

# Human Herpesvirus 6 and Human Herpesvirus 7: Emerging Pathogens in Transplant Patients

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## Abstract

Human herpesvirus 6 (HHV-6) and HHV-7 are two recently identified  $\beta$ -herpesviruses, genetically related to human cytomegalovirus (CMV). Infection with both viruses is common worldwide with rates of seropositivity in adults over 90%. Infection with both viruses usually occurs in early childhood. In this age group HHV-6 is a cause of febrile illness including exanthem subitum, and likewise, primary HHV-7 infection has been associated with febrile illness. Similar to the other human herpesviruses, in particular CMV, the viruses have the potential for enhanced pathogenicity in the immunocompromised host. Active infection with both viruses is common following bone marrow or solid organ transplantation, most likely through reactivation of recipient's virus or re-infection considering their high prevalence in the population. Both viruses can be detected by PCR in the peripheral blood of healthy individuals and although the significance of blood-borne transmission is not clear, a preliminary study suggested that it was not significant for HHV-6. However, there is growing evidence that these viruses may be medically important in the post-transplant period. In bone marrow transplant patients HHV-6 has been associated with a range of clinical disease including encephalitis, interstitial pneumonitis, early and late graft failure and bone marrow suppression. There is also growing evidence for potential interactions among the  $\beta$ -herpesviruses in liver and renal transplant patients. HHV-6 infection has been associated with an increased risk of developing CMV disease and opportunistic infections and HHV-7 infection has also been linked to an increased risk of CMV disease.

*Key Words:* Human herpesvirus 6; Human herpesvirus 7; Immunocompromised; Transplantation; HHV-6; HHV-7

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## 1. Introduction

Human herpesvirus 6 (HHV-6) and HHV-7 are two relatively recently discovered  $\beta$ -herpesviruses, genetically related to human cytomegalovirus (CMV) (for recent reviews Black & Pellett, 1999; Clark, 2000). Both HHV-6 and HHV-7 are highly prevalent worldwide and infection usually occurs in early childhood (Briggs *et al*, 1988; Clark *et al*, 1993). Within this age group, HHV-6 is a causative agent of febrile illness including exanthem subitum (ES) (Yamanishi *et al*, 1988; Hall *et al*, 1994) and primary HHV-7 has also been associated with febrile illness (Tanaka *et al*, 1994).

HHV-6 and HHV-7 are more closely genetically related to each other than CMV and together form the

*Roseolovirus* genus of the  $\beta$ -herpesvirinae subfamily (Gompels *et al*, 1995; Nicholas, 1996). Two variants of HHV-6 have been defined (termed A and B) based on differences in genetic and biological properties, although no serological test can distinguish between antibodies to either variant.

HHV-6 is tropic for T-lymphocytes and neural cells although it has the ability to infect a wide variety of cell types *in vitro* including monocytes, epithelial cells, endothelial cells and fibroblasts. CD46 has been shown to be a cellular receptor for both HHV-6A and B (Santoro *et al*, 1999). Activated CD4<sup>+</sup> T cells appear to be the preferential target for fully permissive replication *in vivo* (Takahashi *et al*, 1989). Using an antigenemia test to detect active HHV-6 infection following

liver transplantation, the majority of infected cells in peripheral blood mononuclear cells (PBMC) were reported to be lymphocytes, with some monocytes also infected (Lautenschlager *et al*, 2000).

The tropism of HHV-7 appears to be more restricted, utilising CD4 as a cellular receptor to infect T cells (Lusso *et al*, 1994). However, the cellular tropism may be wider based on the detection of viral antigen by immunohistochemistry and includes monocytes/macrophages (Kempf *et al*, 1998; Kempf *et al*, 1997).

As is characteristic of all herpesviruses, HHV-6 and HHV-7 persist in the host following primary infection. This persistence is likely to include both a latent state with infectious virus only produced during episodes of reactivation, and chronic replication with continuous or frequent but intermittent production of infectious virus. Salivary glands are a candidate site for chronic infection with HHV-6B and HHV-7 as both have been frequently detectable in saliva (Aberle *et al*, 1996; Wyatt & Frenkel, 1992). Together with epidemiological links of parent to infant infection (Mukai *et al*, 1994; Thawaranantha *et al*, 2002), these findings suggest that salivary contact is likely to be an important vehicle for transmission of both viruses.

Both viruses can be detected in the peripheral blood of healthy individuals by nested PCR when sufficient quantities of DNA are tested (Clark *et al*, 1996; Kidd *et al*, 1996). The actual sites of latency have yet to be established, although candidates for HHV-6 include monocytes (Kondo *et al*, 1991) and early bone marrow progenitor cells (Luppi *et al*, 1999). HHV-6B is more frequently detected in PBMC compared to HHV-6A. HHV-6B has also been shown to be reactivated from latency by infection with HHV-7 but not by T cell stimulation *in vitro* (Katsafanas *et al*, 1996). In addition, HHV-7 was reported to reactivate HHV-6 in children with a past history of ES (Tanaka-Taya *et al*, 2000). The stimuli for HHV-6 or HHV-7 reactivation *in vivo* are uncharacterised, but are likely to include immunosuppression. Razonable *et al* (Razonable *et al*, 2002) investigated  $\beta$ -herpesvirus reactivation in critically ill immunocompetent hosts. Reactivation of HHV-6A, detected by PCR analysis of PBMC, was found in 53 of 101 patients with only 1 further patient being positive for HHV-6B. None of the control group showed evidence of HHV-6 reactivation. HHV-7 DNA was detected more commonly (18/50 PCR positive) compared to the critically ill patients (14/101 PCR positive).

The risk of transmission through blood transfusion or exposure to blood products is presently unknown. The majority of blood donors will be seropositive for HHV-6 and HHV-7 and the viruses have been detected in the PBMC of blood donors (Wilborn *et al*, 1994a; Kozireva *et al*, 2001). In the latter study active HHV-7 infection based on the detection of viral DNA in plasma was identified in 12 of 113 (11%) of blood donors with latent HHV-7 in PBMC. Although it remains a potential mode of transmission the frequency and clinical outcome of transfusion-mediated HHV-6 or HHV-7 infection have

not been adequately addressed. Lunel *et al* (1991) investigated the role of HHV-6 as a causative agent of non-A, non-B posttransfusion hepatitis. No HHV-6 seroconversions or significant rise in HHV-6 antibody titres were identified in their blood recipients suggesting that at least in adults, the risk of blood-borne HHV-6 transmission was low.

## 2. HHV-6 Infection Following Bone Marrow Transplantation

Infection with HHV-6 following bone marrow or stem cell transplantation is common and considering the high seroprevalence in the population, is likely to result predominantly from reactivation of recipient's virus or reinfection from the donor. Restriction fragment length polymorphism analysis has shown in one case that pre-transplant and post transplant HHV-6 strains were the same (Yoshikawa *et al*, 1992). However, the virus has been detected by PCR in 28% of bone marrow samples from healthy individuals suggesting its ability to be transmitted from the donor to the recipient (Gautheret-Dejean *et al*, 2000) and cases of primary infection with the donor marrow as the source of virus have been reported (Lau *et al*, 1998). It has been suggested that detection of HHV-6 DNA by PCR in either the donor's or recipient's PBMCs pre-transplant is a good predictor of developing active HHV-6 infection following allogeneic BMT (Yoshikawa *et al*, 1998).

Depending on the study, the prevalence of HHV-6 infection post bone marrow transplantation ranges from 28% to 75% (median 48%) (Dockrell & Paya, 2001). Rates of detection of HHV-6 infection have been reported to be higher in allogeneic compared to autologous bone marrow transplant patients (Yoshikawa *et al*, 2002) and allogeneic bone marrow compared to allogeneic stem cell transplants (Maeda *et al*, 1999).

Both HHV-6A and B infections have been detected in the post-transplant period, although the latter is more common. HHV-6 infections tend to occur within the first 4 weeks following transplantation (Maeda *et al*, 1999; Imbert-Marcille *et al*, 2000; Yoshikawa *et al*, 2002).

Following bone marrow transplantation, case reports and selective studies have associated HHV-6 with a range of clinical disease including encephalitis, interstitial pneumonitis, thrombotic microangiopathy, early and late graft failure and bone marrow suppression (Singh & Paterson, 2000; Drobyski *et al*, 1994; Cone *et al*, 1993; Matsuda *et al*, 1999; Rosenfeld *et al*, 1995; Drobyski *et al*, 1993). *In vitro* studies have demonstrated suppressive activity of both variants of HHV-6 on the maturation and growth of normal bone marrow precursors, including granulocyte/macrophage, erythroid and megakaryocytic lineages (Isomura *et al*, 1997; Isomura *et al*, 2000).

Table 1 summarises the prospective studies that have been carried out in bone marrow or stem cell transplant patients. In some studies there has been no clear association between HHV-6 and disease when the whole study population was analysed (Wilborn *et al*, 1994b; Kadakia

**Table 1.**

Prospective Studies of HHV-6 Infection Following Bone Marrow/Stem Cell or Solid Organ Transplantation.

Bone marrow/Stem cell transplant		Solid organ transplant		
Study	Observed Disease	Study	Transplant Type	Observed Disease
Wilborn et al (1994)	GvHD*	Schmidt et al (1996)	Liver	None
Appleton et al (1995)	GvHD* (PCR in skin/rectal biopsies)	Herbein et al (1996)	Liver, Renal	None
Kadokia et al (1996)	None	Osman et al (1997)	Renal	None
Wang et al (1996)	Delayed granulocyte/platelet engraftment	Ratnamohan et al (1998)	Renal, Pancreas	Fever
Chan et al (1997)	None	Griffiths et al (1999)	Liver	Graft rejection
Cone et al (1999)	Rash*	Kidd et al (2000)	Renal	None
Maeda et al (1999)	Delayed platelet engraftment	Lautenschlager et al (2000)	Liver	Graft dysfunction*
Ljungman et al (2000)	Delayed platelet engraftment	Rogers et al (2000)	Liver	CNS disease Fungal infections
Imbert-Marcille (2000)	Myelosuppression and fever	Mendez et al (2001)	Liver	CMV disease
Yoshikawa et al (2002)	Rash*	Humar et al (2002)	Liver	Opportunistic infections, CMV disease, graft rejection*

\*analysis on subgroup of patient population; GvHD, graft versus host disease. Updated and adapted from Clark(Clark, 2000).

et al, 1996; Wang et al, 1996; Appleton et al, 1995; Chan et al, 1997; Cone et al, 1999). However, in subgroup analysis the virus was linked to graft versus host disease (GvHD) (Wilborn et al, 1994b), delayed engraftment (Wang et al, 1996) and rash (Cone et al, 1999; Yoshikawa et al, 2002). In other studies (Maeda et al, 1999; Imbert-Marcille et al, 2000) associations between HHV-6 and delayed engraftment, myelosuppression and fever were reported when the whole study populations were analysed. In addition, HHV-6 viral load was significantly correlated with delayed platelet engraftment in stem cell transplant recipients (Ljungman et al, 2000). Most prospective studies have reported a low incidence of the disease types identified by case reports.

### 3. HHV-6 Infection Following Solid Organ Transplantation

HHV-6 is frequently detected following solid organ transplantation ranging from 0-82% (median 32%) (Dockrell & Paya, 2001). Reactivation and re-infection are

likely to account for most infections although primary infection in liver recipients have been reported (Yoshikawa et al, 2000).

Following liver transplantation, case reports have associated HHV-6 with bone marrow suppression particularly leukopenia, interstitial pneumonitis and encephalitis (Singh et al, 1997; Singh & Paterson, 2000). HHV-6 has also been suggested the most common viral cause of febrile episodes in liver transplant recipients (Chang et al, 1998). In living-related liver transplantation in children, primary infections were documented and the virus statistically associated with febrile episodes (Yoshikawa et al, 2000). Hepatitis due to HHV-6 has also been described in liver transplant recipients (Ward et al, 1989).

Some prospective studies have not identified an association between HHV-6 and disease (Table 2) (Schmidt et al, 1996; Herbein et al, 1996; Osman et al, 1996; Kidd et al, 2000; Humar et al, 2002). Lautenschlager et al (2000) identified active infection in 11 of 51 liver transplant patients, with significant graft dysfunction in 8 of these patients. In our prospective study monitoring  $\beta$

**Table 2.**

Prospective Studies of HHV-7 Following Bone Marrow or Solid Organ Transplantation.

Study	Transplant type	Observed disease
Osman et al (1997)	renal	CMV disease
Griffiths et al (1999)	liver	None
Kidd et al (2000)	renal	CMV disease Graft rejection*
Tong et al (2000)	renal	CMV disease
Mendez et al (2001)	liver	CMV disease
Wang et al (1996)	bone marrow	None
Chan et al (1997)	bone marrow	Delayed engraftment*
Maeda et al (1999)	bone marrow	None

\*analysis on subgroup of patient population

-herpesvirus infections in 60 liver transplant patients, all three viruses were temporally associated with altered liver function suggesting each virus was associated with episodes of hepatitis. CMV and HHV-6 were also independently associated with biopsy-proven graft rejection (Griffiths *et al*, 1999).

In liver transplant recipients, HHV-6 has also been associated with CNS complications of unknown aetiology and also as a predictor of invasive fungal infections (Rogers *et al*, 2000). In a recent study of 200 liver transplant recipients, HHV-6 was statistically associated with the development of opportunistic infections (pre-defined viral, fungal and bacterial infections) and also the development of CMV disease (Humar *et al*, 2002). As proposed for CMV, it is possible that there are clinically relevant indirect effects of the virus following organ transplantation. For CMV these include an increased susceptibility to other infectious diseases such as bacterial and fungal infections and allograft rejection (Rubin, 1989).

Interactions among the  $\beta$ -herpesviruses in the post-transplant period could potentially result in disease. In both liver and renal transplant recipients, HHV-6 has been associated with CMV disease (DesJardin *et al*, 1998; DesJardin *et al*, 2001; Ratnamohan *et al*, 1998; Humar *et al*, 2000; Humar *et al*, 2002). Higher viral loads to the three human  $\beta$ -herpesviruses have also been associated with CMV disease (Mendez *et al*, 2001). Thus there is considerable evidence that interactions between  $\beta$ -herpesviruses lead to an increased risk of CMV disease. A study by Lowance *et al* (1999) reported the use of valgacyclovir for the prevention of CMV disease and a reduced level of graft rejection in renal transplant recipients. Future studies will have to consider which virus or viruses are being suppressed.

#### 4. HHV-7 Following Transplantation

Fewer studies have been carried out examining the

role of HHV-7 infection post-transplantation (Table 2). Similar to HHV-6, active HHV-7 infection does occur, and this is likely to be reactivation of recipient's virus or reinfection considering the high seroprevalence in the population. In renal transplant recipients, concomitant HCMV and HHV-7 infection has been associated with a greater risk of developing CMV disease (Osman *et al*, 1996). More recently further prospective studies have reported an association between HHV-7 and an increased risk of CMV disease (Kidd *et al*, 2000; Tong *et al*, 2000; Mendez *et al*, 2001). In bone marrow transplant recipients, there has been no obvious correlation between HHV-7 infection and a range of clinical endpoints including GvHD and engraftment (Wang *et al*, 1996; Maeda *et al*, 1999) (Table II). In one study, the detection of HHV-7 in peripheral blood by PCR during the early post-transplantation period was associated with a longer time to neutrophil engraftment (Chan *et al*, 1997). This study also included a potential case of HHV-7 associated encephalitis.

#### 5. Antiviral Susceptibility

Ganciclovir has been reported to be an effective inhibitor of HHV-6 and HHV-7 replication *in vitro* (Takahashi *et al*, 1997), although not consistently (Reymen *et al*, 1995; Yoshida *et al*, 1998). Foscarnet and cidofovir have also been shown to exhibit good activity against HHV-6 and HHV-7 *in vitro* (Takahashi *et al*, 1997) although again not consistently for the latter virus (Yoshida *et al*, 1998).

There have been no controlled trials of antiviral therapy against HHV-6 or HHV-7 infection. However, clinical response to treatment of HHV-6 disease (encephalitis/CNS disease and bone marrow suppression) following bone marrow transplantation with either ganciclovir or foscarnet or both have been reported (Wang *et al*, 1999; Mookerjee & Vogelsang, 1997; Rieux *et al*, 1998; Bethge *et al*, 1999; Johnston *et al*, 1999). A decrease in viral load concurrent with ganciclovir and/or foscarnet therapy has recently been reported in the CSF of haematopoietic stem cell transplant recipients with HHV-6 CNS disease (Zerr *et al*, 2002). Although aciclovir has little or no activity against HHV-6 *in vitro*, fewer HHV-6 PCR positive blood samples were reported in bone marrow transplant patients receiving high dose aciclovir compared to those without the drug (Wang *et al*, 1996). It remains possible that *in vivo*, aciclovir may be effective at inhibiting HHV-6 replication as it is for CMV (Prentice *et al*, 1994), albeit at a reduced level compared to ganciclovir and foscarnet. These preliminary data suggest that currently licensed anti-herpetic compounds may be effective in inhibiting HHV-6 replication, although treatment strategies will have to be addressed by appropriate clinical trial.

#### 6. Conclusions

Much effort has been targeted at investigating the medical significance of HHV-6 in the immunocompro-

mised host. In transplant recipients, case reports suggest an association of the virus with severe disease including encephalitis, pneumonitis and marrow suppression. Prospective studies certainly show that active HHV-6 infection is common in the post transplant period in both bone marrow and solid organ recipients. Although these prospective studies have reported associations of the virus with disease, they are perhaps not to the extent and severity suggested by case reports. It would certainly be unwise to dismiss HHV-6 infection as being clinically irrelevant in the post transplantation period. Importantly, there is considerable evidence of interactions among the human  $\beta$ -herpesviruses, including HHV-7 in solid organ transplant recipients resulting in a greater risk of developing CMV disease, fungal/bacterial infections and graft rejection. Thus, although severe disease directly attributable to HHV-6 and HHV-7 may be relatively uncommon post transplantation, indirect effects of these viral infections may be significant.

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