 41% of patients at 1, 3, 5 and 6–10 years (Yilmaz et al, 2007).

Mortality rate

Gane et al (1996) published outcome data for HCV-infected liver transplant recipients in the King's/Cambridge programme. Those transplanted before the discovery of HCV were tested retrospectively using contemporary samples. Between January 1982 and April 1994 149 patients infected with HCV were transplanted out of a total of 946 transplants. Cumulative survival for HCV-infected transplants was 79% at 1 year, 74% at 3 years and 70% at 5 years compared to non-infected transplants of 75% at 1 year, 71% at 3 years and 69% at 5 years (P=0.12); 27 patients (18%) lost their graft at a median of 303 days.

A 2002 study using United Network for Organ Sharing (UNOS) data for transplants between 1992 and 1998 showed that HCV increased the risk of death (hazard ratio=1.23; 95% confidence interval=1.12–1.35) and the risk of graft failure (hazard ratio=1.30; confidence interval=1.21–1.39). Outcome was noticeably worse in females with an increased risk of death (hazard ratio=1.56; confidence interval=1.35–1.81), and an increased risk of graft failure (hazard ratio=1.51; confidence interval=1.34–1.70) (Forman et al, 2002).

In light of Berenguer et al (2000)'s observations of worsening outcome with time, the UNOS Registry data of all liver transplants for HCV in the USA from 1991–2001 were reviewed (Thuluvath et al, 2007). There was no corresponding increase in mortality rates or decline in graft survival. Out of a total of 28 193 transplants in this period 7459 patients had transplants for HCV. The 3-year mortality rate was 76.3% for those transplanted between 1991 and 1993, 78.4% between 1994 and 1997 and 75.4% between 1997 and 2001. There was no significant trend in mortality with time. However, in the same period 3-year mortality rates for transplants unrelated to HCV improved significantly from 77.5% in 1991–3 to 81.4% in 1994–7 and 80.0% in 1997–2001; this improvement with time was significant (P<0.001). Overall the 3-year mortality was 78.5% for HCV-related transplants *vs* 81% for HCV-unrelated transplants (P=0.001) (hazard ratio=1.14; 95% confidence interval=1.05–1.23).

An Italian series (Gringeri et al, 2007) looked at all patients placed on the liver transplant waiting list between January 1999 and June 2004. They analysed 373 patients who waited between 0.1 and 72.2 months (median 20.0 months.) Univariate analysis revealed a number of poor prognostic factors, encephalopathy, ascites, poor nutritional status, Childs–Pugh class C cirrhosis, UNOS class 2, HCV infection and a bilirubin greater than 2 mg/dl (34 mmol/litre). However, a multivariate analysis revealed only HCV-related cirrhosis as an independent prognostic factor with a 5-year survival rate of 67% as opposed to 79% for those without HCV infection (P<0.001). A total of 53 patients (14%) died on the waiting list without receiving a transplant.

The Cambridge and UK experience reveals no significant difference in mortality or graft survival between 1994 and 2006 between patients transplanted for HCV-related disease and those transplanted for other indications (*Figures 1* and *2*).

However, when patients transplanted for HCV were compared to a cohort of patients transplanted for alcohol-related liver disease using a large pan-European database (Mutimer et al, 2006) there were echoes of the UNOS data. Since 1987 there has been steady improvement in the outcome of transplants for alcohol-related liver disease, but no corresponding improvement in the HCV cohort.

Barber et al (2007) used an alternative method to look at survival post-liver transplant; patient life expectancy or alternatively life years lost were compared to the normal adult population. HCV scored very poorly; those transplanted for primary sclerosing cholangitis (another condition that can affect the graft) lost 3.2 years and those transplanted for alcohol-related liver disease lost 14.2 years, while patients transplanted for HCV lost 23.9 years compared with age-matched controls.

Thus HCV carries a clear and greater risk of graft failure and death than many other disorders post-liver

transplant. However, most people who die after a liver transplant for HCV do not die of graft infection with HCV (*Figure 3*); only 14 of 58 deaths were HCV related and the remainder were attributed largely to cardiovascular disease, infections and cancer.

Rapidly progressive cholestasis

A small but significant proportion of patients follow an aggressive course (Dickson et al, 1996). These patients have an especially poor prognosis with graft loss within 12–24 months. The clinical picture is one of early and severe cholestasis with characteristic histology of centrilobular ballooning degeneration and bridging fibrosis. Unfortunately, these patients often follow an even more rapid and progressive course in subsequent transplants (see below).

Risk factors

A number of pre-transplant, perioperative and post-transplant factors identify those with a poor outcome after liver transplantation for HCV and are summarized in *Table 1*.

Pre-transplant

A worse overall baseline level of liver disease (Model for End-Stage Liver Disease (MELD) score, UNOS status, Childs–Pugh grade) is associated with a worse prognosis following liver transplantation for HCV-related liver disease. Renal function, measured by log serum creatinine, is also associated with a poor prognosis (Ghobrial et al, 2001). However, these prognostic factors are not disease specific and reflect fitness for the procedure and/or other organ involvement. Pre- and post-transplant diabetes mellitus has a poor prognosis, probably in a non-specific manner by increasing co-morbidity and end organ damage. However, this is more pronounced for HCV-related liver disease than for other indications and HCV-related fibrosis is accelerated in the presence of diabetes mellitus, which is considered a pro-fibrotic factor in HCV-positive recipients (Foxton et al, 2006). Other disease-specific factors associated with a poor prognosis and accelerated HCV-related fibrosis are human immunodeficiency virus co-infection (Roche and Samuel, 2007), infection with genotype 1b (Gane et al, 1996) and female gender (Belli et al, 2007). A number of studies have shown that high pre-transplant HCV RNA levels are associated with severe and early recurrence of disease (Ghobrial et al, 2001).

Perioperative

Donor age has been identified in a number of studies as a major determinant of the severity of graft infection with HCV and poor prognosis (Belli et al, 2007) such that a donor age of greater than 60 years in a female recipient has a risk of severe graft infection of close to 100%. HLA mismatch is also a marker of the severity of graft infection, especially for HLA B14 and HLA DRB1*04 (Belli et al, 2000). The length of warm ischaemia time before implantation is also related to a poor prognosis (Ghobrial et al, 2001).

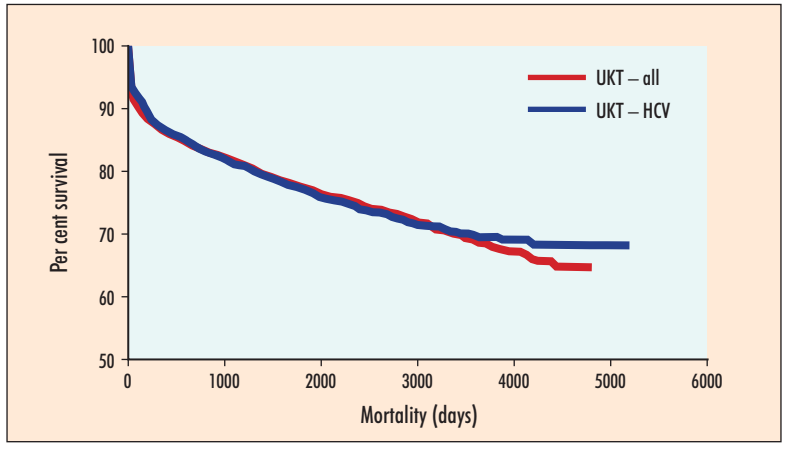

Figure 1. Patient survival in UK transplants (UKT) 1994–2006. Patients transplanted for hepatitis C virus (HCV) infection vs all indications. There is no difference between the curves, P=0.748 by Logrank test (author's own data).

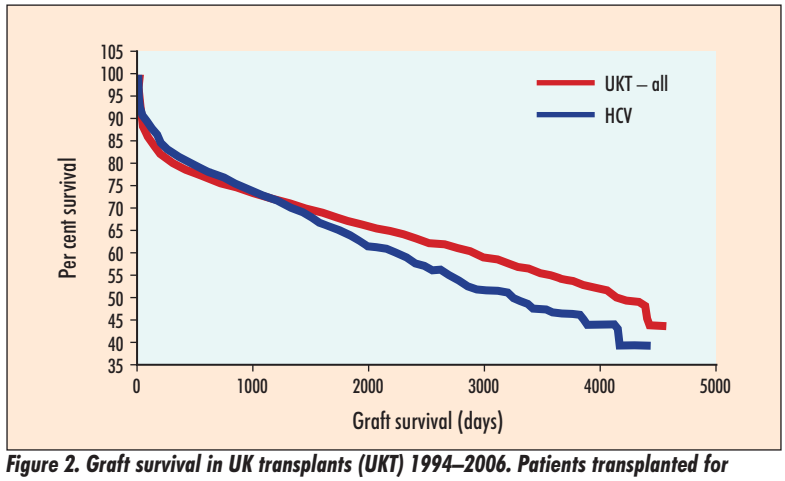

Figure 2. Graft survival in UK transplants (UKT) 1994–2006. Patients transplanted for hepatitis C virus (HCV) infection vs all indications. There is no difference between the curves, P=0.367 by Logrank test (author's own data).

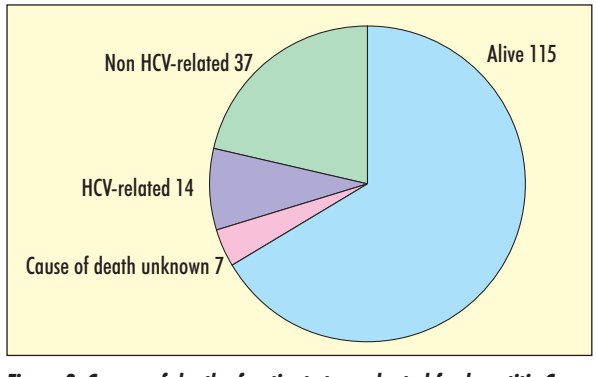

Figure 3. Causes of death of patients transplanted for hepatitis C virus (HCV) infection in Cambridge from 1994 to 2007.

Postoperative

Just as high titres of HCV RNA are associated with poor prognosis, early graft infection confers a high risk of severe graft damage (Berenguer et al, 2000).

Table 1. Risk factors associated with progressive fibrosis and a poor prognosis after liver transplantation for hepatitis C virus-related liver disease

Pre-transplant	High hepatitis C virus RNA levels
	Female sex
	Infection with genotype 1b
	Human immunodeficiency virus co-infection
	Diabetes
	Serum creatinine
Perioperative	Donor age
	HLA mismatch
	Warm ischaemia time
Post-transplant	High hepatitis C virus RNA levels
	Early hepatitis C virus graft infection
	High levels of immune suppression
	Steroid boluses
	Anti-lymphocyte globulin
	Diabetes
	Biliary complications
	Cytomegalovirus infection
	Histological changes: steatosis, cholestasis, hepatocyte ballooning

Immune suppression regimens undoubtedly play a role in progressive fibrosis after graft infection with HCV. However, with important exceptions, it appears that the intensity of immunosuppression is more important than the choice of agent (Roche and Samuel, 2007). Corticosteroid boluses and the strategy of rapidly reducing steroid regimens are associated with a poor prognosis. The use of anti-lymphocyte globulin as part of induction is also associated with a poor outcome (Everson, 2002).

Postoperative diabetes, cytomegalovirus co-infection and episodes of cytomegalovirus infection are associated with a poor outcome; cytomegalovirus infection may be a surrogate marker of the intensity of immune suppression (Roche and Samuel, 2007).

One correctable factor is the intriguing finding (which mirrors the authors' clinical experience) of accelerated disease in those with concurrent biliary tract complications (Katz et al, 2006); there appears to be a synergistic effect of the two pathological processes.

Immune suppression

Tacrolimus and ciclosporin

Calcineurin inhibitors have been the mainstay of immune suppression since the 1980s and the superiority of one over the other has been debated at length with contrasting data. A meta-analysis of five medium-sized studies (Berenguer et al, 2006) showed no difference between the drugs for mortality, graft survival, biopsy-proven acute rejection or fibrosing cholestatic hepatitis. Although no clinical differences have been observed to date between the calcineurin inhibitors, there are intriguing data limited to in-vitro studies that ciclosporin and not tacrolimus inhibits HCV replication specifically at therapeutic doses through an interferon-independent pathway via blockade of the intracellular signal cyclophilin and regulation of HCV RNA polymerase (Watashi et al, 2005).

Mycophenolate mofetil

Mycophenolate mofetil has also been shown to inhibit HCV replication in vitro. It has synergistic effects with interferon-α and ciclosporin. However, studies of clinical outcome have been mixed. Some studies have shown a decrease in viral load with mycophenolate mofetil (Jain, 2002), while others have shown no change or even an increase (Zekry et al, 2004).

A large US retrospective analysis of UNOS data (Wiesner et al, 2005) showed improvements in long-term graft survival and mortality for patients transplanted for HCV discharged home on tacrolimus, corticosteroids and mycophenolate mofetil compared to those discharged on only tacrolimus and steroids. Results reached statistical significance with a 4-year mortality of 81% for the mycophenolate mofetil group *vs* 77% for the group without ($P<0.0001$) and 4-year graft survival of 76.4% in mycophenolate mofetil group as opposed to 72.9% in those without ($P<0.0001$.)

Corticosteroids

Corticosteroids were the first immune suppressive agents to be used in liver transplant recipients and remained an important option for many years. However, their continued use has been questioned, especially in HCV infection, as alternatives have different metabolic and cardiovascular risk profiles.

Corticosteroid boluses and treatment have been associated with increased viral load and increased histological activity (Barcena et al, 2006; Henry et al, 2007). It has also been shown that corticosteroid-free regimens are safe and effective with no increase in the rate of rejection (Wietzke-Braun et al, 2004). Most deaths following transplantation for HCV-related liver disease are unrelated to the liver but instead to malignancy, infections and cardiovascular disease. This should be an important factor in selecting immune suppressive regimens. Patients receiving minimal corticosteroid therapy have fewer metabolic complications such as diabetes mellitus (Lladó et al, 2006) and obesity, with improved cardiovascular risk profile.

For those treated with corticosteroids, slow tapering withdrawal is associated with a better outcome than rapid withdrawal (Brillanti et al, 2002), although the authors' practice is to avoid corticosteroids altogether.

Antiviral therapy

The use of antiviral therapy in transplantation is controversial. As described, high pre-transplant HCV

RNA levels and early graft infection are important risk factors for hepatic fibrosis. With this in mind, two antiviral strategies have been tried: pre-transplant and post-transplant.

Pre-transplant treatment has been limited because of unacceptable rates of mortality and morbidity in an already fragile population. An American study of patients on the transplant waiting list found that less than half of patients screened were suitable for treatment, usually because of haematological parameters. In one study, of 15 patients who were treated, there were 23 adverse events, 20 of which were serious and one fatal (Crippin, 2002).

Post-transplant antiviral treatment has been used more extensively, although the supporting evidence is not robust. There are few randomized trials to prove benefit and in all studies there is a high incidence of worrying side effects that include death from graft loss as a result of interferon-induced rejection. There is also a small but significant proportion of patients who tolerate treatment, achieve sustained virological response and still develop cirrhosis and graft loss (Mukherjee, 2006)

Carrión et al (2007) described their experience of 81 patients with HCV graft infection post-transplant. These patients were divided into 54 with mild disease and 27 with severe disease. Patients assessed as mild were randomized to either receive no treatment or pegylated interferon-α2b (peg-IFN) and ribavirin for 48 weeks. Patients assessed as severe (cholestatic hepatitis) were also treated with peg-IFN and ribavirin. Results were impressive; 70% of untreated mild disease progressed one stage in 1 year as opposed to 26% of those treated for mild disease (P=0.001) and 54% of those treated for severe recurrence. Sustained virological response was achieved in 48% of those treated for mild disease and 18.5% of those treated for severe disease. However, the high morbidity and mortality associated with treatment in this study cause one to draw breath. Ten patients died during the study on treatment, nine unsurprisingly in the severe group, but one in the mild disease group. There were also four episodes of rejection within the treatment groups and none in the untreated. Despite trial conditions only 21 out of 27 patients with mild disease completed therapy.

Berenguer et al (2008) studied 89 patients with HCV graft infection post-transplant who were treated with either interferon alone or a combination of peg-IFN and ribavirin and compared outcomes with 75 disease-matched controls. Survival was the primary end-point and treatment seemed to confer a survival advantage; of the 44 patients who died during follow up, 18 died on treatment (20%), whereas 26 died in the control group (35%) (P=0.05). Sustained virological response was achieved in 37% of patients on treatment. However, the control group was significantly older than the treated group (mean age 59 years as opposed to 54 years; P=0.0001). In the control group there were two deaths from de novo cancers and three recurrent hepatocellular carcinomas whereas there were no cancer deaths in the treatment group. In the treated group there were two deaths secondary to interferon-induced rejection and two further deaths resulting from a combination of progressive HCV infection and interferon-induced rejection. Four patients progressed to cirrhosis and liver failure despite achieving sustained virological response.

There is undoubtedly a role for antiviral treatment in recurrent HCV infection, but the risks and complications are great. The authors suggest antiviral therapy is used with care and in selected cases.

Re-transplantation

Donated livers for transplantation are a precious and increasingly rare commodity. Re-transplantation for graft failure caused by HCV is a contentious issue because of perceived poor outcomes. Balanced against this is the investment of time and resources already placed in the transplanted patient. The severity of HCV-related graft disease increases with each subsequent transplant (Berenguer, 2003). The distinction is not always made clear between those requiring a second transplant because of HCV infection and those with another cause of graft failure with concurrent HCV infection; the outcomes may be very different.

Published data suggest that re-transplantation for HCV-related graft failure is questionable. In a Spanish single centre survey, 18 patients were listed for re-transplantation; six died on the waiting list and eight of the 12 patients who received a transplant died with a median survival of 8 months (Berenguer, 2003). A similar US single centre study yielded more promising results (Ghabril et al, 2007); 48 patients re-transplanted with HCV infection were compared to 60 patients re-transplanted without HCV. In keeping with previous findings the HCV cohort had younger donors (P<0.001). There was no significant difference in survival between the two cohorts at 1 and 3 years (79% HCV *vs* 63% non-HCV and 71% *vs* 63% respectively). Twenty-five of the 48 patients were re-transplanted for HCV-related disease, with a similar survival to those with HCV infection re-transplanted for other reasons.

However, a larger multicentre US study using the UNOS database (McCashland et al, 2007) examined re-transplants between 1996 and 2004, and found 43 patients had re-transplantation for graft infection with HCV with a 1-year survival of 69% and 3-year survival of 49% (compared to 73% 1-year survival and 55% 3-year survival in those re-transplanted for reasons unconnected to HCV). This difference does not appear significant and numbers are small, but an overall 3-year survival rate under 50% should prompt reflection on the wisdom of this approach, which would be untenable according to current UK liver advisory group guidelines. Multicentre European and UK data are awaited and an open debate should begin about the utility of second and subsequent transplants with HCV infection.

Conclusions

Hepatitis C-related liver failure is a major problem for the foreseeable future. It demands a large proportion of the donor liver pool and the management of the condition pre- and post-transplant remains problematic especially in the cohort of patients with aggressive graft infection. There are no clear guidelines for immune suppression. While survival rates for first transplants are good and comparable with other diseases (although not improving as quickly), antiviral therapy and re-transplantation remain thorny issues. BJHM

Conflict of interest: none.

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KEY POINTS

- Hepatitis C virus is the most common indication for liver transplantation in the western world and will remain so in the foreseeable future
- Hepatitis C infection recurs post transplantation but the natural history differs from that of the immunocompetent patient.
- Improvements in outcome in transplantation for hepatitis C have not mirrored improvements in outcome for transplants for other indication.
- Heavy immune suppression and high levels of virus are important predictors of poor outcome
- Antiviral therapy is problematic and limited by side effects and tolerability in the transplant and peri-transplant setting.