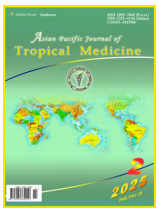

Review Article

Asian Pacific Journal of Tropical Medicine

apjtm.org

doi: 10.4103/apjtm.apjtm_491_24

Antiviral immune responses in human reproductive tract: Pathogenic mechanisms and therapeutic implications

Kim−Ling Chin[1,2]✉, Nurhafiza Zainal[1]

[1]*Department of Medical Microbiology, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia*

[2]*Institute for Advanced Studies, Universiti Malaya, Kuala Lumpur, Malaysia*

ABSTRACT

Viral reproductive tract infections (VRTIs) are a significant global health concern with severe consequences, including infertility, chronic pelvic pain, and increased risk of HIV transmission. Complex interplay between pathogens and the host immune system plays a critical role in the pathogenesis and treatment of VRTIs. This review aims to provide a comprehensive overview of the multifaceted roles of the immune system in both contributing to and combating VRTIs. The review will also address the consequent perturbations in immune homeostasis and the implications for disease manifestation and progression. The interrelation between systemic immunity and local immune responses is discussed, providing insights into the challenges and breakthroughs in managing these infections. By providing a comprehensive overview of the mechanisms, implications, and therapeutic strategies associated with viral reproductive tract infections and immune dysfunction, this review also informs future research and clinical practice in this important area of reproductive health.

KEYWORDS: Viral reproductive tract infections (VRTIs); Immune response; Human papillomavirus (HPV); Herpes simplex virus (HSV); Cytomegalovirus (CMV); Human immunodeficiency virus (HIV); Zika virus (ZIKV); Hepatitis B virus (HBV); Hepatitis C virus (HCV)

1. Introduction

Viral reproductive tract infections (VRTIs) are infections caused by viruses that specifically target both male and female reproductive system. These infections can range from mild to severe, even leading to chronic health issues or complications in reproductive health such as infertility, miscarriage, chronic pelvic pain, and an increased risk of HIV transmission[1]. VRTIs can be transmitted among humans through various routes, including sexual contact, which is the primary route of transmission, but also through blood, vertical transmission from mother to child, or occasionally through non-sexual contact with infected body fluids. A community-based cross-sectional study conducted in Kancheepuram District, Tamil Nadu, revealed that a high prevalence of VRTIs at 50.3% with the majority of affected individuals (61.3%) were women aged 28-37 years[2]. The elevated prevalence among lower-middle-class and nuclear families could be attributed to factors such as social stigma, restricted healthcare access, substandard hygiene practices, and inadequate awareness of preventive measures.

VRTIs encompass a diverse array of viruses, each with distinct pathogenic mechanisms and implications for health. Notable viruses such as the human papillomavirus (HPV), herpes simplex virus (HSV), cytomegalovirus (CMV), human immunodeficiency virus (HIV), Zika virus (ZIKV), hepatitis B and C viruses (HBV and HCV) pose significant risks to human reproductive health through various mechanisms such as infertility[3], pregnancy complications (*e.g.*, miscarriage, preterm labour and low body weight)[4], congenital infections[5], co-infections[6], neurological manifestations[7] and potential cancer development[8]. Understanding the biology and

✉To whom correspondence may be addressed. E-mail: kimling@um.edu.my

How to cite this article: Chin KL, Zainal N. Antiviral immune responses in human reproductive tract: Pathogenic mechanisms and therapeutic implications. Asian Pac J Trop Med 2025; 18(2): 67-76.

Article history: Received 7 August 2024 Revision 13 February 2025
Accepted 26 February 2025 Available online 28 February 2025

pathogenesis of these viruses is essential in developing effective prevention and management strategies for VRTIs.

Viral infections in the human reproductive system trigger a complex interplay between the immune response and the pathogenesis of these infections. For instance, T cell-mediated immunity, especially CD8+ T cells, play a crucial role in clearing virus-infected cells from the reproductive tract. Moreover, immunoglobulins generated by B cells can recognize and neutralize viruses, limiting viral infections in the reproductive tract. However, some viruses can escape both cellular and humoral immunity by altering their surface antigens or through interactions with immune suppressive factors, leading to persistence of the viruses[9]. On the other hand, the over-activation immune response to VRTIs, marked by excessive production of pro-inflammatory cytokines and interferons, frequently results in inflammation in the reproductive tract, which can cause tissue damage and disrupt normal reproductive function[10]. By delving into the intricate interactions between viruses and the immune system within the reproductive tract, researchers aim to unravel key mechanisms driving viral pathogenesis and immune responses to develop targeted interventions for managing these infections effectively.

2. Immune response in human reproductive tract

2.1. Innate immune response in human reproductive tract

The immune mechanisms found the human reproductive tract, which includes the fallopian tubes, uterus, vagina in females and the penis, epididymis, and urethra in males, are tailored to provide both immediate and long-lasting defense against pathogens while maintaining the delicate balance necessary for reproductive functions. The human reproductive tract possesses a sophisticated innate immune response system as its first line of defense.

Epithelial cells lining the reproductive tract act as a critical physical barrier, providing continuous protection against pathogens (*e.g.*, bacteria, viruses and fungi) by forming tight junctions composed of transmembrane proteins like occludin, claudin, and junctional adhesion molecules[11]. For instance, primary genital epithelial cells, particularly endocervical and endometrial cells, have been isolated from hysterectomy tissue and shown to form tight junctions[12]. Epithelial cells play a role in bolstering the immunological barrier through the secretion of antimicrobial peptides (AMPs), including defensins and cathelicidin, as well as cytokines. They express pattern recognition receptors, especially Toll-like receptors, which recognize microbial-associated molecular patterns and initiate immune responses to eradicate pathogens[13]. In addition, sex hormones, such as estrogen and progesterone, regulate epithelial cell function within the reproductive tract. These hormones influence epithelial permeability, microbicidal activity, cytokine/chemokine secretion, immune cell recruitment, and activation to ensure protection for both maternal and fetal health[12].

Immune cell recruitment in the human reproductive tract is a highly dynamic and complex process that serves contradictory roles: maintaining immunity against vaginal pathogens in the lower tract while establishing immune tolerance for sperm and embryo/fetus in the upper tract. Following insemination, neutrophils play a crucial role in eliminating excess spermatozoa and potential bacterial cells that could pose a risk of infection[14]. Antigen-presenting cells, including dendritic cells (DCs) and macrophages, are the key players in triggering the immune response upon detection of pathogens. Langerhans cells, a specific type of DC found in the vaginal and cervical epithelium, recognize pathogens and trigger initial immune responses. Activated immune cells can then eliminate pathogens through various mechanisms, such as phagocytosis, production of antimicrobial peptides, and release of cytokines and chemokines to recruit additional immune cells. On the other hand, endometrial/decidual natural killer (NK) cells expand during the late secretory phase and early pregnancy, playing important roles in decidual angiogenesis, trophoblast migration, and immune tolerance during pregnancy[15]. Dysregulation of these immune cells is strongly associated with infertility, miscarriage and other obstetric complication[14].

2.2. Adaptive immune response in human reproductive tract

The adaptive immune response in the human reproductive tract is a critical aspect of reproductive health, involving a complex interplay of immune cells and responses tailored to the unique microenvironments of these tissues. The adaptive immune response consists of two main components: humoral immunity and cell-mediated immunity.

Research has shown that specialized immune cells, particularly T and B lymphocytes, are distributed throughout the reproductive organs, including the uterus, fallopian tubes, and ovaries, where they contribute to immune surveillance and protection against pathogens[16]. These immune cells undergo activation and differentiation upon encountering specific antigens present in the reproductive environment, leading to the generation of antigen-specific immune responses tailored to local threats. Moreover, immune tolerance mechanisms are crucial for preventing the rejection of the semi-allogeneic fetus during pregnancy. Research has elucidated the role of regulatory T cells (Tregs) and other immune regulatory molecules in maintaining immune tolerance at the maternal-fetal interface[16]. Dysregulation of adaptive immune responses in the reproductive tract has been implicated in various

reproductive disorders, including infertility, recurrent miscarriage, and preterm birth. Understanding the complexities of adaptive immunity in the reproductive tract is essential for advancing reproductive medicine and developing targeted therapeutic strategies to optimize reproductive outcomes. For instance, research has shown that the oestrous cycle can influence vaccine-induced immunity in the reproductive tract, and the development of successful vaccines to prevent the spread of sexually transmitted diseases (STDs) may require the use of female sex hormones as adjuvants to ensure effective immunity[17].

3. Immunopathogenesis in the human reproductive tract

3.1. Human papillomavirus (HPV)

HPV is the most common viral infection of both male and female reproductive tract, leading to various clinical manifestations, including anogenital warts, precancers, and cancers. HPV is a family of small, double-stranded DNA viruses that infect the epithelium, with approximately 200 different strains, some of which are notably oncogenic. Notably, HPV 13, 16 and 18 are responsible for the majority of cervical cancer cases, while HPV 6 and 11 primarily cause genital warts[18]. HPV can integrate into host chromosomes, leading to the upregulation of viral oncoproteins like E6 and E7, direct disruption of tumor suppressor genes, induction of chromosome instability, thereby disrupting normal cell-cycle control and contributing to oncogenic processes[19]. HPV infections are prevalent worldwide, accounting for 5% of human cancers, including oral and respiratory squamous cell carcinomas, as well as cervical and anogenital cancers. Annually, an estimated 625 600 women and 69 400 men develop an HPV-related cancer[20].

In the context of HPV infection, the immune response is critical for clearing the infection. However, HPV has evolved mechanisms to evade the immune response, enabling for persistent infection and the development of clinical manifestations. One such mechanism is the downregulation of major histocompatibility complex (MHC) class Ⅰ molecules, which are vital for presenting viral antigens to CD8+ cytotoxic T lymphocytes (CTLs)[21]. This downregulation hampers the ability of the immune system to recognize and respond to the virus effectively. Consequently, the evasion of CD8+ T cell detection allows HPV to persist in the host, contributing to prolonged infection and disease progression. Another mechanism by which HPV evades the immune response is through the production of viral proteins. For example, the E6 and E7 proteins of high-risk HPV types possess the capability to hinder the activation and function of CD4+ T cells, further contributing to immune evasion[22]. The HPV-16 E6 and E7 has been also found to suppress the transcription of macrophage inflammatory protein (MIP)-3β, leading to inhibition of immature Langerhans precursor-like cells migration[23]. Moreover, HPV can induce the production of immune suppressive cytokines, such as IL-2 receptor alpha/forkhead box P3 (CD25/FOXP3), interferon-gamma (IFN-γ), interleukin-10 (IL-10) and transforming growth factor-β (TGF-β), which can inhibit the immune response and promote the persistence of the virus[24]. Additionally, the HPV-associated tumor microenvironment can be immunosuppressive, further contributing to the persistence of HPV and the development of cancer[22]. Tumor-associated macrophages can produce immune suppressive cytokines, such as IL-10 and TGF-β, which can inhibit the immune response and promote tumor growth[25].

3.2. Herpes simplex virus (HSV)

HSV infection is one of the most common sexually transmitted infections worldwide, characterized by two predominant types: HSV-1 and HSV-2. HSV-1 is typically associated as oral herpes, which manifest as cold sores or fever blisters around the mouth, lips and occassionally the facial region. Meanwhile, HSV-2 primarily associates with genital herpes, causing sores or blisters in the genital area. The complications of genital herpes can be severe such as lumbosacral myeloradiculitis, which may result in urinary retention or obstipation. Additionally, neonatal HSV infection poses significant risks, contributing to substantial morbidity and mortality in newborns, while postnatal exposure increases the susceptibility to severe disease manifestations[26]. Notably, genital HSV-2 infections exhibit a recurrence rate sixfold higher than oral-labial HSV-1 infections[27]. In the United States, an estimated 18.6 million prevalent cases and 572 000 incident genital herpes infections were reported among individuals aged 18-49 years[28]. In Asia, HSV-2 contributes to 75% of genital herpes cases, with prevalence rates of 12.1% in general populations and 23.6% among men who have sex with men and transgender people[29].

HSV-2's immunopathogenesis involves a complex interplay between the virus and the host's immune response, resulting in latency establishment and severe symptoms development. HSV-2, like many viruses, has developed mechanisms to evade immune recognition, such as MHC class Ⅰ molecules downregulation on infected cells. For instance, herpes viruses disrupt the MHC class Ⅰ peptide-loading complex, hindering antigen presentation and evading immune response, by disrupting transporter associated with antigen-processing (TAP)-mediated peptide translocation[30]. Besides, HSV-2 directly infects CD4+ T cell subpopulations, including T follicular helper cells, promoting HIV reactivation in individuals co-infected with HIV[31]. Another mechanism in which HSV-2 impairs the immune system's ability to generate a robust localized response

to the infection is by hindering the migration of immune cells to the infection site. For instance, HSV-2 inhibits the migration of monocyte-derived DCs, potentially hampering antiviral immunity by hindering antigen delivery to secondary lymphoid organs[32]. HSV-2 possesses the distinctive ability to establish latency in the sensory dorsal root ganglia, a less immune-surveilled environment[33]. This allows the virus to remain dormant for extended periods, contributing to its persistence and evasion of immune detection.

3.3. Cytomegalovirus (CMV)

CMV is a leukocytotropic human herpesvirus that can cause severe clinical complications affecting multiple organs in the body. CMV seroprevalence in the general population globally range from 40% to 100%, with an average of 83% among the general population, 86% among women of childbearing age, and 86% among blood or organ donors[34]. In immunocompromised patients, such as those who have undergone hematopoietic stem cell transplant recipients, the risk of CMV recurrence is significantly elevated, with rates of 37% after allogeneic transplant and 12% after autologous transplant[35]. CMV infection can also impact reproductive health by infecting the cervix, potentially causing cervical inflammation and potential scarring that may affect fertility. Congenital CMV infection is the leading cause of non-genetic sensorineural hearing loss, as well as impairments in virion function and cognitive abilities in children. Although rare, CMV infection can also trigger autoimmune responses, such as Guillain-Barré syndrome, characterized by severe sensory deficits and the presence of anti-GM2 IgM antibodies following recent CMV infection[36].

Immune evasion is a pivotal strategy employed by viruses to establish infection, persist within the host, and occasionally trigger chronic or recurrent diseases. In case of CMV, a notable immunopathogenesis mechanisms involves the expression of homologs of MHC class Ⅰ molecules, such as unique long (UL) proteins (*e.g.*, UL16, UL18, UL142) that bind to NK-inhibitory ligands, thereby allowing the virus to evade NK cell responses[37]. Other than UL, CMV employs a repertoire of genes known as unique short (US) genes (*e.g.*, US2, US3, US6, US11) to interfere with MHC class Ⅰ antigen processing, preventing the development of a cytotoxic T-cell response to CMV infection through MHC retention in the ER, facilitation MHC degradation, and downregulate MHC expression[37]. The immunosuppressive milieu formed by CMV is integral to its immunopathogenesis, as it contributes significantly to the virus's persistence and pathogenicity. CMV infection elicits a robust and chronic antigenic response, leading to transient yet substantial immunosuppression against virus itself and other pathogens[38]. For instance, patients with CMV mononucleosis often exhibit delayed-type hypersensitivity reactions to recall antigens, highlighting CMV's ability to weaken host immune system[39]. Moreover, CMV has been found to modulate host immune response to facilitate persistent infection and exploit immunological consequences. Notably, CMV-encoded genes mimic host cytokines and chemokines, exemplified by the IL-10 homolog UL111A and the C-X-C and C-C chemokine homologs UL146, UL147 and UL148, serving to downregulate host inflammation and promote viral dissemination[37,40,41].

3.4. Human immunodeficiency virus (HIV)

HIV is a significant viral reproductive tract infection characterized by its impact on the immune system. HIV belongs to the Retroviridae family and manifests in two primary forms: HIV-1 and HIV-2, which target CD4+ lymphocytes, leading to compromised cell-mediated immunity and increased susceptibility to various opportunistic infections and certain cancers. Research indicates that women living with HIV are at increased risk of RTIs, such as vaginal candidiasis, trichomoniasis, and HPV infections, along with potential experiences of cervical inflammation and genital neoplasia[42]. The global burden of HIV/AIDS is estimated to be 37 million cases, with 0.8% of the world population aged 15-49 years living with HIV and a vast majority in sub-Saharan Africa[43]. The incidence of HIV infection has shown a declining trend in many regions, yet challenges persist in achieving the World Health Organization's Fast-Track strategy to end the AIDS epidemic by 2030.

The immunopathogenesis of HIV involves several complex mechanisms through which the virus impacts and ultimately leads to the deterioration of the immune system. One of the key mechanisms of HIV immune evasion involves downregulation of cell surface CD4 and MHC class Ⅰ molecules. This is achieved through the viral accessory proteins such as negative regulatory factor (Nef) and virion protein U (Vpu), which interact with cellular trafficking machinery to eliminate these molecules from the cell surface and target them for degradation[44]. Additionally, HIV impairs the function of NK cells through the manipulation of interactions between NK cell receptors and their ligands. For example, the HIV-1 Nef protein downregulates ligands such as MHC class Ⅰ polypeptide-related sequence A and UL16-binding protein, which bind to NKG2D, an activating receptor expressed by all NK cells[45]. The HIV protein Nef has also been found to downregulate HLA class Ⅰ molecules while selectively preserving the ligands for inhibitory killer-cell immunoglobulin-like receptors such as HLA-C and HLA-E, allowing HIV-infected cells to evade recognition by both CD8+ T cells and NK cells[46]. On the other hand, chronic immune activation is considered a driving force of CD4+ T-cell depletion and AIDS progression in HIV infection. Persistent viral antigen exposure, microbial translocation, and inflammation lead to the activation and exhaustion of HIV-specific

T cells, as well as the induction of immunosuppressive mechanisms such as the upregulation of programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)[47,48].

3.5. Zika virus (ZIKV)

ZIKV, a member of the Flaviviridae family, is a mosquito-borne virus that has gained significant attention due to its association with adverse fetal outcomes, including congenital microcephaly and neurological complications. Originally discovered in 1947, it remained relatively obscure until outbreaks in Micronesia and French Polynesia, then surged in the Americas, notably Brazil, causing microcephaly and Guillain-Barré syndrome[49]. The virus has been found to persist in various bodily fluids, including semen and vaginal secretions, raising concerns about sexual transmission and the potential for long-term health consequences[50].

The pathogenicity of ZIKV is initiated by viral infection and propagation across multiple placental and fetal tissue barriers, bolstered significantly by subverting host immunity. ZIKV employs various mechanisms to evade the immune system, particularly targeting interferon (IFN) signaling, which is pivotal for antiviral defense. The ZIKV non-structural protein, NS5, degrades the cellular signal transducer and activator of transcription 2 (STAT2) protein, resulting in inhibition IFN-stimulated JAK-STAT signaling, thereby reducing the expression of IFN-stimulated genes (ISGs)[51]. Apart from the JAK-STAT pathway, the ZIKV NS2B3 protease has been found to degrade the cGMP-AMP synthase/stimulator of IFN genes (cGAS/STING) signaling pathway to evade host antiviral defenses[52]. ZIKV-induced blockade of TANK-binding kinase 1 (TBK1) phosphorylation is indeed related to the modulation of IFN signaling. NS1 and NS4B has been found to interact with TBK1, inhibiting interferon regulatory factor 3 (IRF3) phosphorylation and its nuclear translocation, which results in reduced expression of IFN-β[53,54]. Moreover, research reveals that ZIKV is able to interfere with intracellular signal pathways to enhance its survival and replication. For example, the ZIKV NS3 protein mimics the 14-3-3-binding motif by interacting with both 14-3-3 and its scaffold protein, thereby counteracting RIG-1 and MDA5-mediated innate immune responses[55]. On the other hand, ZIKV-induced extracellular HMGB1 release may contribute to ZIKV immunopathogenesis, with its release coinciding with ZIKV neuroinvasion[56] and inhibition of its translocation correlating with reduced ZIKV replication[57,58].

3.6. Hepatitis B virus (HBV) and hepatitis C virus (HCV)

HBV and HCV are major etiological agents of chronic liver disease globally, infecting millions of individuals and posing significant public health challenges. The World Health Organization estimates that approximately 296 million people worldwide are living with HBV, while 58 million people are living with HCV[59]. In addition to liver cirrhosis and hepatocellular carcinoma, both HBV and HCV can also impact the reproductive tract through sexual transmission, with implications for vertical transmission during pregnancy. In men, HBV infection negatively impacts sperm quality, reducing motility, mitochondrial membrane potential, and fertilizing ability[60]. Women with HBV undergoing assisted reproduction technologies have lower cumulative live birth rate compared to those with chronic hepatitis, possibly due to less favorable ovarian reserve parameters[61]. HCV infection has been associated with adverse pregnancy outcomes, including intrahepatic cholestasis of pregnancy and postpartum hemorrhage[62].

Both HBV and HCV have developed sophisticated immune evasion strategies to persist within the host and evade immune surveillance. One key strategy is impairing the host's innate immune sensing mechanisms to avoid recognition. For instance, HBV interferes with host immune responses by targeting host microRNAs, such as the downregulation of miR-615-3p, which contributes to dysfunction of DCs in chronic HBV infection, facilitating HBV immune evasion[63]. The HCV core protein physically interacts with STAT-1, inhibiting its activation and consequently blocking Jak-STAT signaling, thereby disrupting the downstream IFN signaling cascade[64]. In addition, impairing innate immune sensing, both HBV and HCV exert mechanisms to dampen both T cell and B cell functions, promoting immune tolerance and viral persistence. HBV-specific T cells exhibit significant dysfunction during chronic infection due to elevated expression of inhibitory checkpoint receptor/ligands, such as PD-1 and CTLA-4[65]. HCV's NS3/4A has also been found to enhance B cell receptor signaling in human primary B cells by increasing the pathway's association with human antigen R protein, potentially contributing to B cell dysfunction and impaired antibody production against the virus[66].

4. Therapeutic implications: Immunomodulatory therapies

Treating viral reproductive tract infections presents numerous challenges, including antimicrobial resistance, asymptomatic infections, co-infections, incurability of certain viral RTIs, severe complications, and emerging infections. These factors complicate management strategies and necessitate innovative approaches to improve patient outcomes. Emerging therapies such as immunotherapies, vaccines, and combination treatments offer new strategies beyond traditional antiviral drugs, boosting the immune response against various viral pathogens and lowering resistance risks compared to specific antiviral treatments, especially beneficial for immunocompromised patients.

One of the most successful strategies has been the development of

prophylactic vaccines, notably against HPV. FDA-approved vaccines like Cervarix, Gardasil and Gardasil-9, along with the vaccine candidate VGX-3100 (currently undergoing Phase ⅢⅢ clinical trials) have been highly effective in preventing persistent HPV infections and pre-malignant neoplasias by inducing a strong humoral and cellular immune response[67-69]. This represented therapeutic vaccination, where the goal is not just to prevent infection but also to treat existing HPV-related diseases, offers new hope for patients with persistent infections or early-stage cancers. Besides vaccines, immunomodulation using immune checkpoint inhibitors (ICIs) like nivolumab, an anti-PD-1 agent and ipilimumab, a CTLA-4 blocker, has demonstrated efficacy in treating various cancers[70]. ICIs serve to enhance effector T-cell anti-tumor responses by inhibiting the T-cell-inhibitory PD-1/PD-L1 and CTLA-4/CD80/86 signaling axes, leading to sustained effector T-cell activity and circumventing the immune evasion of tumor cells, thereby improving their antiviral functionality[71]. For instance, emerging studies suggest that ICIs can be safely administered to cancer patients with chronic HBV or HCV infections with low rates of viral reactivations (1.4% for HBV and 0.5% for HCV)[72,73].

The development of an HSV-2 vaccine remains ongoing, with HSV529 and Moderna's mRNA-1608 being prominent candidates. HSV529 has completed a Phase Ⅰ clinical trial, demonstrating efficacy in eliciting both antibody and T-cell responses, although it has not yet advanced to Phase ⅢⅢ clinical trials[74]. Moderna's mRNA-1608, a trivalent HSV-2 vaccine targeting glycoproteins gC2, gD2, and gE2, is currently undergoing Phase 1/2 clinical trials (NCT06033261) that began in September 2023, with preclinical studies showing complete protection in mice and induction of strong immune responses[75]. Additionally, immunomodulatory agents such as imiquimod and alitretinoin gel have shown potential in managing HSV-2 infections. For example, imiquimod has been effective in providing protection against genital herpes in guinea pig models by reducing the recurrence of HSV-2 lesions[76]. Similar to imiquimod, alitretinoin gel may offer a new therapeutic approach for the treatment of other cutaneous viral diseases, including HSV-2 infections[77].

There is currently no approved vaccine for CMV, but several candidate vaccines are in various stages of clinical development. Notable examples include CMV PepVax[78] and gB/MF59[79], both in Phase Ⅱ clinical trials, and mRNA-1647 that has progressed to Phase ⅢⅢ clinical trials[80]. In parallel, CMV-specific immunoglobulins have the potential to lessen the severity and duration of CMV reactivation in paediatric hematopoietic stem cell transplant recipients without causing adverse events[81]. Furthermore, CMV-specific adoptive T-cell therapy has shown promise as a clinically safe and potentially beneficial treatment for solid organ transplant recipients with recurrent or drug-resistant CMV infection or disease[82].

Antiretroviral therapy remains the cornerstone of HIV treatment, suppressing viral replication and restoring immune function. However, antiretroviral therapy is not curative, as treatment interruption typically leads to a viral rebound in most cases. Developing an effective preventive HIV vaccine has been an ongoing challenge due to virus's rapid mutation rate and ability to evade host immune responses. Clinical trials of various vaccine candidates have been conducted, including the HIV eOD-GT8 60-mer nanoparticle vaccine, which showed promising results in a first-in-human trial by eliciting a robust immune response in healthy adult volunteers[83]. Other than vaccine, chimeric antigen receptor T cell therapy shows potential to target and eliminate HIV-infected cells, with promising preclinical results, though more research is needed for human safety and efficacy[84]. A wide variety of immunomodulatory latency reserving agents are under investigation in order to eliminate the latent HIV reservoir, including histone deacetylase inhibitors, protein kinase C agonists, bromodomain inhibitors, and immune modulators like cytokines and Toll-like receptor agonists[85]. Combination strategies using immunomodulatory latency reserving agents alongside other interventions like CD8+ T cell depletion or broadly neutralizing antibodies have shown promising results in reducing viral reservoirs in animal models, but have not yet demonstrated remission in human[86].

ZIKV prevention is being pursued through vaccines like the DNA vaccines VRC-ZKADNA085-00-VP and VRC-ZKADNA090-00-VP in Phase Ⅱ trials, and Moderna's mRNA vaccines mRNA-1893 and mRNA-1325 in Phase Ⅰ and Ⅱ trials, respectively, aiming for robust immune protection[87]. Recently, a single-dose circular RNA vaccine encoding ZIKV envelope proteins has demonstrated effective protection in mice, highlighting the advantages of circRNA technology in generating robust immune responses without the risk of antibody-dependent enhancement (ADE) seen with other viral vaccines[88]. Additionally, monoclonal antibodies such as ZIKV-117, Z20 and ZIKV-195[89], along with immune modulators such as interferons (IFN-α and IFN-β) represent promising approaches for treating and managing Zika virus infections[90].

The FDA has approved three recombinant hepatitis B vaccines-Engerix-B, Heplisav-B and Recombivax HB, which have demonstrated safety and efficacy in clinical trials across all age groups[91]. In contrast, while several candidate vaccines of HCV have been evaluated in clinical trials, such as NCT02772003, NCT01055821, NCT02027116, NCT00606086, NCT00124215, NCT01701336, NCT01094873, and NCT04318379, none have yet received FDA approval for commercial use[92]. The development of an effective HCV vaccine remains challenging due to the high genetic variability of the virus and the lack of an ideal animal model for preclinical testing. Interferon-based therapy, specifically pegylated interferon-alpha (PEG-IFN-α), is a key component in the treatment of chronic HBV and HCV infections by binding to type

1 IFN receptors, activating the JAK/STAT pathway, and stimulating the body's innate antiviral response[93]. The use of checkpoint inhibitors, particularly those targeting the PD-1/PD-L1 pathway, has shown promise in enhancing antiviral immunity against both HBV and HCV infections. For instance, Camrelizumab, an anti-PD-1 antibodies, has been evaluated in clinical trials for their potential to enhance T cell responses and control HBV and HCV infections[94,95].

Overall, emerging therapies, including immunotherapies, vaccines, and combination treatments, are transforming the management of infectious diseases and cancer. Immunotherapies, such as checkpoint inhibitors and adoptive cell therapies, leverage the immune system to boost responses against pathogens and tumors. Advances in vaccines for diseases like HIV and ZIKV are notable, though rapid viral mutations and cross-reactivity remain challenges. Combination treatments that blend therapeutic modalities have shown promise in enhancing efficacy. However, significant challenges persist, including managing latent infection reactivation, the need for personalized treatment plans, and ensuring safety across diverse populations. Continued research and innovation are essential to overcome these challenges and refine therapeutic strategies for improved patient outcomes.

5. Conclusions

The immune responses elicited during VRTIs are complex and multifaceted. While the host immune system mounts various defense mechanisms to combat these infections, the viruses have evolved sophisticated strategies to evade and subvert the immune response. Understanding the intricate interplay between the host immune defenses and viral evasion tactics is crucial for developing effective therapeutic interventions. Advances in elucidating the pathogenic mechanisms underlying VRTIs, such as the dysregulation of cytokine signaling, impairment of antigen presentation, and modulation of innate and adaptive immune responses, have paved the way for innovative treatment approaches. However, while this review offers a comprehensive analysis of immune responses in VRTIs across a broad range of viruses, it does not extensively address the variability in immune interactions within the reproductive tract due to genetic, environmental, and hormonal influences. The exploration of immunomodulatory therapies, including the targeting of specific immune pathways, the enhancement of antiviral immunity, and the optimization of combination strategies, hold promise for improving clinical outcomes and reducing the burden of these challenging viral infections. Continued research and clinical translation of these insights will be essential to address the unmet medical needs and improve the quality of life for individuals affected by VTRIs.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Funding

This study was supported by the Universiti Malaya ArtScience Fellowship Grant (UMG004-2024IAS) and UM Community Engagement Grant 2023 (Project RUU002-23KS).

Authors' contributions

K.L.C. conducted a comprehensive literature search and contributed to manuscript preparation. N.Z. contributed in the manuscript editing, reviewing, and refining the content. All the authors have reviewed and approved the final manuscript.

References

[1] Katawa G, Tchopba C, Ritter M, da Silva M, Ameyapoh A, Arndts K, et al. Female reproductive tract health: Prevalence and risk factors associated with infections in Lomé. (Female reproductive tract infections in Lomé). *Clin Res Trials* 2021; **7**: 1-9.

[2] Balakrishnan S, Carolin A, Sudharsan B, Shivasakthimani R, Balasubramanian S. The prevalence of reproductive tract infections based on the syndromic management approach among ever-married rural women in Kancheepuram District, Tamil Nadu: A community-based cross-sectional study. *Cureus* 2022; **14**(3). doi:10.7759/cureus.23314.

[3] Garolla A, Pizzol D, Bertoldo A, Menegazzo M, Barzon L, Foresta C. Sperm viral infection and male infertility: Focus on HBV, HCV, HIV, HPV, HSV, HCMV, and AAV. *J Reprod Immunol* 2013; **100**(1): 20-29.

[4] Chan M, Smith M. Infections in pregnancy. *Compr Toxicol* 2018; **5**: 232-249.

[5] Hon K, Leung KK, Leung AK, Man E, Ip P. Congenital infections in Hong Kong: Beyond TORCH. *Hong Kong Med J* 2020; **26**(4): 323-330.

[6] Grayo S. Is the ZIKV congenital syndrome and microcephaly due to syndemism with latent virus coinfection? *Viruses* 2021; **13**(4): 669.

[7] Dos Santos T, Rodriguez A, Almiron M, Sanhueza A, Ramon P, de Oliveira WK, et al. Zika virus and the Guillain-Barré syndrome-case series from seven countries. *N Engl J Med* 2016; **375**(16): 1598-1601.

[8] Bowden SJ, Doulgeraki T, Bouras E, Markozannes G, Athanasiou A, Grout-Smith H, et al. Risk factors for human papillomavirus infection, cervical intraepithelial neoplasia and cervical cancer: An umbrella review and follow-up Mendelian randomisation studies. *BMC Med* 2023; **21**(1): 274.

[9] Chan YK, Gack MU. Viral evasion of intracellular DNA and RNA sensing. *Nat Rev Microbiol* 2016; **14**(6): 360-373.

[10]Sheldon IM, Owens SE, Turner ML. Innate immunity and the sensing of infection, damage and danger in the female genital tract. *J Reprod Immunol* 2017; **119**: 67-73.

[11]Wira CR, Grant-Tschudy KS, Crane-Godreau MA. Epithelial cells in the female reproductive tract: A central role as sentinels of immune protection. *Am J Reprod Immunol* 2005; **53**(2): 65-76.

[12]Plesniarski A, Siddik AB, Su RC. The microbiome as a key regulator of female genital tract barrier function. *Front Cell Infect Microbiol* 2021; **11**: 1292.

[13]Amjadi F, Salehi E, Mehdizadeh M, Aflatoonian R. Role of the innate immunity in female reproductive tract. *Adv Biomed Res* 2014; **3**: 1.

[14]Visnyaiová K, Varga I, Feitscherová C, Pavlíková L, Záhumensk J, Mikušová R. Morphology of the immune cells in the wall of the human uterine tube and their possible impact on reproduction-uterine tube as a possible immune privileged organ. *Front Cell Dev Biol* 2024; **12**: 1325565.

[15]Liu S, Diao L, Huang C, Li Y, Zeng Y, Kwak-Kim JY. The role of decidual immune cells on human pregnancy. *J Reprod Immunol* 2017; **124**: 44-53.

[16]Yüzen D, Arck PC, Thiele K. Tissue-resident immunity in the female and male reproductive tract. *Semin Immunopathol* 2022; **44**(6): 785-799.

[17]Beagley KW, Gockel CM. Regulation of innate and adaptive immunity by the female sex hormones oestradiol and progesterone. *FEMS Immunol Med Microbiol* 2003; **38**(1): 13-22.

[18]Okunade KS. Human papillomavirus and cervical cancer. *J Obstet Gynaecol* 2020; **40**(5): 602-608.

[19]Mittal S, Banks L. Molecular mechanisms underlying human papillomavirus E6 and E7 oncoprotein-induced cell transformation. *Mutat Res Rev Mutat Res* 2017; **772**: 23-35.

[20]Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021; **71**(3): 209-249.

[21]Hirata Y, Kondo K, Yamanishi K. Human herpesvirus 6 downregulates major histocompatibility complex class Ⅰ in dendritic cells. *J Med Virol* 2001; **65**(3): 576-583.

[22]Smola S. Immunopathogenesis of HPV-associated cancers and prospects for immunotherapy. *Viruses* 2017; **9**(9): 254.

[23]Guess JC, McCance DJ. Decreased migration of Langerhans precursor-like cells in response to human keratinocytes expressing human papillomavirus type 16 E6/E7 is related to reduced macrophage inflammatory protein-3 production. *J Virol* 2005; **79**(23): 14852-14862.

[24]Bonin CM, Padovani CT, Ferreira AMT, Ávila LS, Machado AP, Prata T, et al. Predominant overexpression of CD25/FOXP3, IFN-γ, and suppressive cytokines in high-grade lesion samples infected with human papillomavirus. *J Bras Patol Med Lab* 2017; **53**: 53-60.

[25]Lin Y, Xu J, Lan H. Tumor-associated macrophages in tumor metastasis: Biological roles and clinical therapeutic applications. *J Hematol Oncol* 2019; **12**(1): 76.

[26]Pittet LF, Curtis N. Postnatal exposure to herpes simplex virus: To treat or not to treat? *Pediatr Infect Dis J* 2021; **40**(5S): S16-S21.

[27]Lafferty WE, Coombs RW, Benedetti J, Critchlow C, Corey L. Recurrences after oral and genital herpes simplex virus infection. *N Engl J Med* 1987; **316**(23): 1444-1449.

[28]Spicknall IH, Flagg EW, Torrone EA. Estimates of the prevalence and incidence of genital herpes, United States, 2018. *Sex Transm Dis* 2021; **48**(4): 260-265.

[29]AlMukdad S, Harfouche M, Wettstein A, Abu-Raddad LJ. Epidemiology of herpes simplex virus type 2 in Asia: A systematic review, meta-analysis, and meta-regression. *Lancet Reg Health West Pac* 2021; **12**: 100176.

[30]Praest P, Liaci AM, Förster F, Wiertz EJ. New insights into the structure of the MHC class Ⅰ peptide-loading complex and mechanisms of TAP inhibition by viral immune evasion proteins. *Mol Immunol* 2019; **113**: 103-114.

[31]Pierce CA, Loh LN, Preston-Hurlburt P, Herold KC, Herold BC. HSV-2 infects T follicular helper cells to promote HIV reactivation. *J Immunol* 2020; **204**(Suppl_1). doi: 10.4049/jimmunol.204.Supp.247.24.

[32]Grosche L, Mühl-Zürbes P, Ciblis B, Krawczyk A, Kuhnt C, Kamm L, et al. Herpes simplex virus type-2 paralyzes the function of monocyte-derived dendritic cells. *Viruses* 2020; **12**(1): 112.

[33]Yanez AA, Harrell T, Sriranganathan HJ, Ives AM, Bertke AS. Neurotrophic factors NGF, GDNF and NTN selectively modulate HSV1 and HSV2 lytic infection and reactivation in primary adult sensory and autonomic neurons. *Pathogens* 2017; **6**(1): 5.

[34]Zuhair M, Smit GSA, Wallis G, Jabbar F, Smith C, Devleesschauwer B, et al. Estimation of the worldwide seroprevalence of cytomegalovirus: A systematic review and meta-analysis. *Rev Med Virol* 2019; **29**(3): e2034.

[35]Styczynski J. Who is the patient at risk of CMV recurrence: A review of the current scientific evidence with a focus on hematopoietic cell transplantation. *Infect Dis Ther* 2018; **7**: 1-16.

[36]Dowling PC, Cook SD. Role of infection in Guillain-Barré syndrome: Laboratory confirmation of herpesviruses in 41 cases. *Ann Neurol* 1981; **9**(Suppl_1): 44-55.

[37]Schleiss MR. Congenital cytomegalovirus infection: Molecular mechanisms mediating viral pathogenesis. *Infect Disord Drug Targets* 2011; **11**(5): 449-465.

[38]Varani S, Landini MP. Cytomegalovirus-induced immunopathology and its clinical consequences. *Herpesviridae* 2011; **2**: 1-14.

[39]Griffin D. Potential mechanisms of immune suppression. In: Nathanson N. (ed.) *Viral Pathogenesis.* Philadelphia, PA: Lippincott-Raven; 1996, p. 207-235.

[40]Kotenko SV, Saccani S, Izotova LS, Mirochnitchenko OV, Pestka S. Human cytomegalovirus harbors its own unique IL-10 homolog

(cmvIL-10). *Proc Natl Acad Sci U S A* 2000; **97**(4): 1695-1700.

[41]Siddiquey MN, Zhang H, Nguyen CC, Domma AJ, Kamil JP. The human cytomegalovirus endoplasmic reticulum-resident glycoprotein UL148 activates the unfolded protein response. *J Virol* 2018; **92**(20): e00896-18.

[42]Sharma A, Marfatia Y, Modi M. Reproductive tract infections in HIV positive women: A case control study. *Indian J Sex Transm Dis AIDS* 2009; **30**(1): 16-18.

[43]Del Rio C. The global HIV epidemic: What the pathologist needs to know. *Semin Diagn Pathol* 2017; **4**: 314-317.

[44]Haller C, Müller B, Fritz JV, Lamas-Murua M, Stolp B, Pujol FM, et al. HIV-1 Nef and Vpu are functionally redundant broad-spectrum modulators of cell surface receptors, including tetraspanins. *J Virol* 2014; **88**(24): 14241-14257.

[45]Cerboni C, Neri F, Casartelli N, Zingoni A, Cosman D, Rossi P, et al. Human immunodeficiency virus 1 Nef protein downmodulates the ligands of the activating receptor NKG2D and inhibits natural killer cell-mediated cytotoxicity. *J Gen Virol* 2007; **88**(1): 242-250.

[46]van Stigt Thans T, Akko JI, Niehrs A, Garcia-Beltran WF, Richert L, Stürzel CM, et al. Primary HIV-1 strains use Nef to downmodulate HLA-E surface expression. *J Virol* 2019; **93**(20): 110-128.

[47]Kaufmann DE, Walker BD. PD-1 and CTLA-4 inhibitory cosignaling pathways in HIV infection and the potential for therapeutic intervention. *J Immunol* 2009; **182**(10): 5891-5897.

[48]Paiardini M, Müller-Trutwin M. HIV-associated chronic immune activation. *Immunol Rev* 2013; **254**(1): 78-101.

[49]WHO. *Zika virus, microcephaly and Guillain–Barré syndrome situation report. 2016.* [Online]. Available from: https://iris.who.int/handle/10665/242439. [Accessed on 13 February 2025].

[50]Atkinson B, Thorburn F, Petridou C, Bailey D, Hewson R, Simpson AJ, et al. Presence and persistence of Zika virus RNA in semen, United Kingdom, 2016. *Emerg Infect Dis* 2017; **23**(4): 611.

[51]Grant A, Ponia SS, Tripathi S, Balasubramaniam V, Miorin L, Sourisseau M, et al. Zika virus targets human STAT2 to inhibit type Ⅰ interferon signaling. *Cell Host Microbe* 2016; **19**(6): 882-890.

[52]Ding Q, Gaska JM, Douam F, Wei L, Kim D, Balev M, et al. Species-specific disruption of STING-dependent antiviral cellular defenses by the Zika virus NS2B3 protease. *Proc Natl Acad Sci U S A* 2018; **115**(27): E6310-E6318.

[53]Sarratea MB, Alberti AS, Redolfi DM, Truant SN, Lopez LVI, Bivona AE, et al. Zika virus NS4B protein targets TANK-binding kinase 1 and inhibits type Ⅰ interferon production. *Biochim Biophys Acta Gen Subj* 2023; **1867**(12): 130483.

[54]Xia H, Luo H, Shan C, Muruato AE, Nunes BT, Medeiros DB, et al. An evolutionary NS1 mutation enhances Zika virus evasion of host interferon induction. *Nat Commun* 2018; **9**(1): 1-13.

[55]Riedl W, Acharya D, Lee JH, Liu G, Serman T, Chiang C, et al. Zika virus NS3 mimics a cellular 14-3-3-binding motif to antagonize RIG-I- and MDA5-mediated innate immunity. *Cell Host Microbe* 2019; **26**(4): 493-503.

[56]de Carvalho GC, Borget MY, Bernier S, Garneau D, da Silva Duarte AJ, Dumais N. RAGE and CCR7 mediate the transmigration of Zika-infected monocytes through the blood-brain barrier. *Immunobiology* 2019; **224**(6): 792-803.

[57]Chin KL, Zainal N, Sam SS, Hassandarvish P, Lani R, AbuBakar S. Intracellular translocation of HMGB1 is important for Zika virus replication in Huh7 cells. *Sci Rep* 2022; **12**(1): 1054.

[58]Chin KL, Zainal N, Sam SS, Abu Bakar S. Resveratrol treatment-induced nuclear HMGB1 retention is critical for inducing host interferon responses against Zika virus. *Nat Prod J* 2023; **13**(6): 91-107.

[59]WHO. *Global viral hepatitis: Millions of people are affected 2021*. [Online]. Available from: https://www.cdc.gov/hepatitis/global/index.htm. [Accessed on 13 February 2025].

[60]Wang Z, Liu W, Zhang M, Wang M, Wu H, Lu M. Effect of hepatitis B virus infection on sperm quality and outcomes of assisted reproductive techniques in infertile males. *Front Med (Lausanne)* 2021; **8**: 744350.

[61]Bourdon M, Garnier A, Maignien C, Marcellin L, Dulioust E, Sogni P, et al. Assisted reproductive technology outcomes in women with a chronic viral disease. *AIDS* 2021; **35**(7): 1073-1081.

[62]Kushner T, Djerboua M, Biondi MJ, Feld JJ, Terrault N, Flemming JA. Influence of hepatitis C viral parameters on pregnancy complications and risk of mother-to-child transmission. *J Hepatol* 2022; **77**(5): 1256-1264.

[63]Zheng P, Dou Y, Wang Q. Immune response and treatment targets of chronic hepatitis B virus infection: Innate and adaptive immunity. *Front Cell Infect Microbiol* 2023; **13**: 1206720.

[64]Lin W, Kim SS, Yeung E, Kamegaya Y, Blackard JT, Kim KA, et al. Hepatitis C virus core protein blocks interferon signaling by interaction with the STAT1 SH2 domain. *J Virol* 2006; **80**(18): 9226-9235.

[65]Fisicaro P, Barili V, Rossi M, Montali I, Vecchi A, Acerbi G, et al. Pathogenetic mechanisms of T cell dysfunction in chronic HBV infection and related therapeutic approaches. *Front Immunol* 2020; **11**: 849.

[66]Dai B, Chen AY, Corkum CP, Peroutka RJ, Landon A, Houng S, et al. Hepatitis C virus upregulates B-cell receptor signaling: A novel mechanism for HCV-associated B-cell lymphoproliferative disorders. *Oncogene* 2016; **35**(23): 2979-2990.

[67]Schiller J, Lowy D. Explanations for the high potency of HPV prophylactic vaccines. *Vaccine* 2018; **36**(32): 4768-4773.

[68]Lu B, Kumar A, Castellsagué X, Giuliano AR. Efficacy and safety of prophylactic vaccines against cervical HPV infection and diseases among women: A systematic review & meta-analysis. *BMC Infect Dis* 2011; **11**: 1-16.

[69]Trimble CL, Morrow MP, Kraynyak KA, Shen X, Dallas M, Yan J, et al. Safety, efficacy, and immunogenicity of VGX-3100, a therapeutic synthetic DNA vaccine targeting human papillomavirus 16 and 18 E6 and E7 proteins for cervical intraepithelial neoplasia 2/3: A randomised, double-blind, placebo-controlled phase 2b trial. *Lancet* 2015; **386**(10008): 2078-2088.

[70]Gao P, Lazare C, Cao C, Meng Y, Wu P, Zhi W, et al. Immune checkpoint inhibitors in the treatment of virus-associated cancers. *J Hematol Oncol* 2019; **12**: 1-10.

[71]Kuske M, Haist M, Jung T, Grabbe S, Bros M. Immunomodulatory properties of immune checkpoint inhibitors-more than boosting T-cell responses? *Cancers (Basel)* 2022; **14**(7): 1710.

[72]Mustafayev K, Mallet V, Torres HA. Management of hepatitis B virus and hepatitis C virus infections in patients with cancer receiving immune checkpoint inhibitors. *J Immunother Precis Oncol* 2024; **7**(2): 111-121.

[73]Ziogas DC, Kostantinou F, Cholongitas E, Anastasopoulou A, Diamantopoulos P, Haanen J, et al. Reconsidering the management of patients with cancer with viral hepatitis in the era of immunotherapy. *J Immunother Cancer* 2020; **8**(2): e000943.

[74]Dropulic LK, Oestreich MC, Pietz HL, Laing KJ, Hunsberger S, Lumbard K, et al. A randomized, double-blinded, placebo-controlled, phase 1 study of a replication-defective herpes simplex virus (HSV) type 2 vaccine, HSV529, in adults with or without HSV infection. *J Infect Dis* 2019; **220**(6): 990-1000.

[75]Hook LM, Awasthi S, Cairns TM, Alameh MG, Fowler BT, Egan KP, et al. Antibodies to crucial epitopes on HSV-2 glycoprotein D as a guide to dosing an mRNA genital herpes vaccine. *Viruses* 2022; **14**(3): 540.

[76]Harrison CJ, Miller RL, Bernstein DI. Posttherapy suppression of genital herpes simplex virus (HSV) recurrences and enhancement of HSV-specific T-cell memory by imiquimod in guinea pigs. *Antimicrob Agents Chemother* 1994; **38**(9): 2059-2064.

[77]Conant MA. Immunomodulatory therapy in the management of viral infections in patients with HIV infection. *J Am Acad Dermatol* 2000; **43**(1): S27-S30.

[78]Nakamura R, La Rosa C, Yang D, Hill JA, Rashidi A, Choe H, et al. A Phase ⅡⅡ randomized, double-blind, placebo-controlled, multicenter trial to evaluate the efficacy of cmvpepvax for preventing CMV reactivation/disease after matched related/unrelated donor hematopoietic cell transplant. *Blood* 2021; **138**: 2887.

[79]Bernstein DI, Munoz FM, Callahan ST, Rupp R, Wootton SH, Edwards KM, et al. Safety and efficacy of a cytomegalovirus glycoprotein B (gB) vaccine in adolescent girls: A randomized clinical trial. *Vaccine* 2016; **34**(3): 313-319.

[80]Whitacre T. *mRNA-1647: A promising CMV vaccine advances to phase 3 trial. Infect Control Today 2023*. [Online]. Available from: Gale Academic OneFile, link.gale.com/apps/doc/A777426371/AONE?u=anon~ed5ff46d&sid=googleScholar&xid=d169f726. [Accessed on 13 February 2025].

[81]Geurten C, Ghinai R, Munford H, Lawson S. Efficacy of cytomegalovirus specific immunoglobulins to reduce CMV reactivation in pediatric hematopoietic stem cell transplant recipients. *J Pediatr Hematol Oncol* 2023; **45**(1): e82-e86.

[82]Smith C, Beagley L, Rehan S, Neller MA, Crooks P, Solomon M, et al. Autologous adoptive T-cell therapy for recurrent or drug-resistant cytomegalovirus complications in solid organ transplant recipients: A single-arm open-label phase Ⅰ clinical trial. *Clin Infect Dis* 2019; **68**(4): 632-640.

[83]Cohen KW, De Rosa SC, Fulp WJ, deCamp AC, Fiore-Gartland A, Mahoney CR, et al. A first-in-human germline-targeting HIV nanoparticle vaccine induced broad and publicly targeted helper T cell responses. *Sci Transl Med* 2023; **15**(697): eadf3309.

[84]June CH, O'Connor RS, Kawalekar OU, Ghassemi S, Milone MC. CAR T cell immunotherapy for human cancer. *Science* 2018; **359**(6382): 1361-1365.

[85]Delagrèverie HM, Delaugerre C, Lewin SR, Deeks SG, Li JZ. Ongoing clinical trials of human immunodeficiency virus latency-reversing and immunomodulatory agents. *Open Forum Infect Dis* 2016; **3**(4): ofw189.

[86]Li Y, Hong J, Zhang L. The rational combination strategy of immunomodulatory latency reversing agents and novel immunotherapy to achieve HIV-1 cure. *Infect Dis Immun* 2022; **2**(4): 263-273.

[87]Wang Y, Ling L, Zhang Z, Marin-Lopez A. Current advances in Zika vaccine development. *Vaccines* 2022; **10**(11): 1816.

[88]Liu X, Li Z, Li X, Wu W, Jiang H, Zheng Y, et al. A single-dose circular RNA vaccine prevents Zika virus infection without enhancing dengue severity in mice. *Nat Commun* 2024; **15**(1): 8932.

[89]Adams C, Carbaugh DL, Shu B, Ng TS, Castillo IN, Bhowmik R, et al. Structure and neutralization mechanism of a human antibody targeting a complex Epitope on Zika virus. *PLoS Pathog* 2023; **19**(1): e1010814.

[90]Hu H, Feng Y, He ML. Targeting type Ⅰ interferon induction and signaling: How Zika virus escapes from host innate immunity. *Int J Biol Sci* 2023; **19**(10): 3015.

[91]U.S. FDA. *Hepatitis B vaccine (recombinant) 2018.* [Online]. Available from: https://www.fda.gov/vaccines-blood-biologics/hepatitis-b-vaccine-recombinant. [Accessed on 13 February 2025].

[92]Elbahrawy A, Atalla H, Alboraie M, Alwassief A, Madian A, El Fayoumie M, et al. Recent advances in protective vaccines against hepatitis viruses: A narrative review. *Viruses* 2023; **15**(1): 214.

[93]Huang YW, Qin A, Tsai CY, Chen PJ. Novel pegylated interferon for the treatment of chronic viral hepatitis. *Viruses* 2022; **14**(6): 1128.

[94]Rakké YS, Sprengers D, Kwekkeboom J, IJzermans JNM. Camrelizumab-targeting a novel PD-1 epitope to treat hepatocellular carcinoma. *AnnTransl Med* 2020; **8**(23): 1614.

[95]Zhou J, Chen G, Wang J, Zhou B, Sun X, Wang J, et al. Anti-PD-1 therapy achieves favorable outcomes in HBV-positive non-liver cancer. *Oncogenesis* 2023; **12**(1): 22.

Publisher's note

The Publisher of the *Journal* remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Edited by Zhang Q, Lei Y, Pan Y