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Human Cytomegalovirus (HCMV): Pathogenesis, Clinical Features, Diagnostic Methods, and Therapeutic Challenges

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Abstract

Background: Human cytomegalovirus (HCMV), a member of the Betaherpesvirinae subfamily, is a widespread pathogen that poses a major health concern, particularly in newborns and immunocompromised individuals. The virus possesses a linear double-stranded DNA genome of approximately 230 kb enclosed within an icosahedral nucleocapsid surrounded by a lipid envelope.
Results: Expression of the viral genome is regulated through complex transcriptional events leading to the production of immediate-early and late proteins, which play essential roles in viral replication and latency. HCMV can infect various epithelial tissues, including the gastrointestinal, respiratory, and reproductive tracts. The infection often establishes latency in host cells, and complete viral clearance is rarely achieved. Reactivation may occur under conditions of immune suppression, posing a serious threat during organ transplantation, pregnancy, and breastfeeding. Diagnosis is by virological, molecular, and serological tests for viral DNA or specific antibodies. Although various antivirals are available, the treatment is still troublesome owing to drug resistance and low bioavailability, as well as toxicities over long-term administration. These restrictions highlight the importance of developing new therapeutic interventions against viral replication and latency pathways.
Conclusion: HCMV remains an important clinical and public health concern owing to its potential for persistence and reactivation in the host. Advances in molecular diagnostics have improved detection accuracy, but effective management still depends on early diagnosis, immune monitoring, and the development of safer and more potent antiviral therapies. Further research is essential to understand viral latency and to design innovative treatment approaches.
Keywords: Human cytomegalovirus; viral pathogenesis; Diagnosis; Latency; Antiviral therapy; Clinical outcomes.

1. Introduction

Human cytomegalovirus (HCMV) is a public viral infection worldwide. It causes lifelong, sub-clinical disease in healthy adults and is the main cause of congenital infection. It is a type 5 beta-herpes virus, which is a DNA virus. It belongs to the herpes virus family, known for its widespread spread in many mammals, including humans [1]. CMV is a widespread virus that can be transmitted from one individual to another through exposure to bodily fluids such as saliva, blood, vaginal secretions, feces, or breast milk. The majority of individuals infected with CMV remain asymptomatic; however, some may experience symptoms including fever, tiredness, and muscle pain during the initial phase of infection. After entering the body, the virus establishes lifelong persistence. In an individual with a competent immune system, viral activity is typically controlled.

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It is also possible for individuals to acquire multiple CMV strains over their lifetime. Frequent close interaction with children under three years of age, particularly in day care environments, represents a common route of CMV transmission [2].

The severity of the infection and the appearance of disease symptoms depend on the efficiency of the immune system of those infected. The infection is often not accompanied by the appearance of disease symptoms in immunocompetent people, and increasing. The pathogenicity of the virus in immunosuppressed patients, and thus the serious pathogenic impact of this virus, and the extent of its spread in both newborn and sick children. Immunosuppression has made this virus an important opportunistic pathogen, which may end in symptoms of a serious illness that may threaten the life of someone infected with this virus [3].

The risk of infection with this virus also rises when the pregnant mother carries the virus and transmits it to her fetus, causing many abnormal changes in the tissues and cells of the developing fetus, which may lead to miscarriage in the early stages of pregnancy or death of the child after birth. And that is modified. Its transmission from mother to fetus is 30-40%, and the incidence also varies [4]. Although most infections with this virus are asymptomatic, there are some patients whose lives are in danger as a result of long-term infection with this virus, as this virus infects any living cell in the body. Its presence is distributed in all geographical regions and affects all age groups.

Diseases can cause it to be fatal. As the name suggests, the virus amplifies in the infected cell. It gives it its distinctive shape. The virus reproduces slowly inside the cell, causing it to swell and the appearance of embedded bodies inside the infected cell nucleus [5]. This study aimed to investigate the most common congenital malformations and recurrent miscarriages, identify the risks caused by the virus, and clarify the measures that can be taken to limit the spread of the virus.

2. Virus Morphology and Classification

This virus is considered one of the largest viruses in this group. The diameter of the complete virus is 230 nm. This virus contains deoxyribonucleic acid, is filamentous, and enveloped. Proteases consist of non-phosphorylated proteins. A center pleomorphic tegument compartment, an inner pseudo-icosahedral nucleocapsid, and an outer lipid bilayer envelope make up the distinctive three-layer structure of HCMV. Complex interactions between several capsid proteins produce the nucleocapsid in HCMV and other herpesviruses. The four primary components of HCMV capsids are the main capsid protein (MCP), the triplex dimer (Tri2), the triplex monomer (Tri1), and the smallest capsid protein (SCP). The nucleocapsid enters host cells during HCMV infection through membrane fusion between the cell membrane and the viral envelope. After that, the nucleocapsid moves through the cytoskeletal system to the nucleopore, where the portal—which is situated at a certain vertex of the nucleocapsid- releases the viral genome into the host nucleus under pressure [6].

Herpesviruses are classified into three groups under the family depending on the structure, including: Alphaherpesvirinae, Beta herpesvirinae, and Gammaherpesvirinae family [7]. Members of the alpha herpesvirus sub-family are described by rapid destruction of host cells, an exceptionally short replication cycle (measured in hours), and the ability to replicate across a wide variety of host tissues. The varicella-zoster virus and herpes simplex viruses 1 and 2 make up this subfamily. The host range of beta herpesviruses is smaller than that of alpha herpesviruses. In cell culture systems, infection advances slowly during their lengthy (days) reproductive life cycle. As demonstrated by

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the human cytomegalovirus infection, these viruses have the capacity to produce larger cells. Latent infection in the kidneys, reticuloendothelial system cells, and secretory glands latent infection in the kidneys, reticuloendothelial system cells, and secretory glands can be cause by these viruses [9]. Gamma herpes viruses, Epstein-Barr virus and human herpesviruses 6 and 7, demonstrate host range characteristics typical of the beta subfamily. From a genetic perspective, Kaposi's sarcoma associated herpes virus shows the closest relationship to Epstein-Barr virus [9].

3. Epidemiology and Transmission

Human cytomegalovirus (HCMV) is a ubiquitous pathogen with global distribution, affecting populations in both developed and developing countries. Because of its widespread presence, there are no specific geographical or seasonal risk factors for infection. In most healthy individuals, HCMV infection is asymptomatic or produces only mild, self-limiting symptoms such as fever, fatigue, or sore throat. After primary infection, the virus establishes lifelong latency and can reactivate under conditions of immune suppression. Infection is considered to be a pandemic and there is no obvious seasonality [10]. Seroprevalence of HAV in different regions varies widely and depends mainly on socioeconomic status, hygiene habits, and knowledge about health. Worldwide, ~60% of adults in industrialized nations (e.g., Western Europe and the United States) [10], and more than 90% of those residing in developing regions (e.g., South America, Africa, and Asia), are CMV-seropositive. The difference reflects differing living standards, healthcare systems and childhood contact with infected people.

CMV infection can also be acquired at any point in life: congenitally, neonatally, as a child, or as an adult. Congenital CMV infection occurs following primary maternal infection or reinfection/maternal viral reactivation during pregnancy and is the most common congenital viral infection globally. In a meta-analysis, the overall pooled prevalence of congenital CMV infection was 0.67%, and it significantly varied from 1.42% in low- and middle-income countries to 0.48% in high-income countries [11]. Congenital infection rates are high and associated with low socioeconomic status, young maternal age, and high prevalence of HIV infections, as well as undiagnosed maternal CMV infection during pregnancy [12].

Numerous regions have multiple studies supporting the high prevalence of CMV. In Nigeria, the seroprevalence of IgG in pregnant women was 86.8% [13]. In Malaysia, maternal seropositivity was reported between 74% and 84%, determined by PCR diagnosis of CMV DNA [14]. IgM was also present at 8.2% of women and IgG antibodies in 88.7% [15]. A report from Iran documented IgM positivity in 1.6%, IgG in 73.6% and both IgM/IgG in 1.6% of patients, while CMV DNA was detected in 8% of pregnant women [16]. Similarly, a Moroccan study indicated an almost universal exposure as reflected by 1% seronegativity on one hand and on the other side the 99% prevalence of anti-ToxoIgG antibodies, except IgM, indicating residual risk for primary infection in pregnant women [17].

CMV hyperendemicity is observed in Iraq. 95% prevalence was detected among healthy women without a history of miscarriages in Diyala Province, while the rate was 100% for those with a history of miscarriages. IgM of 7.5% in the control group, 47.5% in the pregnant group (with miscarriage history) and, to a lesser extent, 40% found during pregnancy with previous miscarriage-related non-pregnant women [18]. Another study in Diyala found 53.3% as IgG and 8.7% as IgM

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seropositivity [19]. CMV IgG positivity was 96.2% in Diwaniyah Province and CMV IgM was 1.8% [20]. Studies conducted in Al-Basrah and Duhok provinces of Al-Basrah province found that the seropositivity rate of IgG against the virus was above 98% with a low positivity rate to IgM (6-7%), necessitating the continuous circulation of WUPyV among Iraqi women, promoting frequent pregnancy loss in their population [21], [22].

One of the most common viral infections in the world is CMV. Transmission occurs mainly through direct contact with infected bodily fluids such as saliva, urine, semen, vaginal secretions, blood, and breast milk, or via vertical transmission from mother to fetus. Although typically asymptomatic in healthy individuals, CMV can cause serious complications in immunocompromised patients and during pregnancy, leading to congenital abnormalities, fetal growth restriction, or miscarriage [23].

4. Clinical Manifestations and Morbidity

Histopathological studies have proven the presence of CMV in various types of Various organs and cells, including salivary glands Adrenal gland, Pancreas, Kidney, Salivary gland and the lungs, and the liver, and the eyes, and the ears, and the placenta, and the organ Digestive tract Gastrointestinal, heart, ovaries, skin, and blood and the brain [24]. An important characteristic of infection that is associated with pathogenesis is the ability of the virus to destroy the host cell. Interfering with the host's defences. HCMV has developed a number of complex strategies to avoid and inhibit host innate immune responses, such as reducing IFN-I production and signalling, controlling NK cell activity, preventing the production of inflammatory factors, and modifying cell apoptosis and autophagy. Instead of existing separately, these strategies work together to create a complicated network. These multi-level, multi-targeted immune evasion strategies allow HCMV to effectively evade host innate immune monitoring, therefore fostering an environment that is conducive to viral latent infection and continuous transmission [25].

When infecting the central nervous system (CNS), cytomegalovirus (CMV) exhibits widespread cellular dissemination, infecting neurons, glial cells, endothelial cells, microglia, tanycytes, and radial glia, as well as cells of the meninges and choroid plexus, causing structural and vascular damage and CNS dysfunction. Furthermore, CMV actively infects monocytes, exploiting their ability to migrate across endothelial cells and differentiate into macrophages to spread throughout the body [26], [27]. A small subset of mononuclear cells in CMV-infected individuals specially in monocyte hold latent viral genome. CMV latent infection can reactivate and spread to many host tissues after differentiating into phagocytic macrophages [28]. Furthermore, by disrupting monocyte activation, such as antigen presentation and phagocytosis, and increasing trans-endothelial migration and pro-inflammatory cytokine production, CMV methodically undermines host defence, promoting viral persistence and propagation [29]. By suppressing MCH-1 AND11 presented, avoiding NK-mediated cytotoxicity, preventing apoptosis and complement-mediated lysis, and modifying immune signalling through encoded immunomodulatory protein, this virus further eludes immune detection [30].

In immunocompetent individuals, infections are typically mild or asymptomatic, but they can occasionally result in a variety of clinical syndromes. An extensive review of literature published up to April 2024 reveals that CMV can affect the skin, lungs, heart, gastrointestinal tract, eyes, hematological system, central and peripheral neurological systems, and more. Despite the fact that

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most cases resolve themselves [31]. Splenomegaly is an uncommon symptom of HCMV infection compared to other diseases like Epstein-Barr 34, and other rare complications such as Colitis [32], pneumonia, Hepatitis, meningitis, aseptic inflammation, and myositis Myocarditisheart [33]. Cytomegalovirus is an important opportunistic viral disease in immunocompromised patients. The immune system, especially in acquired immunodeficiency disease and solid organ transplant recipients, causes many diseases to multiply and increases the death rate. In patients with HIV/AIDS, opportunistic infections are more common and more severe.

These individuals frequently have CMV viral infections, which can impact the eyes, lungs, brain system, and digestive system, among other organs and systems. The virological and immunological features of uncomplicated CMV infection [34], particularly those observed in women and children, have been the subject of numerous investigations. However, in individuals with HIV/AIDS who are already immunocompromised, the immunological characteristics of CMV infection are somewhat distinct. HIV patients with CMV infection differ from those with CMV infection alone in terms of clinical features, treatment approaches, and prognostic variables [35]. In those HIV patients with complications (retinitis, pneumonia, CMV encephalitis, enteritis, and solid organ transplant), the main cause of morbidity and mortality rates (SOT) is solid organ transplant [36].

The virus causes many diseases, ranging from cytomegalovirus syndrome to tissue-invasive diseases. CMV syndrome resembles the symptoms of influenza, which may be characterized by fever, malaise, leukopenia, a deficiency of platelets, and a slight increase in liver enzymes, as with tissue-invasive diseases. It varies depending on the transplanted organ. Research indicated that the rate of CMV infection in lung transplant disease 35%-75% and the heart (9%-35%) in the absence of prevention [37]. Infection of the fetus or newborn may be severe, and is the result of CMV transmission across the placenta. Its transmission to the fetus occurs due to the primary infection or secondary infection of the mother, and the possibility of transmission within the loss of the uterus after the primary infection during pregnancy is (30-40%) compared to only 1% after the secondary infection.

About (15-50%) of congenital fetal infections are accompanied by symptoms at birth, including identification of Fetal growth, microcephaly, hepatomegaly, spleen, petechiae, jaundice and infections of the placenta and retina, thrombocytopenia, and anemia. These IgG antibodies have the ability to cross through the placenta to the fetus. CMV multiplies in epithelial glandular cells and endometrial cells. It spreads to cellular trophoblasts, as the CMV virus transplacental transfer of Fc-Receptor to fetus [38].

5. Diagnosis

When CMV infection is suspected in a healthy person, the antibodies it produces can be found. The body, against the virus in the blood, or even finding the virus itself in the blood, in body fluids, or in a sample of tissue. Also, it is important, before the beginning of pregnancy, to check whether you have been infected with the virus before, because of the possibility. In women, if you first became infected with the virus during pregnancy. The incidence of disease during pregnancy is very low. It is possible to consider performing an amniotic fluid test to check whether the fetus has been injured. The need for this examination increases, sometimes immediately, when a birth defect is discovered in an ultrasound examination [39].

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6. Pathogenesis and Immune Response

Viral Entry and Initial Immune Activation / Human cytomegalovirus (HCMV) infection begins when the virus enters host cells via fusion between the viral envelope and the cell membrane. The virus primarily targets epithelial, endothelial, and myeloid cells, initiating a cascade of immune responses aimed at controlling viral replication [23]. During the acute phase, both the innate and adaptive immune systems are activated. Natural killer (NK) cells play a crucial role in the early defence by recognizing and destroying infected cells that display altered surface molecules. Concurrently, the adaptive immune system, particularly $CD8^+$ cytotoxic T lymphocytes and $CD4^+$ helper T cells, mounts a strong antiviral response to restrict viral dissemination [40], as shown in Fig. 1.

Latency and Viral Persistence/In spite of this strong immune response, HCMV is rarely cleared from the host but instead drives lifelong latency. The viral genome remains transcriptionally silent in selected host cells, $CD14^+$ monocytes, and $CD34^+$ hematopoietic progenitor cells [41] during latency. Only a restricted viral gene subpopulation, the latency-associated transcripts (LATs), is expressed during this period, and these coding regions enable the virus to escape immune-surveillance and retain its potential to be reactivated. The virus may be reactivated by factors such as immunosuppression, inflammation, and cellular differentiation with consequent reinfection of the host and development of disease [41].

Immune Evasion Strategies / HCMV uses a series of complex immune-evasion mechanisms to survive in the host. A major mechanism is downregulation of MHC-I molecules on the infected cell surface, which leads to a neutralization of recognition by $CD8^+$ T cells and consequently immune escape from CTL killing [42]. The virus also expresses viral proteins that resemble MHC, and thereby hinder immune recognition and antibody-neutralizing activity. Furthermore, HCMV expresses multiple glycoproteins and regulatory proteins that inhibit the production of interferon (IFN), thereby preventing natural killer (NK) cell activation, allowing the virus to evade early innate immune responses as displayed in Fig. 1 [40].

Modulation of Host Cell Survival/ for its own continued survival, HCMV redefines the cellular host's survival programs. The virus also produces anti-apoptotic proteins, which suppress programmed cell death, thus keeping the infected cells alive and maintaining a reservoir for latent viral particles [41]. In addition, HCMV modulates cellular signalling pathways to promote viral replication and inhibit the expression of antiviral genes. This modulation of both apoptosis and autophagy not only extends the life of an infected cell, but also enables viral reactivation upon favourable conditions [40].

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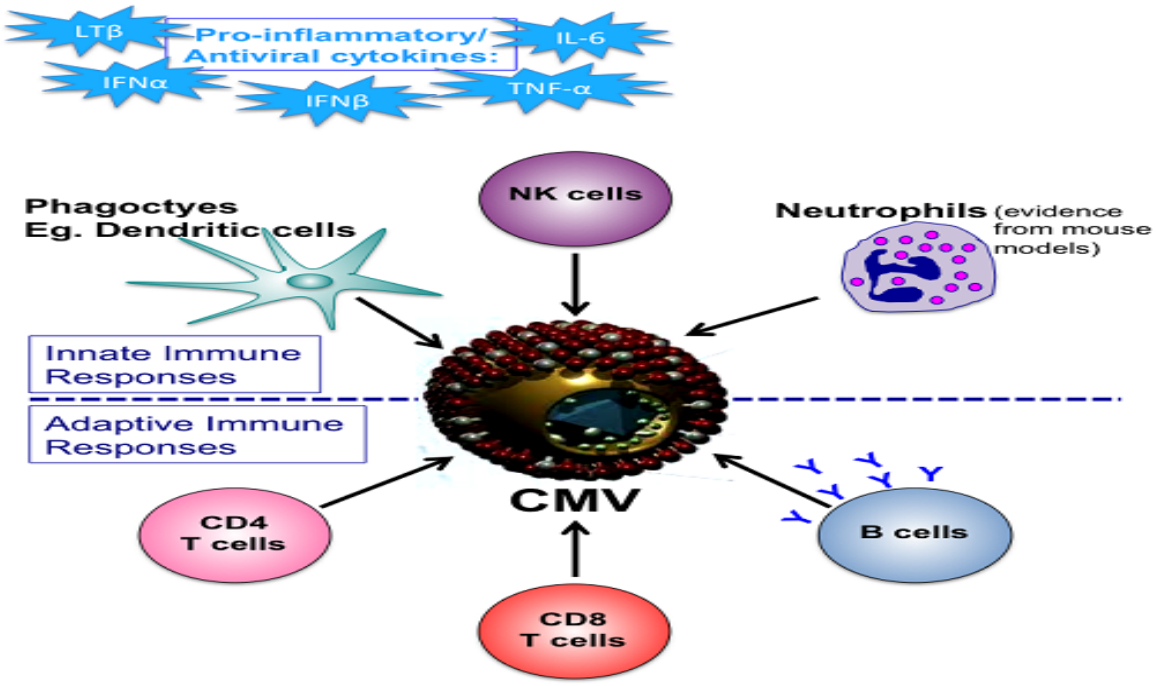

Fig. 1 Summary of immune responses to CMV infection.

Reactivation of Latent CMV and Clinical Features / The world was not infected with active CCMV, and the world was horrified to learn a few years ago, when the phenomenon became widely known, that, truly, people can be walking time bombs. A reactivated virus can disseminate to multiple organs, resulting in diseases such as pneumonitis, hepatitis, retinitis, or congenital infection in newborns [23]. The capacity of CMV to establish latency, evade immunity and reactivate demonstrates the delicate equilibrium between viral persistence and host defence. Insight into these strategies is important for the development of antiviral therapies and vaccines to target viral latency and immune evasion.

7. Treatment and Management

Once a person is diagnosed with CMV, treatment of the disease aims to suppress all forms of the disease. Forms of the disease and elimination of unpleasant symptoms. In fact, doctors today do not have the means to destroy. Immunocompetent patients are self-limiting, have little or no symptoms, and only require symptom management. However, antiviral therapy should be considered in immunocompromised patients with severe CMV mononucleosis, CMV infection, and CMV sickness. Because toxicity is common, the risks of utilizing these drugs must be weighed against the benefits of beginning treatment. Prophylactic evaluations should be performed on all high-risk patients. Usually, CMV sickness or CMV end-organ disease is treated with antivirals. Patients should be regularly monitored for treatment failure and, if it does occur, the causes, such as the emergence of resistance, should be considered. In these cases, testing for antiviral drug resistance should be done [43].

Treatment for cytomegalovirus (CMV) is classified based on the clinical situation: either prophylactic therapy to prevent disease or treatment of active infection, which ranges from a mild

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viral syndrome to severe tissue-invasive disease. First-line drugs: Intravenous ganciclovir (IV GCV) and oral valganciclovir (VGC) are the main treatments [44]. Patients with severe and life-threatening CMV disease, those with a very high viral load, and those with impaired gastrointestinal absorption should still receive intravenous antiviral medications, such as ganciclovir and foscarnet, as their initial treatment. Clinical improvement and a satisfactory decrease in viral load are prerequisites for a safe switch from intravenous therapies to oral antiviral medications [45].

8. Prevention and Vaccine Development

Because CMV spreads through contact with infected body fluids such as saliva, urine, breast milk, and semen, frequent hand washing, safe sexual behavior, and avoidance of contact with potentially contaminated materials are essential preventive measures (10). Pregnant women are particularly encouraged to avoid direct contact with the saliva and urine of young children, who are often major reservoirs of the virus [12].

In healthcare settings, infection-control measures such as screening of blood and organ donors and adherence to standard sterilization procedures play a critical role in preventing CMV transmission, especially among immunocompromised patients and transplant recipients [44]. Immunocompromised individuals, including organ transplant recipients and patients with HIV/AIDS, benefit from prophylactic or pre-emptive antiviral therapy—using drugs such as valganciclovir or ganciclovir-to prevent CMV disease [41]. Despite these interventions, long-term antiviral use is limited by drug resistance, toxicity, and cost, highlighting the need for improved preventive approaches [44].

Constructing a successful vaccine for CMV is among the highest public health priorities, as it has an extraordinarily high prevalence and can be very serious in newborns and immunocompromised members of any population [1]. Multiple vaccine approaches have been pursued, such as recombinant subunit vaccines against CMV glycoprotein B (gB), live attenuated virus vaccines, viral vectors and an mRNA-based platform [27]. Phase II trials of this led to partial protection (~50% efficacy) for such gB-based vaccines, but they were not advanced further because only limited duration immunity was detected [46]. An mRNA vaccine expressing six major CMV envelope glycoproteins, including gB and the pentameric complex, was reported recently to be highly immunogenic with strong neutralizing antibody and T cell responses in clinical studies [43].

This vaccine, which was developed using a vector approach from Moderna with the National Institute of Allergy and Infectious Diseases (NIAID), is currently being tested in phase III in CMV-seronegative women to test its efficacy in preventing primary infection and congenital CMV (46). If it is proven effective, this may become a major contribution in preventing congenital CMV-related morbidity around the world [27]. While no vaccine against CMV has been licensed to date, there is hope for the development of a global prevention strategy and long-term control of CMV transmission based on ongoing progress in molecular immunology and mRNA technology [23].

9. Conclusion

Human cytomegalovirus (HCMV) is a ubiquitous pathogen that is associated with significant disease burden in immunosuppressed individuals, transplant recipients, and the developing foetus. Its ability to establish life-long latency and reactivation makes infection elimination quite difficult. Recent progress in molecular diagnostics has facilitated earlier diagnosis, but therapy with available

antiviral agents is limited by toxicity and resistance. Hygiene and immune control are also important for at-risk groups. Exciting developments in the field of mRNA-based vaccines provide a promising avenue for the prevention of CMV transmission and congenital infection. Continued investigation into viral latency and immune evasion is vital for developing more effective treatments and achieving long-term control of this persistent virus.

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