Journal of MEDICINE–24
May 2026, Vol. 3, Issue 1, pp. 29–37
DOI: https://doi.org/10.36719/3104-4700/4/29-37

Comparative Analysis of Cytokine Interactions in Herpes and Opportunistic Infections: The Role of Th1, Th2, and Regulatory Cytokines

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Abstract. *Herpes viruses are widespread pathogens that reactivate, particularly in immunosuppressive conditions, eliciting complex and variable immune responses. In this context, the role of cytokine networks is crucial for understanding inter-viral differences and clinical outcomes. In this article, I presented a comparative analysis of cytokine responses between herpes viruses (HSV-1, HSV-2, VZV) and opportunistic herpes viruses (EBV, CMV) in immunosuppressed patients. Based on scientific articles published between 2020 and 2026, I investigated the roles of Th1, Th2, and regulatory cytokines (IL-6, IL-10, IFN-γ, TNF-α). EBV induces a robust Th1/cytotoxic response (IFN-γ and TNF-α), while CMV is in most cases associated with an increase in IL-10 and exhibits a regulatory immunomodulatory profile. HSV-2 and VZV are characterized by a marked local increase in IFN-γ. However, there is insufficient data for IL-6, and information on systemic cytokine profiles in immunosuppressed populations for HSV/VZV is limited. The findings indicate that the pathogenesis of herpes viruses is closely linked not only to antiviral mechanisms but also to immunoregulatory processes, which requires new approaches to clinical management and lays the theoretical foundation for the future development of biomarker-based diagnostics and immunotherapeutics.*

Keywords: *Th1, Th2, cytokine, opportunistic herpes viruses, immune response*

Introduction

Herpesviruses are widespread latent pathogens that can lead to severe clinical courses, particularly upon reactivation in immunosuppressed individuals. Herpes viruses are divided into two main groups: standard herpes viruses (HSV-1, HSV-2, VZV) and opportunistic herpes viruses (EBV, CMV, HHV-6, KSHV). The immune responses to these viruses, particularly through cytokine networks, exhibit distinct characteristics (Ramos-Nino, M. E. 2026). The coordination of the immune response relies on a balance between Th1 cytokines (IFN-γ, TNF-α), which activate antiviral cell-mediated immunity; Th2 cytokines (IL-4, IL-5), which drive humoral responses; and regulatory cytokines (IL-10, TGF-β), which mitigate excessive inflammation. In this context, IL-6 exerts a pleiotropic effect, performing both pro-inflammatory and regulatory functions. The purpose of this work is to comparatively analyze the cytokine profiles among different groups of herpes viruses based on recent literature and to determine the functional role of key immune mediators.

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Received: 24 January 2026; Accepted: 9 April 2026; Published online: 15 May 2026

Regulation of the Immune Response Through T-Helper Cell Subsets and Cytokines

The immune response is complexly regulated by cytokines secreted by various T-helper (Th) cell subsets. These cytokines ensure both pathogen elimination and tissue homeostasis by balancing effector and regulatory mechanisms. A disruption of the immune balance between T-helper cell subsets plays a key role in the pathogenesis of pregnancy-induced hypertension.

In particular, Th1 and Th17-oriented pro-inflammatory cytokines (e.g., IFN-γ, IL-17) increase, which amplifies systemic inflammation and endothelial dysfunction, while a decrease in Th2 and Treg-derived cytokines (IL-4, IL-10) leads to a weakened immune tolerance (Zhou et al., 2023). The functional characteristics of follicular T-helper (Tfh) cells are differentially shaped depending on their cytokine profile. Cytokine-skewed Tfh subsets—particularly the populations producing IL-21, IL-4, and IFN-γ—selectively regulate B cell proliferation, isotype switching, and the generation of high-affinity antibodies. Thus, Tfh–cytokine serves as one of the key determinants of the specificity, strength, and durability of the humoral immune response (Olatunde et al., 2021). Th1-type cytokines primarily enhance cell-mediated immunity. Interferon-gamma (IFN-γ) plays a crucial role in the activation of macrophages and the formation of antiviral defense. Tumor necrosis factor-alpha (TNF-α) stimulates apoptosis and activates effector mechanisms against infection by enhancing the inflammatory response. Interleukin-2 (IL-2) supports the adaptive immune response by increasing the proliferation and cytotoxic activity of T lymphocytes. Th2-type cytokines are involved in the development of humoral immunity. Interleukin-4 (IL-4), interleukin-5 (IL-5), and interleukin-13 (IL-13) stimulate B cell differentiation and antibody production, while also playing a key role in the development of allergic reactions. Regulatory cytokines prevent the overactivation of the immune response. Interleukin-10 (IL-10) has a potent anti-inflammatory effect, inhibiting the production of pro-inflammatory cytokines and reducing tissue damage. Interleukin-6 (IL-6) is pleiotropic, performing both pro-inflammatory (acute phase response) and, in some cases, regulatory functions. Transforming growth factor-beta (TGF-β) plays a key role in maintaining immune tolerance and tissue regeneration (Goetzke et al., 2025).

Cytokine Dynamics and Immune Regulation in HSV-1 Infections

Herpes viruses are characterized by their ability to establish latent infection and evade immune control; their reactivation occurs under immunosuppressive conditions, and the cytokine profile varies depending on the virus type, tissue tropism, and the host's immune status. In HSV and other alphaherpesviruses, immune surveillance during the latent infection period is primarily provided by weakly activated Th1 and resident T cell-mediated cytokine signals, which allows the virus to remain hidden long-term. During reactivation, an increase in IFN-γ and other pro-inflammatory cytokines enhances the antiviral response, limiting viral replication (Cao et al., 2024). In HSV-associated uveitis, the immune response is characterized by a predominantly Th1-oriented cytokine profile (particularly IFN-γ and TNF-α), which enhances cell-mediated recognition of viral antigens. Immuninformatics approaches aimed at multiepitope vaccine design, however, aim to optimize this Th1 dominant cytokine response while simultaneously balancing an excessive inflammatory reaction (Cao et al., 2025). During acute HSV oral mucosal infection, the immune response is characterized primarily by the activation of early Th1-type cytokines (particularly IFN-γ and TNF-α), which plays a key role in establishing local antiviral defense. At the same time, cytokines secreted from resident T cells effectively limit viral spread by ensuring the elimination of infected cells (Shannon et al., 2021). Viruses like HSV block interferon signals, weakening the host's antiviral defense and thereby shaping tissue tropism and the ability of the infection to spread. As a result of this interferon antagonism, the early Th1-mediated cytokine response (particularly IFN-α/β and IFN-γ signaling) is weakened, which allows the virus to evade the immune system (Streicher et al., 2025).

Cytokine Dynamics and Immune Regulation in HSV-2 Infections

The cytokine profile in herpes simplex virus type 2 infection is differential depending on the clinical phenotype of the disease. In HSV-2 meningitis, elevated pro-inflammatory cytokines and chemokines (particularly IL-6, IL-8, TNF-α) reflect a strong inflammatory response in the central nervous system. In contrast, during genital herpes, the cytokine response is more local, Th1-dominant (IFN-γ-mediated), and characterized by relatively limited immune activation, reflecting the localized course of the infection (Bjerhem et al., 2025). In HSV-2 infection, cytokines secreted by tissue-resident T cells form the basis of local antiviral defense. In particular, IFN-γ-mediated signaling limits viral replication and prevents the spread of infection by inducing an antiviral state in infected cells. This underscores the acute, local, and effective Th1-dominant character of the immune response against HSV-2 (Roychoudhury et al., 2020). HSV-2 is characterized by a very rapid local increase in IFN-γ. Studies in mucosal lesions show that the local increase of IFN-γ and granzyme B correlates with viral load and occurs before viral clearance (Souquette et al., 2026). This is consistent with an acute tissue-resident T cell cytokine alarm response and constitutes the primary mechanism of local antiviral defense against HSV-2. In HSV-2 infection, the prime/pull vaccine approach enhances the antiviral immune response by increasing the number of protective CD4+ and CD8+ T cells in the tissue. As a result, viral reactivation is better controlled and the likelihood of disease recurrence is reduced (Quadiri et al., 2024). The infection is accompanied by a higher pro-inflammatory cytokine profile, especially in the context of HIV-1 co-infection. In particular, an increase in IL-6, TNF-α, and other inflammatory mediators is associated with elevated levels of immune activation and persistent viral replication. These findings indicate that the cytokine response in HSV-2 infection is significantly dependent on the host's immune status and that it creates a more pronounced imbalance in the presence of HIV-1 (Aravantinou et al., 2022).

Cytokine Dynamics and Immune Regulation in EBV Infections

EBV is the most potent inducer of a Th1 response among opportunistic herpes viruses. Studies in lung transplant recipients show that EBV lytic antigen stimulation activates polyfunctional CD8+ T cells, which simultaneously express IFN-γ and TNF-α (Muruganandah et al., 2018). This indicates strong Th1/cytotoxic immunity against EBV antigens. Activation of CD150 (SLAM) signaling in EBV-transformed B cells induces the secretion of various cytokines. This regulates the differentiation of peripheral blood monocytes. The released cytokines cause reprogramming of the immune microenvironment by enhancing the interaction between the innate and adaptive immune responses. In conclusion, this demonstrates that in EBV infection, cytokines play a crucial role not only in the antiviral response but also in cell differentiation and the modulation of immune networks (Kim et al., 2024). The EBV virus enhances the local inflammatory microenvironment by increasing the production of pro-inflammatory cytokines (e.g., IL-6, IL-8) in gingival fibroblasts. At the same time, this cytokine environment contributes to tissue resorption and periodontal destruction processes by stimulating RANKL-mediated osteoclast differentiation. These findings indicate that EBV links the cytokine response not only to immune activation but also to tissue remodeling (Yokoe et al., 2022). The effect of EBV on the immune system is dependent on the viral state. Detection of latent EBV is associated with decreased cytokine levels, which has an immunomodulatory or tolerogenic effect. Conversely, when EBV enters lytic replication, systemic cytokinemia increases and the risk of graft rejection rises (Gabeleh et al., 2025). This dual nature reflects the complex immunological profile of EBV. TNF-α accompanies the EBV-specific IFN-γ response and enhances the role of Th1 inflammation in CD8 responses (Muruganandah et al., 2018). This underscores the importance of TNF-α in the formation of an effective cytotoxic response against EBV.

Cytokine Dynamics and Immune Regulation in CMV Infections

Cytomegalovirus stands out among opportunistic herpes viruses for its immunomodulatory properties. Detection of HCMV in transplant recipients is associated with an increase in IL-10, IL-4, and IL-8, and these changes correlate with the immune injury of the allograft (Saldan et al., 2023), indicating the formation of a Th2-like environment. During CMV infection, inflammasome activation mounts an intense innate immune response by increasing the secretion of key pro-inflammatory cytokines, including IL-1β and IL-18, and simultaneously induces pyroptosis-mediated cell death. Administration of inflammasome inhibitors significantly reduces cytokine secretion and pyropotic processes. These findings highlight the inflammasome–cytokine axis as a key regulatory mechanism of immune activation and tissue damage in CMV pathogenesis (Deng et al., 2024). The CC-type chemokines encoded by the CMV virus indirectly influence the formation of the local cytokine environment by modulating the migration of immune cells. Additionally, gH/gL-complex-mediated cell tropism acts as a separately regulated mechanism, independent of immune activation and viral spread. These findings indicate that in CMV infection, cell tropism is regulated by chemokine-mediated immune modulation in a partially independent manner from the cytokine response (Eletreby et al., 2023). Low IFN-γ production (IFN-γ +874 A>T) is associated with an increased risk of CMV disease (Vu et al., 2014; Ciccocioppo et al., 2025), which underscores the protective role of the Th1 response. However, CMV infection is often accompanied by an increase in regulatory cytokines. The lack of an effect of asymptomatic CMV shedding in early HIV on the systemic cytokine profile suggests that the immune effects of this virus are context-dependent (Vanpouille et al., 2022).

Cytokine Dynamics and Immune Regulation in VZV Infections

This prospective study conducted in the context of herpes zoster associated with the varicella-zoster virus shows a significant increase in serum pro-inflammatory cytokines (particularly IL-6, IL-8, and TNF-α). This increase correlates positively with the clinical severity of the disease. In particular, the elevation of IL-6 levels is associated with the development of postherpetic neuralgia (PHN), highlighting its role in the pathogenesis of persistent neuroinflammatory processes. This suggests that the cytokine response during VZV is not limited to antiviral effector mechanisms but also contributes to the development of chronic pain syndromes (Gu et al., 2023). In the context of COVID-19, activation of the IL-17/Th17 axis becomes a key component of the immune response. Enhanced IL-17 signaling promotes the recruitment of inflammatory cells and tissue damage by increasing the expression of cytokines and chemokines (e.g., IL-6, CXCL8) through NF-κB and other pro-inflammatory pathways. These findings indicate that VZV reactivation is closely associated not only with the classic Th1-mediated antiviral response but also with Th17-induced inflammatory networks, and that the virus–host interaction is particularly modulated at a systemic level (Yu et al., 2021). In rheumatoid arthritis patients receiving Janus kinase (JAK) inhibitors, the cellular-mediated immune response after herpes zoster vaccination is weakened. Accordingly, cytokine production, particularly the Th1 response characterized by IFN-γ, is significantly reduced. This may limit the effectiveness of antiviral defense, leading to inadequate immune control of VZV. The results indicate that inhibition of the JAK signaling pathway disrupts the mechanisms critical for the development of a cytokine-based immune response against herpes zoster (Källmark et al., 2026). This study, conducted in the context of the varicella-zoster virus-based live herpesvirus vaccine, shows that the strength of the innate immune response and its cytokine profile vary significantly depending on an individual's biological sex and prior viral exposure. In particular, the intensity of initial IFN-type I and pro-inflammatory cytokine responses (e.g., IL-6 and TNF-α) is modulated by prior immune memory and hormonal factors. Consequently, the innate immune response against herpesviruses is not static but is context-dependent and individualized (Cheung et al., 2023). VZV reactivation is associated with higher-frequency IFN-γ and IL-2-producing CD4+ memory T cells and increased cytotoxic markers during acute illness. The increase in IL-2 occurs during acute VZV reactivation and is accompanied

by polyfunctional CD4+ T cell responses associated with effector function. This indicates that VZV also elicits a strong Th1 response (Ma et., 2022).

Comparative Approach: Common and Distinguishing Features

Comparative Analysis of Th1-Type Immune Responses

All herpesviruses establish a core conserved mechanism of antiviral control early in infection by inducing a Th1-dominant response via IFN-γ, IL-2, and cytotoxic effector molecules (e.g., granzyme B). In HSV infection, the local IFN-γ-mediated antiviral effect of tissue-resident T cells plays a key role in virus control (Roychoudhury et al., 2020), whereas in HSV-2 meningitis, a more pronounced proinflammatory cytokine increase is observed (Bjerhem et al., 2025). Common herpes viruses (HSV-1/HSV-2) primarily induce a local Th1-dominant response during mucocutaneous infections, whereas Varicella-zoster virus manifests as varicella during primary infection and as herpes zoster upon reactivation. In CMV, the IFN-γ response acts as a protective factor, and its reduction is associated with an increased risk of infection (Vu et al., 2014; Ciccocioppo et al., 2025). In EBV, however, the Th1 response is phase-dependent: a strong IFN-γ/TNF-α response is observed in the lytic phase, while this activity weakens in the latent phase (Goetzke et al., 2025; García-Jiménez et al., 2026). Although a Th1 response is present in VZV infections, additional activation of the Th17 axis is noted, particularly during herpes zoster (Yu et al., 2021). Although the Th1 response is a common antiviral mechanism in all viruses, its intensity and duration vary depending on the virus type and clinical context.

Comparative Analysis of Regulatory Cytokines

Immunoregulatory cytokines in herpes viruses are a key component of mechanisms for chronic infection and immune evasion. In opportunistic herpes viruses (especially CMV and EBV), an increase in IL-10 is associated with the formation of an immunosuppressive microenvironment. Elevated IL-10/IL-4 levels in cases of CMV detection and EBV co-reactivation correlate with graft rejection (Saldan et al., 2023; Gabeleh et al., 2025). In EBV-associated inflammatory syndromes, TGF-β-mediated signaling plays a critical role in both immune suppression and the organization of pathogenic processes (Goetzke et al., 2025). In CMV, additional secretion of IL-1β and IL-18 is observed as a result of inflammasome activity, which is associated with pyroptosis and tissue damage (Deng et al., 2024). An increase in systemic pro-inflammatory cytokines (especially IL-6) in VZV correlates with postherpetic neuralgia (Gu et al., 2023). In HSV infections, the regulatory cytokine component operates primarily at a local level, and the systemic profile is relatively poorly characterized. While systemic immunoregulatory dominance is observed in EBV and CMV, in HSV and VZV, it is more local and episodic in nature.

Determinants Affecting the Immune Response

In herpes virus infections, the heterogeneity of cytokine responses is shaped not only by the intrinsic properties of the virus but also by the interplay of multifactorial host determinants. In Epstein-Barr virus infection, the viral phase is characterized by a sharp shift in the cytokine profile from the latent-to-lytic transition, from an immunoregulatory environment to a pro-inflammatory response (Goetzke et al., 2025). In transplant recipients, the immunosuppressive state significantly alters the cytokine balance; in this group, CMV and EBV infections are often characterized by the development of an immunomodulatory environment dominated by IL-10, and this change is associated in clinical practice with the risk of immune-mediated damage to the allograft (Saldan et al., 2023). In contrast, during the early HIV infection stage, the impact of CMV replication on the systemic cytokine network may be limited (Vanpouille et al., 2022), which underscores the influential role of the immune background. Among opportunistic herpes viruses, EBV remains latent in B lymphocytes, causing lymphoproliferative disorders in the context of transplantation, while CMV is associated with

systemic and highly morbid infections in cases of immunodeficiency (Lu et al., 2025). While HSV and VZV infections are characterized by a predominantly local (mucocutaneous or neurotropic) Th1-dominant response, EBV and CMV are more associated with the reprogramming of systemic cytokine networks (Lu et al., 2025). Host-genetic and immunological factors determine the amplitude of the cytokine response and clinical outcomes; particularly polymorphisms such as IFN-γ +874 A>T affect CMV susceptibility by modulating the effectiveness of the antiviral Th1 response, while prior exposure and individual immune history also contribute to the formation of innate and adaptive cytokine profiles (Vu et al., 2014; Cheung et al., 2023). Thus, in herpes virus infections, the cytokine response must be considered a multifactorial, dynamic, and context-dependent system; this approach provides the basis for a more precise understanding of clinical phenotypes and the personalization of therapeutic strategies.

Discussion

Confirms that cytokine responses in herpes virus infections are shaped not only by virus-specific characteristics but also by clinical context and host factors. Evaluation of viral nucleic acids in conjunction with cytokine markers (e.g., CXCL9, IL-8, IL-10), particularly in transplant and other immunosuppressive settings, allows for the simultaneous monitoring of both viral reactivation and allograft-related inflammation. The mRNA level of CXCL9, however, can be used as a useful biomarker indicating the link between Th1-type immune activation and graft injury. In CMV and EBV infections, however, it overlaps with the described IL-10-dominant immunoregulatory profile; this cytokine environment both facilitates viral persistence and is associated with immune-mediated damage of the allograft in the transplant context (Saldan et al., 2023). In contrast, infections caused by Herpes simplex virus and Varicella-zoster virus are characterized by a predominantly localized immune response with a Th1-type defense predominating, which is consistent with their primary involvement of the skin, mucosal surfaces, and neural tissues. However, the lack of direct comparative data with bacterial and fungal opportunistic infections also hinders the assessment of immune response specificity. The protective role of Th1 cytokines, particularly IFN-γ, is a common feature for all herpes viruses. In the context of CMV, a reduced ability to produce IFN-γ has been associated with susceptibility to infection, indicating that the effectiveness of the Th1 response is one of the key determinants of clinical outcomes (Vu et al., 2014; Ciccocioppo et al., 2025). In EBV, however, the cytokine profile changes depending on the virus's biological state. While an immunoregulatory environment predominates in the latent phase, pro-inflammatory cytokines increase in the lytic phase, leading to enhanced immune activation (Goetzke et al., 2025). Clinically, in the management of herpes virus infections, not only the viral load but also the cytokine signature (especially the IFN-γ/IL-10 balance) serves as a critical biomarker. Disruption of this balance determines the risk of disease by leading to either insufficient antiviral control (low IFN-γ) or excessive immunosuppression (high IL-10).

Conclusion

In herpes virus infections, the basis of the immune response is an early Th1-type antiviral response (IFN-γ, IL-2, and cytotoxic cells), which is a common defense mechanism for all herpes viruses. However, the clinical course is determined primarily by the degree and balance of this response. In opportunistic herpes viruses such as EBV and CMV, an increase in IL-10 (partially along with IL-6) creates an immunosuppressive environment, enhancing viral persistence and the likelihood of reactivation; this is particularly associated with clinical complications in immunosuppressive conditions such as transplantation. In contrast, the immune response in HSV and VZV infections is characterized by predominantly local and Th1-type control, and systemic immune alterations are less pronounced. Considering the existing gaps, future research should focus on the standardized and quantitative profiling of cytokines in HSV and VZV infections, as well as a more precise

determination of the virus-specific functional role of IL-6. At the same time, the joint assessment of genetic factors and cytokine markers can help to more accurately determine individual risks for patients. From a therapeutic perspective, it is important to test approaches targeting mechanisms related to IL-10, IFN-γ, and IL-6R in clinical trials. Finally, the joint analysis of different biological data and the comparison of different types of infection within the same groups could allow for a broader and more systematic understanding of the immune response. In conclusion, the optimal clinical approach should be based on the complex monitoring of immune markers and the enhancement of the Th1 response or the modulation of immunosuppressive cytokines. This approach lays the foundation for the future development of personalized immunotherapy strategies.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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