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Introduction

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HERPESVIRUS INFECTIONS IN IMMUNOCOMPROMISED PATIENTS; GENERAL ASPECTS

Background

The family of Herpesviridae contains hundreds of herpesviruses of which eight naturally infect humans (Table 1).[1] Herpes simplex virus type 1 (HSV-1), varicella-zoster virus (VZV) and cytomegalovirus (CMV) are the human herpesviruses that are investigated in this thesis. All are double-stranded DNA viruses with a lipid envelope.[1] Infections with these herpesviruses are among the most commonly encountered viral infections, occurring in virtually any indivdual.[2]

Table 1. Human herpesviruses.

Virus	Name	Abbreviation
Human herpes virus 1	Herpes simplex virus type 1	HSV-1
Human herpes virus 2	Herpes simplex virus type 2	HSV-2
Human herpes virus 3	Varicella-zoster virus	VZV
Human herpes virus 4	Epstein-Barr virus	EBV
Human herpes virus 5	Cytomegalovirus	CMV
Human herpes virus 6	Human herpes virus 6	HHV-6
Human herpes virus 7	Human herpes virus 7	HHV-7
Human herpes virus 8	Kaposi's sarcoma-associated herpes virus	HHV-8

Herpesviruses are extremely well adapted to their host as they establish widespread lifelong latent infection in humans while causing only low morbidity in healthy individuals. At the first encounter with a herpesvirus, primary infection occurs in which active viral replication leads to death of the infected cells and to the production of infectious progeny virus, so called lytic infection.[1] Primary infection can be either asymptomatic or symptomatic. Examples of common symptomatic primary herpesvirus infections are infectious mononucleosis due to Epstein-Barr virus (EBV) or CMV[3] and chickenpox due to VZV.[4]

After this phase of lytic viral replication, a stage of merely inactive infection occurs which is called latent infection.[1] Latency persists throughout life and is controlled by antiviral immune responses; at times of diminished immunity reactivation towards lytic viral infection can occur.[5,6] Waning antiviral immunity can be seen as an age-dependent phenomenon in otherwise healthy persons and lead to the common, usually mild reactivations of herpesviruses.[1;2;7-11] Because reactivation causes viral shedding at mucosal surfaces it contributes to viral spread between individuals.[2] As such, the latent infection contributes to the high prevalence of herpesvirus infections. Furthermore, viral reac-

tivation may cause symptomatic disease. Common and well known manifestations of herpesvirus reactivation are, for example, herpes labialis due to HSV-1[12] and shingles due to VZV. [4]

Infections in immunocompromised patients

Both primary infections and reactivations from latency are more frequent and more severe in immunocompromised individuals. The more frequent occurrence of primary infections is mostly a feature of infections in transplant recipients and is due to the risk of transmission of herpesviruses by transplantation of cells, tissues or organs latently infected with herpesviruses. This mode of transmission puts transplant recipients at risk of acquisition of a viral infection at a time when they are maximally immunosuppressed.[13]

The more frequent and more severe reactivations in patients with acquired immunodeficiencies occur because immunity against herpesviruses can be severely impaired.[13] For example patients with hematological malignancies receiving chemotherapy and especially hematopoietic stem cell transplant (HSCT) recipients have a temporarily suppressed or eradicated bone marrow function and thus no production of immune cells of any kind.[13] Recipients of a solid organ transplant receive immunosuppressive medication that suppresses mainly T-cell function, although in the induction phase shortly after transplantation and in case of rejection they also receive broader (including B-cell) immunosuppressants.[10;11] Severe herpesvirus reactivations in such patients may cause systemic symptoms, such as fever due to CMV,[14] or may cause organ manifestations, such as VZV retinitis,[4] or malignancies (EBV-related lymphoma).[15]

Asymptomatic herpesvirus reactivation is commonly indicated as herpesvirus infection, whereas a symptomatic reactivation is called herpesvirus disease. Not all immunosuppressed patients develop severe or protracted herpesvirus infection or disease. Various factors may contribute to the successful prevention or control of herpesvirus reactivations, including antiviral immunity[16-27] and antiviral treatment[28-34].

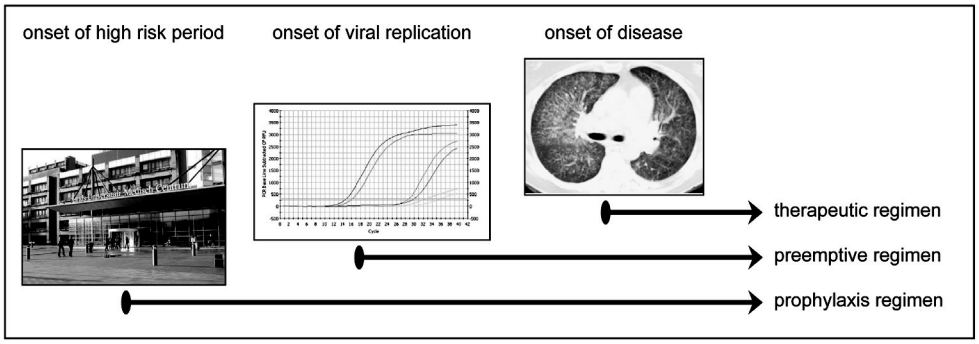
Treatment and treatment failure

Different antivirals can be used to treat infections with HSV-1, VZV and CMV (Table 2). Various strategies for preventing disease due to herpesvirus infections in immunosuppressed patients have been developed. Both prophylaxis, preemptive and symptomatic treatment are applied. In prophylactic regimens antivirals are administered from the time a patient is at risk of infection, whereas in preemptive regimens antivirals are initiated when viral infection is diagnosed before symptomatic infection has occurred (Figure 1). Symptomatic treatment is initiated when viral infection becomes clinically manifest (Figure 1).

Table 2. Antiviral agents used for the treatment of infections with HSV-1, CMV and VZV.

Agent	Abbreviation	Route of administration	Active against
Aciclovir	ACV	Intravenous/ oral	HSV, VZV
Valaciclovir	vACV	Oral	HSV, VZV
Ganciclovir	GCV	Intravenous/ oral	CMV (HSV, VZV)
Valganciclovir	vGCV	Oral	CMV (HSV, VZV)
Foscarnet	FOS	Intravenous	HSV, VZV, CMV
Cidofovir	CDV	Intravenous/ topical	HSV, VZV, CMV

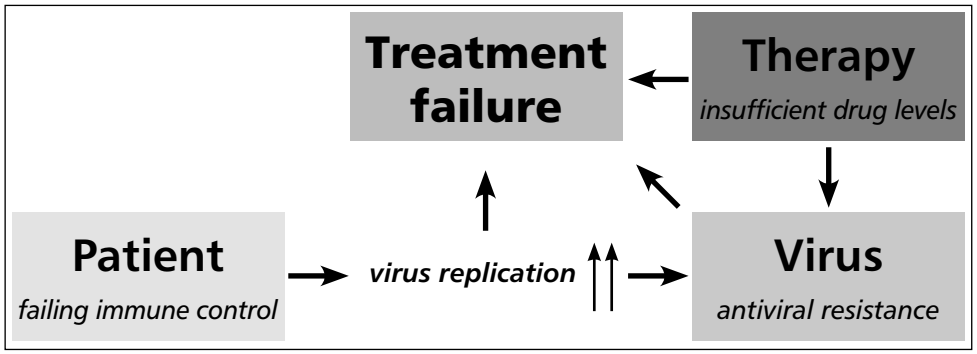
Figure 1. Treatment strategies for herpesvirus infections.



All three strategies can be effective at prevention of morbidity and mortality, but all have their disadvantages as well. Prophylaxis has a high number needed to treat and high costs of medication, while preemptive treatment has the requirement and the costs of regular diagnostic monitoring. Symptomatic treatment does not prevent disease but can only reduce the duration and severity of symptoms and is usually considered inferior and risky. The optimal approach for the various herpesvirus infections in different patient categories at risk has not been established completely.[30;35-37]

Treatment of herpesvirus infections with antiviral medication aims at reduction of viral replication and hence limitation of symptoms of infection. Eventually, only antiviral immunity can cause a return to asymptomatic latent infection. Antivirals merely suppress viral replication awaiting restoration of antiviral immunity. Continuing viral replication despite antiviral medication is considered virological failure of treatment. This may be accompanied by persistent or progressive symptoms, which is considered clinical treatment failure.

Figure 2 Causes of treatment failure of herpesvirus infections.



Treatment failure, either virological or clinical can have various causes (Figure 2). Firstly, it may be due to a profound state of immunodeficiency in which the patient's immune system is unable to control viral replication to any extent. Secondly, inadequate dosing or impaired drug absorption of antivirals can play a role. Lastly, resistance of the virus to antivirals can cause failure of treatment. These factors are interrelated; resistant virus that is less fit may only survive in an immunocompromised host and high levels of viral replication due to immunodeficiency increase the chance of viral resistance (see below).

Antiviral resistance

Resistance of herpesviruses to antivirals is the result of spontaneously occurring mutations during viral replication (Figure 3a). The proportion of spontaneous mutants in a viral population depends on the error rate of the viral DNA polymerase and on the site of the mutations; mutations in viral enzymes that are crucial to viral replication are mostly 'lethal' to the virus and such mutants will disappear from the viral population.[38-41] In the absence of adequate antiviral immunity, viral replication levels are high which increases the chance of a resistance associated mutation occurring. Upon selection pressure due to the administration of an antiviral agent, a resistant mutant subpopulation may become dominant over the wildtype susceptible population (Figure 3b). This is more likely to occur during prolonged therapy and when there is no complete inhibition of viral replication, for example due to low levels of the antiviral drug at the site of replication.[38;42] The latter can be due to incorrect drug dosing, impaired drug absorption or poor penetration of the drug in so called sanctuary sites, such as the cerebrospinal fluid or the eye.

Figure 3a. Illustration of development of resistance in uncomplicated herpesvirus infection.

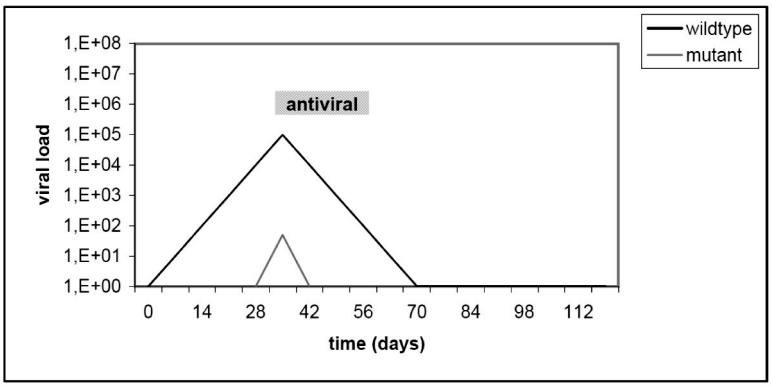
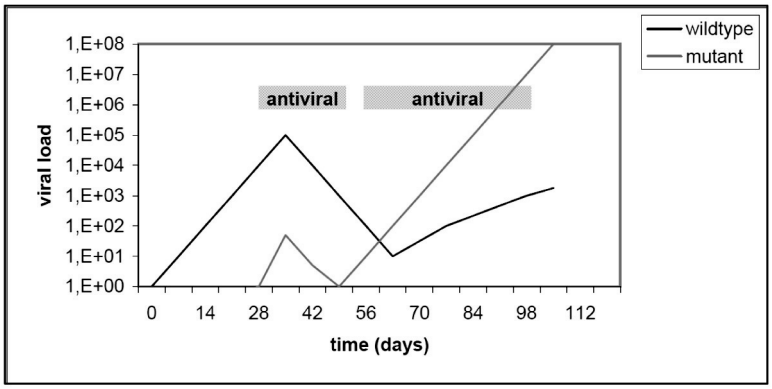


Figure 3b. Illustration of development of resistance in complicated herpesvirus infection.



Spontaneous resistant mutants appear during treatment and disappear after cessation of treatment and after clearance of the infection by the immune system in uncomplicated infections (3a). When immune restoration does not occur and persistent infection with high viral loads necessitates prolonged treatment, the resistant subpopulation may become dominant (3b).

Resistance to antivirals can be detected by culturing a viral isolate in the presence of antivirals and measuring the concentration of antiviral that inhibits viral replication in a so called plaque reduction assay. The success of this phenotypical approach depends on the ability to obtain a viral isolate, which can be difficult for some viruses and body sites (e.g. VZV and CMV in plasma or cerebrospinal fluid). Culture based assays may select for the best replicating viral subpopulation which can lead to false-susceptible results. Furthermore, this type of assay is time consuming and labor intensive. An alternative approach is to detect resistance-associated mutations in the viral genome in a clinical sample by molecular techniques. This approach avoids the need for culture and is fast

and technically easy to perform. However, its applicability depends on the knowledge of the significance of mutations. If this knowledge is not complete or if there is a frequent occurrence of polymorphisms, phenotypical confirmation remains necessary.

HERPES SIMPLEX VIRUS TYPE 1

Background

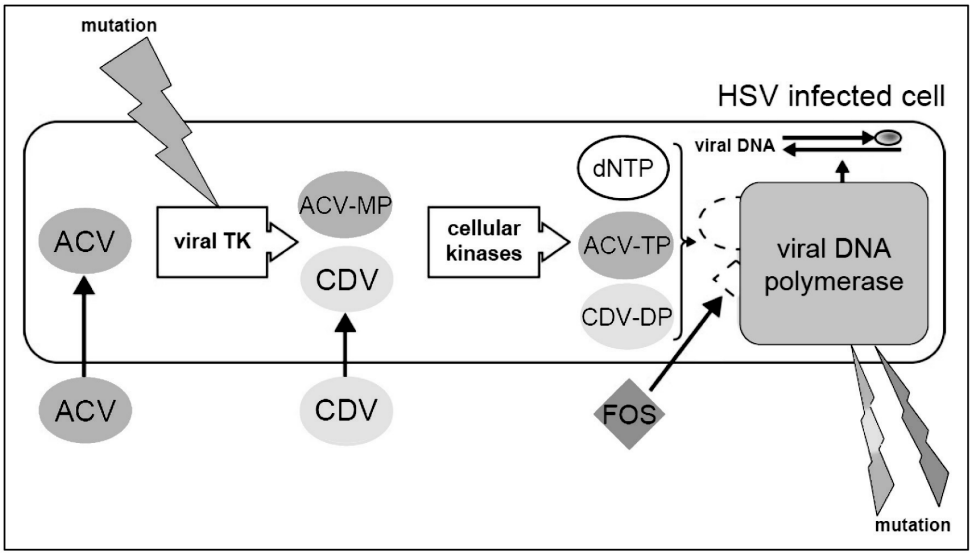
Primary HSV-1 infection occurs by inoculation of susceptible (usually oral) mucosal surfaces or minor skin lesions through direct contact.[43] After viral replication at the inoculation site, the virus traverses the neuroepithelial gap and is transported to a ganglion, most often the trigeminal ganglia in case of HSV-1.[6;12] Latent infection is maintained for life in the infected ganglia. The seroprevalence of HSV-1 in adults depends on geographic area and socioeconomic class and is on average between 50% and 85%.[44-48]

The mechanisms of HSV-1 reactivation are not well understood, but immune control by T-cells appears to play a pivotal role in the prevention of reactivation.[6;12;43;49] The rate of reactivation may be influenced by the site of infection,[50] local (micro)trauma,[51;52] exposure to UV light[53-56] and, possibly, hormonal factors[54;57-59] and psychosocial stressors.[60;61] Upon reactivation, viral replication is reinitiated and HSV-1 travels back along the nerves to the skin or mucosa which leads to local shedding of infectious virus.[43] Primary infection can be asymptomatic, but can also lead to ulcerative stomatitis.[62] Reactivation is most often asymptomatic, but can also lead to painful blistering or ulceration of the affected skin or mucosa.[2;12;43]

Infections in immunocompromised patients

The most common manifestation of HSV-1 reactivation in immunocompromised patients, such as HSCT recipients is (peri)oral ulceration.[13;63] Oral herpetic lesions can cause severe pain and difficulties with eating and drinking.[43] However, chemotherapy with or without total body irradiation can lead to ulcerative oral mucositis as well.[64-68] Chemoraditation usually causes ulcerations of the non-keratinized oral mucosa, whereas HSV-1 infection usually affects the keratinzed oral mucosa.. However, HSV-1 infection may also occur at sites of chemoradiation induced mucositis or aggravate this.[69] Therefore, in clinical practice it can be difficult to distinguish different causes of ulcerations. In addition, a possible role for other Herpesviruses such as CMV[70] and EBV[71] in oral ulceration has been suggested. Knowledge on the relative contribution of chemoradiation and herpesvirus infection to oral ulceration after HSCT is relevant to guide prevention and treatment strategies.

Figure 4. Mechanisms of HSV resistance to antivirals.



Aciclovir (ACV) is activated through phosphorylation by firstly a viral thymidine kinase (TK) and seondly cellular kinases. The other antiviral agents, cidofovir (CDV) and foscarnet (FOS) do not depend on phosphorylation by viral enzymes. After phosphorylation all antivirals inhibit viral replication by the viral DNA polymerase. Resistance associated mutations can occur in the viral TK gene (ACV resistance) or in the viral DNA polyermase gene (ACV, FOS and CDV resistance). Picture adapted from: Gilbert C, Boivin G. Human cytomegalovirus resistance to antiviral drugs. Antimicrob Agents Chemother. 2005, 49(3): 873-83.

Treatment and treatment failure

Oral ulcerations due to HSV-1 in immunocompromised patients are commonly treated with aciclovir (ACV) or its oral prodrug valaciclovir (vACV).[35;72] vACV and ACV have identical working mechanisms. ACV is a deoxyguanosine-analogue which is built into the viral DNA by the viral DNA-polymerase during replication and then inhibits viral replication (Figure 4).[73] Aciclovir only becomes active after phosphorylation by a viral thymidine kinase (TK) and two subsequent phospohrylation steps by cellular kinases (Figure 4).[74] Second line antivirals are TK independent viral DNA polymerase inhibitors (Figure 4), foscarnet[75;76] (FOS) and cidofovir[77-79] (CDV). However, both drugs are nephrotoxic.

Especially in immunocompromised patients debilitating and prolonged HSV reactivations can occur despite antiviral treatment.[13] The relative contribution of antiviral resistance to persistent HSV infections is unknown.

Antiviral resistance

The prevalence of ACV resistance has been shown to be very low in immunocompetent subjects (<1%), whereas in immunocompromised patients with HSV-1 infections, resis-

tance levels up to 27% have been described.[80-82] Investigating antiviral susceptibility of HSV-1 to antivirals can be done using various techniques. Sequence analysis of a viral isolate is the fastest approach. Resistance to ACV in HSV-1 is mostly caused by mutations in the UL23 gene of the viral TK or in the UL30 gene of the viral DNA polymerase (Figure 4).[83-85] Sequencing of these genes may reveal a resistance conferring mutation, but since nucleotide variations are common, mutations of unknown significance are also found frequently.[83-85] In such cases, phenotypical susceptibility testing of HSV-1 is required which is traditionally performed by a plaque reduction assay.[86] This type of assay is labor intensive and time consuming and, hence, results are often not available in a clinically relevant time frame. Real-time pcr based phenotypical susceptibility assays may overcome these limitations and facilitate timely diagnosis of antiviral resistance.[87;88]

VARICELLA-ZOSTER VIRUS

Background

Primary VZV infection occurs by aerosol transmission or through direct contact.[89] After viral replication in the respiratory epithelium, VZV infects T-cells in Waldeyer's ring and then viremia distributes the virus throughout the body via infected T-cells.[90;91] There is uncertainty whether skin involvement occurs only after a second viremia or results directly from the first viremia.[89-93] The seroprevalance of VZV appears to be climate dependent and reaches 95% during childhood in temperate climates but only 50% in tropical areas yet increases thereafter.[94-96]

Lifelong latent infection is established in dorsal root ganglia and cellular immunodefiency predisposes to reactivation.[89] Upon reactivation, viral replication is reinitiated and VZV travels back along the nerve to the skin of the corresponding dermatome.[89] Both primary infection and reactivation are usually symptomatic; primary infection cuases the clinical picture of chickenpox with disseminated itching vesicles, whereas reactivation causes the clinical picture of herpes zoster or shingles with a dermatomal painfull vesicular eruption.[93] In addition, cutaneous VZV reactivations can lead to postherpetic neuralgia with long-lasting and severe morbidity.[89]

Infections in immunocompromised patients

The most common manifestation of VZV reactivation in immunocompromised patients is herpes zoster; this can be dermatomal but is often disseminated in severely immunodeficient patients.[63] VZV infection occurs in 30-40% of HSCT recipients in the first year after transplantation.[34;97] Visceral, retinal en neurological infections can occur in this

patient category and cause serious morbidity and mortality.[23;63;89;93;98-101] Visceral dissemination occurs especially in patients with graft-versus-host disease.[97]

Treatment and treatment failure

To prevent dissemination or other serious manifestations of VZV reactivation, treatment with antiviral agents is given to immunodeficient patients with clinical signs of herpes zoster. Most VZV reactivations respond to treatment with ACV or vACV or related antiviral agents [99;102], but both progressive and persistent infections despite treatment can occur in severely immunocompromised patients [101;103] This can be due to immunological failure and to insufficient drug levels, but resistance of the virus to the antiviral treatment has been described as well.[104-110]

Antiviral resistance

Resistant VZV has not been shown in immunecompetent patients with primary VZV infections or herpes zoster,[111;112] but it has been demonstrated in AIDS-patients with treatment unresponsive VZV reactivations.[104-107] The prevalence of antiviral resistance in hemato-oncological patients and HSCT recipients is unknown, with only some case reports and case series described thus far.[107-110]

Similar to HSV-1 (Figure 4), VZV resistance to (v)ACV is mainly due to mutations in the viral TK gene of VZV, or, in rare cases, in the viral DNA polymerase.[105;108-110;113;114] Resistance can be diagnosed by culture of the virus in the presence of antiviral agents, but culture-based techniques are difficult because VZV is a slowly growing and highly cell-associated virus.[115] Furthermore, VZV often cannot be cultured from clinical samples such a plasma or cerebrospinal fluid. Direct sequence analysis of the target genes in clinical samples is possible in various types of clinical samples and avoids selection by culture. However, it is not completely clear in which sample type to look for resistance as compartmentalization of resistant strains has been described.[108]

CYTOMEGALOVIRUS

Background

Primary CMV infection occurs through direct contact of susceptible mucosal surfaces with infectious body fluids such as saliva and urine, through sexual contact or perinatally, either in utero or from breast milk.[116-118] CMV has a very broad cell tropism including epithelial cells, endothelial cells and polymorphonuclear cells.[5;119] After a phase of viremia, CMV infects many cell types in the body, where subsequently latent infection

is established.[5;13;14;120] The latent presence in various tissues explains the transmission of CMV to recipients of blood transfusions or stem cell and organ transplants.[5;13;14;120]

The seroprevalence in adults varies with ethnicity and socioeconomic status from 40% up to 100% in developing countries.[44;94;121-123] Primary infection is mostly asymptomatic, but a mononucleosis syndrome can occur.[3] Reactivation from latency is known to occur but is asymptomatically in healthy individuals.[1;117;120]

Infections in immunocompromised patients

In immunocompromised individuals both primary infection and reactivation can affect virtually any organ system, with symptoms ranging from fever and malaise to pneumonitis and hepatitis.[14;120] Reactivation occurs more often and is more frequently symptomatic in immunocompromised persons.[1;117;120] Manifestations of CMV infection in immunocompromised patients vary with the underlying disease, the type of the immunodeficiency and the pre-existing CMV immunity. For example, AIDS-patients often suffered from CMV chorioretinitis in the era when effective anti-retroviral treatment was unavailable, whereas this manifestation is rare in transplant recipients.[124] HSCT recipients suffer mostly from CMV pneumonitis or colitis, whereas those organs are less commonly affected in solid organ transplant recipients.[124]

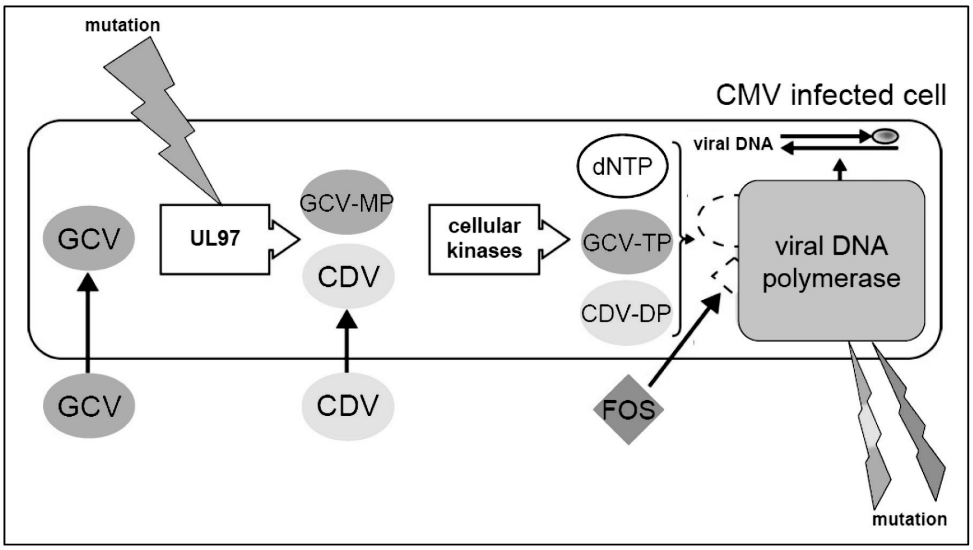
In CMV seronegative individuals, the receipt of a solid organ from a CMV seropositive donor transfers CMV to the recipient. This causes a primary infection at a time when induction immunosuppressive agents are administered and therefore has a high risk of symptomatic and severe disease.[125;126] In contrast, CMV seropositive recipients of a solid organ transplant already have pre-transplant immunity to CMV which decreases the risk of CMV reactivation and of a severe course of CMV infection.[125;126] In the setting of HSCT the situation is reversed. CMV seropositive recipients of an HSCT from a seronegative donor are at a greater risk of severe disease, because of the latently present CMV in the recipient who acquires the CMV-naïve immune system from the seronegative donor.[124;127]

Furthermore, because adaptive immunity is severely suppressed in organ transplant recipients in the early phase after transplantation, the innate immune system probably plays a pivotal role.[128-130] Common single nucleotide polymorphisms in the genes coding for members of e.g. the lectin complement pathway can have potentially important functional implications for the control of CMV infections.[128;131-133]

Treatment and treatment failure

CMV infections can be treated with ganciclovir (GCV)[30;36;37;134] or its oral prodrug valganciclovir (vGCV).[135;136] vGCV and GCV have identical working mechanisms. GCV is

Figure 5. Mechanisms of CMV resistance to antivirals.



Ganciclovir (GCV) is activated through phosphorylation by firstly a viral kinase (UL97) and seondly cellular kinases. The other antiviral agents, cidofovir (CDV) and foscarnet (FOS) do not depend on phosphorylation by viral enzymes. After phosphorylation all antivirals inhibit viral replication by the viral DNA polymerase. Resistance associated mutations can occur in the viral UL97 gene (GCV resistance) or in the viral DNA polyermase gene (GCV, FOS and CDV resistance). Picture adapted from: Gilbert C, Boivin G. Human cytomegalovirus resistance to antiviral drugs. Antimicrob Agents Chemother. 2005, 49(3): 873-83.

a deoxyguanosine-analogue which is built into the viral DNA by the viral DNA-polymerase during replication and then inhibits viral replication (Figure 5).[134;137-140] Ganciclovir only becomes active after phosphorylation by a viral kinase (UL97) and two subsequent phosphorylation steps by cellular kinases (Figure 5).[141;142] FOS[75;76] and CDV[77-79] directly target the viral DNA polymerase of CMV and can be used for treatment as well (Figure 5).

Because symptomatic CMV infection, especially CMV end organ disease, is associated with high morbidity and mortality, most treatment regimens aim at prevention of CMV disease. In high risk solid organ transplant recipients (seropositive donor, D+, seronegative recipient, R-) prophylaxis is often administered and few prospective comparisons with preemptive treatment have been performed.[37;143] For HSCT recipients a preemptive approach is usually preferred to minimize drug toxicity, especially myelosuppression. However, in a preemptive setting, viral DNA can often be detected for days to weeks during and after treatment.[144-147] The significance and optimal management of this finding is unclear.

Antiviral resistance

Only few earlier studies exist in which resistance has been systematically studied in HSCT recipients and none used sensitive CMV monitoring techniques such as real-time pcr.[148;149] Also, the contribution of antiviral resistance to viral persistence despite antiviral treatment is largely unknown. In renal transplant recipients varying rates of resistance have been described; it is unknown which preventive strategy encompasses the lowest risk of development of antiviral resistance. [150-154]

GCV resistance mutations in clinical isolates mainly map to the viral kinase gene UL97 (Figure 5).[154-158] After prolonged treatment, mutations in the viral polymerase gene UL54 can also emerge (Figure 5).[158;159] Sequencing analysis is the fastest method for susceptibility testing of CMV, which often cannot be cultured. Alternative molecular techniques for mutation detection have been studied to reduce hands on time and post-PCR processing,[160-162] but focused on fixed genome positions known to be involved in antiviral drug resistance and, hence, may have missed mutations at other sites. Compared to mutation detection by Sanger based sequencing techniques or by real-time pcr, mass-spectrometry based comparative sequence analysis combines the possibility of detection of all nucleotide variations within a target gene with reduced hands on time due to the automation of post-PCR processing and analysis.[163-165] Application of this technique may facilitate studying and diagnosing antiviral resistance in CMV infections.

SCOPE OF THIS THESIS

The research described in this thesis aims to study determinants of the course and outcome of treatment of herpesvirus infections in immunocompromised patients. Both viral factors, such as antiviral resistance, and patient factors, including immunological parameters, were investigated. Techniques to study antiviral resistance were optimized for use in a clinical diagnostic setting. The aim of this research is to improve and facilitate management of herpesvirus infections in immunocompromised patients.

In **chapter two** the development and validation of a real-time pcr based phenotypical technique to study susceptibility of HSV-1 to antiviral drugs in a routine diagnostic setting is described.

In **chapter three** the role of HSV-1, EBV and CMV in oral ulcerations in HSCT recipients is investigated. Also the course of the oral HSV-1 infections in this setting and the occurrence antiviral resistance are described.

In **chapter four** the course of VZV infections in hematological patients is studied including the role of antiviral resistance in persistent infections. Systematic analysis of the occurrence and localization of resistant VZV is described.

In **chapter five** the application of a novel technique using mass spectrometry-based comparative sequencing to detect ganciclovir resistance in CMV is addressed.

In **chapter six** determinants of the response to antiviral treatment of CMV infections in HSCT recipients are studied, including resistance to antivirals.

In **chapter seven** the response to treatment and the occurrence of antiviral resistance are compared between a preemptive and a sequential prophylactic-preemptive treatment regimen for CMV in D+R- renal transplant recipients.

In **chapter eight** the role of gene polymorphisms influencing components of the innate immunity, mannose-binding lectin and ficolin-2, on CMV infection after orthotopic liver transplantation (OLT) is investigated.

In the discussion, implications for management of herpesvirus infections in immunocompromised patients as well as suggestions for further research are described.

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