Review

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Research Progress on the Epidemiology and Intervention Strategies for Viral Skin Diseases

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This review provides a comprehensive and up-to-date overview of viral skin diseases, integrating recent epidemiological findings, advances in pathophysiological and molecular mechanisms, and the latest diagnostic and therapeutic strategies, with the goal of informing both research and clinical practice. Relevant literature published between January 2015 and January 2025 was retrieved from PubMed, Web of Science, and official documents from the World Health Organization (WHO) and the U.S. Centers for Disease Control and Prevention (CDC). Studies addressing epidemiology, molecular mechanisms, diagnostic approaches, therapeutic strategies, and clinical guidelines for viral skin diseases were systematically reviewed, analyzed, and summarized. Recent epidemiological evidence demonstrates persistent regional disparities in the prevalence of major viral skin infections caused by human papillomavirus (HPV) and herpes simplex virus (HSV). Advances in molecular research have elucidated key mechanisms, including viral immune evasion, latency, and reactivation, which are closely associated with diagnostic refinement and therapeutic development. Diagnostic precision has improved through nucleic acid amplification techniques, while novel therapeutic approaches, including targeted immunomodulatory agents and expanded vaccination programs, offer potential to overcome longstanding treatment bottlenecks. This review highlights the integration of epidemiological trends, molecular insights, and standardized clinical guidelines to provide a comprehensive reference for clinicians and researchers. We propose that elucidating molecular mechanisms underlying viral skin diseases, particularly those involving viral immune evasion and host immune regulation, will facilitate the development of targeted immunomodulatory strategies to enhance patient outcomes.

Keywords: viral skin diseases; papillomaviridae; herpesviridae; epidemiology; intervention; diagnosis; immunotherapy; guideline adherence

Introduction

Viruses are the smallest known pathogenic microorganisms and are capable of causing numerous systemic infectious diseases. Viral skin diseases encompass skin and mucosal lesions induced by viral pathogens, including herpes simplex virus, varicella-zoster virus (responsible for chickenpox and herpes zoster), and human papillomavirus-related warts. These conditions range from mild superficial rashes to complex systemic diseases [1]. Upon infecting the human body, viruses exhibit specific tissue tropism: some display a marked affinity for nerves and epidermal tissues, while others are associated with systemic or multisystem clinical manifestations [2].

Over the past decade, advances in molecular biotechnology, coupled with progress in experimental virology, have deepened understanding of the mechanisms underlying viral skin diseases and facilitated the development of new antiviral agents. Nevertheless, despite considerable progress in epidemiology, diagnostic methods, and therapeutic strategies against viral skin disorders, several key challenges remain unresolved. The pathogenic mechanisms of many emerging and re-emerging viral skin diseases, such as cutaneous manifestations of monkeypox virus (mpox), remain incompletely defined [3]. Moreover, the molecular pathways that govern viral persistence, latency, and reactivation within skin tissues require further investigation [4].

Diagnostic limitations also pose a challenge, as there is a lack of standardized, rapid, and highly sensitive diagnostic tools applicable in diverse clinical settings, particularly in resource-constrained clinical settings [5]. In addition, translating basic molecular insights into effective targeted antiviral or immunomodulatory therapies has been limited, highlighting the urgent need for well-designed clinical trials that bridge laboratory research and clinical application [6].

Addressing these gaps is essential for improving the prevention, early detection, and management of viral skin diseases. In this review, we summarize recent advances in the epidemiology, classification, and intervention strate-

gies of viral skin diseases. We propose that elucidating the molecular mechanisms underlying viral immune evasion and host immune regulation will provide a foundation for the development of targeted immunomodulatory therapies capable of overcoming current therapeutic limitations and improving patient outcomes.

Overview of Viral Infection

Viruses depend on living host cells for replication [7]. Newly identified viral diseases vary in their historical presence and recognition patterns, with some long-known conditions now linked to viral causes, such as pityriasis rosea and erythema infectiosum, and others representing truly novel pathogens, including monkeypox virus (mpox) [8–10]. Emerging viral diseases can be classified into 3 categories based on their historical presence in human populations: (1) Previously observed but not attributed to viruses: For example, infantile roseola and pityriasis rosea are now associated with human herpesvirus (HHV)-6 and HHV-7 infection [8], while erythema infectiosum is linked to human parvovirus B19. (2) Longstanding but recognized only after viral identification: certain diseases persisted among human populations but were identified correctly only once their viral agents were detected, including hepatitis C and hepatitis E. Notably, 40–74% of patients with hepatitis C exhibit at least one extrahepatic manifestation during disease onset [11]. (3) Truly novel viral diseases: These include conditions absent in earlier populations, but recognized as new viral diseases, including Acquired Immune Deficiency Syndrome (AIDS) and Ebola Virus Disease (EVD) [12].

Viruses may infect the skin through diverse routes, including scratches, wounds, and insect bites. The clinical manifestations of viral infections range from mild to severe [13,14]. Some viral diseases are confined to the skin and mucosa, such as human papillomavirus-induced warts, epidermodysplasia verruciformis, bowenoid papulosis, and molluscum contagiosum caused by molluscum contagiosum virus [15]. Others primarily present with cutaneous and mucosal lesions but may also produce systemic or multi-organ symptoms, as seen in chickenpox, smallpox, hand-foot-and-mouth disease, and erythema infectiosum [13]. In addition, certain systemic viral infections manifest with distinctive cutaneous signs, such as papular acrodermatitis of childhood associated with hepatitis B infection [16] and Kaposi sarcoma linked to human immunodeficiency virus (HIV) infection [17].

Epidemic Status of Viral Skin Diseases

Viral skin diseases exhibit distinct epidemiological characteristics shaped by host, pathogen, and environmental factors. Their incidence is generally higher in children and immunocompromised individuals. Key risk factors include immunosuppression, advanced age, sexual exposure, and poor hygiene. Transmission occurs primarily through direct contact, respiratory droplets, and autoinoculation. Preventive strategies, including vaccination, proper hand hygiene, and safe sexual practices, are essential for reducing disease burden. These principal components are illustrated in Fig. 1.

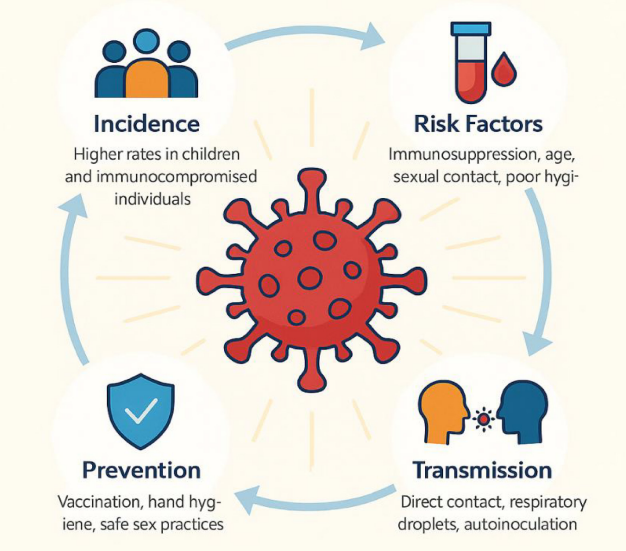

Fig. 1. Epidemiological characteristics of viral skin diseases. Key features are illustrated, including incidence patterns, major risk factors, transmission routes, and established prevention strategies. Self-drawn using Adobe Illustrator, version 27.0, Adobe Inc., San Jose, CA, USA.

Epidemic Status of Human Herpes Simplex Virus

Herpes simplex virus (HSV) is classified into two subtypes: HSV-1 and HSV-2. Infection rate can approach 100% in specific populations, and once acquired, HSV establishes a lifelong condition [18]. Globally, the prevalence of HSV-1 is estimated at 67%, while HSV-2 affects approximately 13% of the population [18]. Recent World Health Organization (WHO) and Global Burden of Disease data (2020) highlight an increasing proportion of genital HSV-1 infections among young adults in high-income countries, largely due to changes in sexual practices and reduced oral transmission during childhood [19].

Most infected individuals experience oral herpes or genital herpes (GH) during acute episodes. HSV-related herpes is both common and ancient, with historical records documenting its persistence in human populations and its predominant transmission via close contact, particularly sexual activity [20]. Since then, herpesvirus has been recognized for its infectivity, sexual transmission route, and latent infection property. For the 1970s onward, epidemiological investigations of HSV expanded alongside a growing understanding of viral biology.

Notable regional differences in HSV prevalence persist. Infection rates are considerably higher in developing countries than in developed nations, and higher in women than in men [21]. Epidemiological analyses indicate that HSV-2 infection is strongly associated with extramarital sexual activity and occurs predominantly among farmers and laborers with lower levels of education. Herpes zoster remains a particularly important manifestation within the spectrum of viral skin diseases, not only because of its high incidence but also due to the severe, often debilitating neuralgia caused in severe cases [22]. A key feature of HSV is its capacity to remain latent in the host for extended periods, with potential for recurrent episodes. Current research on herpesviruses focuses chiefly on host immune responses and the development of vaccines.

Epidemic Status of Human Papillomavirus

Human papillomavirus (HPV), belonging to the family *Papillomaviridae*, represents a diverse group of non-enveloped, epitheliotropic, double-stranded DNA viruses measuring approximately 50–55 nm in diameter, with genomes of 7.8–8.0 kb. To date, over 200 HPV genotypes have been identified and stratified into low-risk and high-risk subtypes according to their oncogenic potential. Low-risk types, such as HPV6 and HPV11, are primarily associated with benign lesions, including condyloma acuminatum. In contrast, high-risk types such as HPV16 and HPV18 are strongly linked to carcinogenesis. Notably, nearly 90% of cervical cancer patients exhibit high-risk HPV infection, with HPV16 and 18 accounting for more than half of these cases [23].

HPV infection is prevalent globally, with prevalence varying according to age and geographic regions. Studies indicate that in women under 25 years of age living in underdeveloped regions, prevalence ranges from 15% to 45%. According to the latest WHO data, the global prevalence of cervical HPV among women remains highest in sub-Saharan Africa (24%), followed by Latin America and the Caribbean (16%), and Eastern Europe (14%), while prevalence is lowest in North America (5%) and Western Asia (2%) [24]. Furthermore, meta-analyses reveal that among women aged $\geq$50 years presenting with abnormal cytology, any HPV is detected in 54.5%, and high-risk HPV in 43.0% [25,26].

Since 2020, expanded HPV vaccination programs have reduced the prevalence of high-risk HPV16 and HPV18 across several countries, with significant herd immunity benefits extending to unvaccinated populations [27]. However, genomic surveillance has documented shifts in circulating HPV type distribution, underscoring the need for next-generation vaccines [28].

Classification of Viral Skin Diseases

According to the 2023 International Committee on Taxonomy of Viruses (ICTV) classification, the major viruses causing viral skin diseases can be grouped as summarized in Table 1, which outlines their order, family, and genus. Based on these causative viruses, viral skin diseases can be further classified by representative diseases and clinical manifestations, as shown in Table 2. The details of each category are described below.

Viral Skin Diseases Induced by Human Herpesvirus Infection

Human herpesviruses are enveloped DNA viruses classified into three subgroups (α, β, γ), eight of which infect humans [29]. Viral infection of host cells may occur through several modes, including dominant infection, latent infection, integrated infection, and congenital infection. The herpesvirus life cycle consists of two major phases: latent infection and lytic infection. During latency, the viral genome replicates synchronously with the host genome, with only a limited number of viral genes expressed, and no mature virions are produced [30]. Conversely, in the lytic phase, the majority of viral genes are expressed, extensive genome replication occurs, and abundant mature virions are produced [31]. Clinical data demonstrate that antiviral agents targeting the lytic phase can effectively alleviate disease symptoms [32].

Currently, herpesvirus infections are primarily treated using antiviral drugs that inhibit lytic replication. Recent studies have revealed additional immune evasion strategies, including suppression of cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) signaling and inhibition of type III interferon responses, which may contribute to latency persistence [33].

Herpes Simplex Virus Infection

HSV belongs to the α-herpesvirus subfamily and comprises two types, HSV-1 and HSV-2. HSV-1 predominantly infects the skin and mucosal surfaces of the mouth, lips and eyes, as well as the central nervous system, though it is occasionally observed in the genital tract. HSV-2 is most frequently linked to genital and neonatal infections, though it can occasionally cause oral lesions. Once infected with HSV-2, individuals remain lifelong carriers of the virus [34]. Following invasion of the skin or mucosa, the virus replicates locally, causing an initial infection. It subsequently travels along the nerve endings to sensory ganglia, where it establishes long-term latency. Reactivation may be triggered by factors such as immunosuppression, at which point the virus migrates along neuronal axons to the epithelial layers where nerve terminals are distributed [35].

Latent infection and recurrence are attributed to viral immune evasion, including suppression of immediate early protein expression by the latency-associated transcript (*LAT*) gene, and interactions between the viral genome and

Table 1. Taxonomic classification of viruses causing viral skin diseases (ICTV 2023).

Virus	Order	Family	Genus	Species
Herpes simplex virus 1 (HSV-1)	Herpesvirales	Herpesviridae	*Simplexvirus*	*Human alphaherpesvirus 1*
Herpes simplex virus 2 (HSV-2)	Herpesvirales	Herpesviridae	*Simplexvirus*	*Human alphaherpesvirus 2*
Varicella-zoster virus (VZV, HHV-3)	Herpesvirales	Herpesviridae	*Varicellovirus*	*Human alphaherpesvirus 3*
Human papillomavirus (HPV)	Zurhausenvirales	Papillomaviridae	*Alphapapillomavirus*, *Betapapillomavirus*	*Human papillomavirus* (specific types, e.g., HPV-6, HPV-11, HPV-16, HPV-18)
Hepatitis B virus (HBV)	Blubervirales	Hepadnaviridae	*Orthohepadnavirus*	*Hepatitis B virus*
Hepatitis C virus (HCV)	Hepelivirales	Flaviviridae	*Hepacivirus*	*Hepatitis C virus*
Coxsackievirus A/B	Picornavirales	Picornaviridae	*Enterovirus*	*Enterovirus A* (e.g., *Coxsackievirus A6*), *Enterovirus B* (e.g., *Coxsackievirus B3*)
Echovirus	Picornavirales	Picornaviridae	*Enterovirus*	*Echovirus* (multiple serotypes)
Parvovirus B19	Piccovirales	Parvoviridae	*Erythroparvovirus*	*Primate erythroparvovirus 1*
Rubella virus	Amarillovirales	Matonaviridae	*Rubivirus*	*Rubella virus*

ICTV, International Committee on Taxonomy of Viruses; HHV, human herpesvirus.

Table 2. Classification of viral skin diseases with representative viruses, major diseases, and typical clinical manifestations.

Category	Virus	Major diseases	Typical clinical manifestations
Human herpesvirus infections	HSV-1, HSV-2	Herpes simplex, genital herpes, neonatal herpes, herpetic keratoconjunctivitis, eczema herpeticum	Clustered vesicles and ulcers on lips, oral mucosa, or genitalia; pain or pruritus
Varicella-zoster virus (VZV) infection	HHV-3	Chickenpox, herpes zoster	Pruritic papules and vesicles diffusely distributed on the body (chicken pox); unilaterally distributed along dermatomal vesicles with severe neuralgia (herpes zoster)
Human papillomavirus (HPV) infection	Low-risk (HPV6, HPV11); High-risk (HPV16, HPV18)	Condyloma acuminatum, common warts, flat warts, plantar warts	Papules or papillomatous lesions with rough or smooth surfaces; risk of autoinoculation
Hepatitis B and C virus-associated skin diseases	HBV, HCV	Papular acrodermatitis of childhood (HBV), cryoglobulinemia, lichen planus (HCV)	Papules, purpura, and lichenoid eruptions depending on condition
Picornavirus infections	Coxsackievirus A/B, Echovirus	Hand-foot-and-mouth disease, eczema coxsackium, exanthematous disease with aseptic meningitis	Vesicular or maculopapular rash on hands, feet, oral mucosa, trunk, or extremities
Human parvovirus infection	Parvovirus B19	Erythema infectiosum, purpura, urticaria	“Slapped cheek” rash, reticular erythema on limbs, or generalized rashes
Rubella virus infection	Rubella virus	Rubella, congenital rubella syndrome	Fine reddish maculopapules spreading from face to trunk, often with lymphadenopathy

host cells. The major types of human herpesvirus infections, their life cycle, and the latency–reactivation process of HSV are illustrated in Fig. 2.

Epidemiological studies show significant age-related differences in HSV infection. The seropositivity rate for HSV-1 antibodies increases linearly with age. Briefly, the rate remains low among children under nine years but rises significantly during adolescence, reaching 40–50% among individuals aged 15–24 years [36].

Clinically, HSV-1 commonly causes cold sores, herpetic stomatitis, keratitis (including herpetic gingivostomatitis), neonatal herpes simplex, eczema herpeticum, incubation herpes, and herpetic keratoconjunctivitis [37]. The infection is typically characterized by vesicular eruptions that may progress to superficial ulceration. HSV-2 infection is primarily associated with genital herpes (GH).

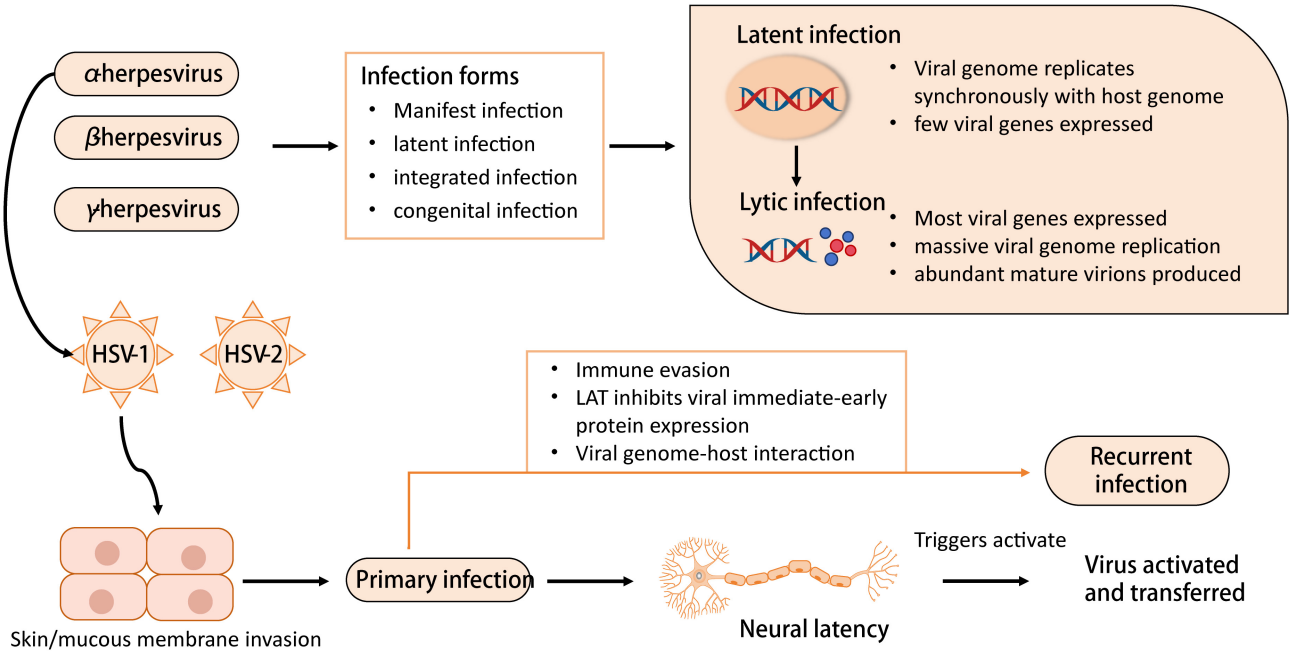

Fig. 2. Types of human herpesvirus (HHVs) infections, their life cycle, and the latent-reactivation process of herpes simplex virus (HSV). Self-drawn using Adobe Illustrator, version 27.0, Adobe Inc., San Jose, CA, USA.

Varicella-Zoster Virus (VZV) Infection

Varicella-zoster virus (VZV), also referred to as HHV-3, is responsible for two common clinical skin diseases: chickenpox and herpes zoster. Primary infection with VZV leads to chickenpox, after which the virus establishes latency within ganglion neurons. With advancing age or a decline in immune function, the virus may reactivate, causing herpes zoster [38]. VZV infects only humans and is transmitted via the respiratory route, leading to viremia and primary infection. Subsequently, the virus persists in the dorsal root ganglia of the spinal cord or cranial sensory ganglia. When triggered by factors such as trauma, fatigue, cancer, or immunosuppression, the latent virus reactivates and travels along sensory axons to the skin of the affected dermatome, where replication induces neural inflammation and necrosis. Clinically, VZV infection presents as clustered vesicular lesions distributed unilaterally along the corresponding nerve [38]. Additionally, herpes zoster may cause chronic pain, neurological complications, or ocular disease [39].

Viral Skin Diseases Induced by Human Papillomavirus

Human papillomavirus (HPV) is divided into cutaneous and mucosal types, reflecting its ability to infect either basal epithelial cells of the skin or mucosal tissues [40,41]. Generally, the cutaneous type affects the skin of the hands and feet, causing verruca vulgaris, whereas the mucosal type primarily involves the epithelium of the oral cavity, pharynx, respiratory tract, or genital region. HPV enters host cells through microabrasions in the skin or mucosa, where it replicates and disrupts epithelial differentiation, leading to benign epithelial proliferations. In contrast to the entry mechanisms of most viruses, HPV specifically invades basal epithelial cells and initiates the disassembly of cellular structures. Following viral genome replication and protein expression, these components are assembled into new viral particles, which interfere with cytokeratin expression and promote abnormal epithelial keratinization. Several studies have also revealed that HPV can drive cell-cycle-dependent abnormal cellular proliferation. Clinically, HPV infection manifests as common, flat, and plantar warts, as well as condyloma acuminatum. Typical lesions present as papular eruptions with variable surface textures and may propagate through autoinoculation following scratching [42]. Over the past five years, evidence has shown that HPV oncoproteins E6 and E7 can also modulate host innate immunity via interferon regulatory factors, in addition to their established roles in p53 and Rb pathway disruption [43].

Viral Skin Diseases Related to Hepatitis Viruses

A recent comprehensive review by Cacoub demonstrated the strong association between chronic HCV infection and multiple cutaneous conditions, including cryoglobulinemic vasculitis, lichen planus, porphyria cutanea tarda, and persistent pruritus, with added evidence from a 2025 study quantifying their prevalence in the affected population [44,45]. Papular acrodermatitis of childhood (Gianotti–Crosti syndrome) is classically linked to hepatitis B virus (HBV) infection, likely mediated by circulating immune complex deposition. However, contemporary re-

ports indicate Epstein–Barr virus (EBV) as the predominant cause, especially in developed countries [46]. Since the widespread introduction of direct-acting antivirals for HCV in 2018, the frequency of extrahepatic cutaneous conditions, including lichen planus and cryoglobulinemia, has markedly declined [47].

Diseases Related to Picornavirus Infection

Coxsackievirus (Cox V) and enteric cytopathic human orphan viruses (echovirus) are members of the Picornaviridae family. Based on pathogenicity in suckling mice, Cox V is divided into two groups: A and B. Moreover, Cox V infection has also been linked to eczema coxsackium [48]. Echoviruses, comprising 38 serotypes, are capable of inducing a broad spectrum of severe clinical syndromes, including aseptic meningitis, polyradiculopathy, myocarditis, epidemic myalgia, respiratory tract infections, and exanthematous diseases. Previous studies have shown that echoviruses 11 and 30 are characterized by high genetic variability, with nearly one-third of their nucleotides displaying sequence diversity [49].

Diseases Induced by Parvovirus Infection

Parvovirus B19 is a well-recognized human pathogen. The pathogen primarily replicates within erythroid precursors and epidermal cells, thereby inducing edema of epidermal keratinocytes, vasodilation of dermal papilla, and endothelial swelling with associated hemorrhage. These processes result in erythema infectiosum, purpura, and urticaria. Characteristic clinical features of B19 infection include erythematous eruptions localized to the face, buttocks, and extremities [50]. Moreover, B19 is notable for its high prevalence and significant disease burden [51].

Rubella

Rubella virus, a member of the Togaviridae family, is an RNA virus restricted to human hosts. Under electron microscopy, rubella virions display an irregular spherical morphology with a core diameter of 50–70 nm. Transmission occurs primarily via respiratory droplets, facilitated by its stable antigen structure. The latency of the rubella virus is approximately 2–3 weeks. Following replication, the virus enters the blood circulation system of patients, leading to the development of systemic rubella infection [52].

Pathophysiological Changes and Molecular Mechanisms of Viral Skin Diseases

Viral skin diseases result from the complex interplay between viral replication, host cell injury, and immune responses, leading to characteristic pathological and physiological alterations in the skin [13,14]. Understanding these processes offers valuable insights into accurate diagnosis and effective therapeutic strategies.

Pathophysiological Changes

Following viral entry—via direct inoculation through cutaneous or mucosal breaches, hematogenous dissemination, or neural pathways—specific viral pathogens demonstrate tropism for keratinocytes, fibroblasts, Langerhans cells, endothelial cells, or sensory neurons [13]. Common histopathological features include keratinocyte ballooning degeneration, multinucleated giant cells, epidermal necrosis, and spongiosis, often accompanied by dermal perivascular lymphocytic infiltration [37]. Infections caused by HSV and VZV are characterized by intraepidermal vesicle formation and multinucleated epithelial cells with ground-glass nuclei and Cowdry type A inclusions [37,38]. HPV induces koilocytosis, manifested by perinuclear cytoplasmic clearing and nuclear enlargement, in the upper epidermis, together with papillomatosis and hyperkeratosis [42]. Hepatitis virus-associated dermatoses often exhibit interface dermatitis with basal vacuolar alterations and lymphocytic infiltrates [53,54]. These morphological features are readily detectable by routine histopathology and can be further confirmed using immunohistochemistry or in situ hybridization, thereby guiding clinical diagnosis, particularly in atypical presentations [55,56].

Molecular Mechanisms

Advances in molecular virology have elucidated key mechanisms through which viral skin pathogens evade immunity, establish persistence, and induce tissue damage. HSV manipulates the cGAS-STING pathway and suppresses type III interferon responses [33], facilitating latency and recurrent reactivation. This mechanistic knowledge supports exploration of STING agonists and interferon modulators as potential therapeutic agents. HPV E6 and E7 oncoproteins not only degrade p53 and retinoblastoma proteins but also interfere with interferon regulatory factors, thereby weakening innate immune signaling [43]. Such findings inform the design of novel immunotherapies and therapeutic vaccines. Transcriptomic studies of VZV have identified latency-associated genes that sustain viral quiescence within dorsal root ganglia [38,39], highlighting molecular targets to prevent herpes zoster reactivation. HCV-associated cutaneous manifestations are partly driven by immune complex deposition and B-cell clonal expansion. Direct-acting antivirals effectively reduce cryoglobulin levels and ameliorate vasculitic symptoms, although B-cell clonal expansion may persist despite virological clearance [47]. Collectively, these insights provide a structural basis for understanding viral pathogenesis and identifying potential novel therapeutic targets (Fig. 3).

Implications for Diagnosis and Treatment

Pathophysiological hallmarks such as multinucleated giant cells or koilocytosis provide valuable morphological diagnostic clues [37,42], while molecular markers, including viral nucleic acids, latency-associated transcripts,

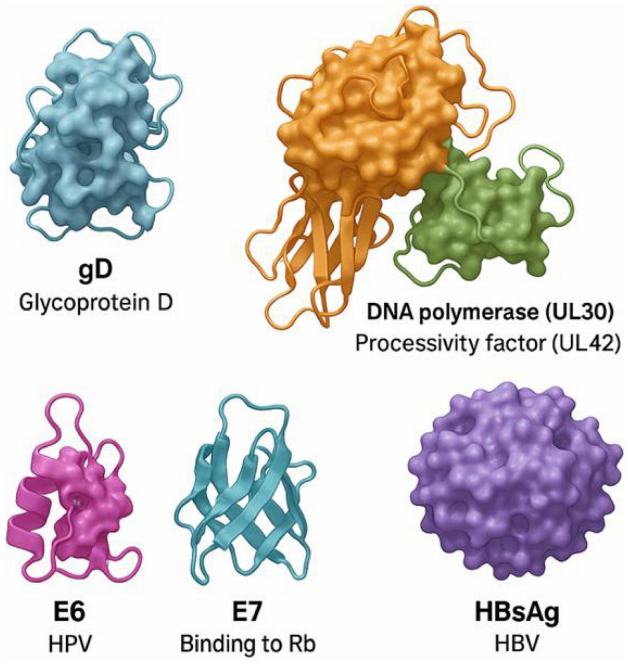

Fig. 3. Representative 3D structures of viral proteins critical for replication and pathogenesis. Self-drawn using PyMOL and finalized in Adobe Illustrator, version 27.0, Adobe Inc., San Jose, CA, USA. Structures include HSV glycoprotein D (gD), the DNA polymerase catalytic subunit (UL30) with its processivity factor (UL42), HPV oncoproteins E6 and E7 (bound to retinoblastoma protein, Rb), and the hepatitis B virus surface antigen (HBsAg). These proteins play critical roles in viral entry, genome replication, immune evasion, and oncogenesis.

and immune evasion-related proteins, can be exploited for early detection and disease monitoring [34,57]. Moreover, understanding these mechanisms informs rational drug development, including antivirals targeting viral replication enzymes [58], immunomodulators counteracting viral immune evasion [59,60], and therapeutic vaccines aimed at restoring pathogen-specific immunity [61,62].

Diagnosis of Common Viral Skin Diseases

Diagnostic Criteria From Authoritative Guidelines

The diagnostic criteria for viral skin diseases vary slightly across international and national guidelines. To harmonize standards in clinical and research settings, the most recent recommendations from the WHO and the United States Centers for Disease Control and Prevention (CDC) are summarized in Table 3. The WHO standards for varicella and herpes zoster are detailed in the Vaccine-Preventable Diseases Surveillance Standards (2018) [63], whereas the CDC's Sexually Transmitted Infections Treatment Guidelines (2021) provide comprehensive criteria for HSV- and HPV-related lesions [64]. In addition, the CDC's surveillance guidance for varicella is outlined in its Manual for Surveillance of Vaccine-Preventable Diseases (2023) [65]. The subsequent four sections follow the diagnostic standards summarized in Table 3.

Herpes Zoster

Herpes zoster can be preliminarily diagnosed by clinical manifestations. Before onset, patients may present with systemic symptoms such as anorexia, mild fatigue, and low-grade fever. Local prodromal symptoms include pruritus, neuralgia, or burning pain in the affected skin. This is followed by erythema, with the development of vesicles or blisters containing clear fluid, typically 3–8 mm in diameter, which subsequently coalesce into clusters. Secondary bacterial infection or hemorrhage within the vesicular fluid may lead to pustules or blood blister formation [66]. Histopathological findings include reticular degeneration of epidermal cells, intraepidermal blister formation, and inflammatory cell infiltration in dermis, often accompanied by vasculitis and erythrocyte extravasation in the subcutaneous tissue layer, resulting in edema and thickening [66]. Polymerase chain reaction (PCR), a highly sensitive diagnostic tool for VZV, contributes to the rapid detection of viral DNA in blood, saliva, or cerebrospinal fluid, with results available within hours [67]. Therefore, PCR facilitates early identification of atypical herpes zoster.

Additionally, non-invasive imaging modalities are increasingly applied. High-resolution ultrasonography allows direct assessment of epidermal, dermal, and subcutaneous thickness, subcutaneous blood flow, and cutaneous nerve diameter. High-frequency ultrasound can further characterize pathological changes of skin and subcutaneous tissue in patients with herpes zoster, including edema, tissue thickening, and inflammatory alterations [68].

Diagnosis of Rubella

In pregnant women infected with the rubella virus, maternal–fetal transmission via the bloodstream may occur during the first trimester, thereby leading to stillbirth, spontaneous abortion, or other adverse symptoms. Neonates with severe rubella virus infection may present with deafness, cataracts, and congenital heart disease, a constellation clinically recognized as congenital rubella syndrome (CRS) [69]. Rubella is characterized by a maculopapular rash, cervical and occipital lymphadenopathy, and arthralgia/arthritis [70]. During the prodromal stage, children are usually asymptomatic, while adolescents and adults commonly display symptoms that persist for one week. The predominant clinical features include upper respiratory symptoms such as sore throat, rhinorrhea, cough, and low-to-moderate fever. Some patients may also experience diarrhea, vomiting, gingival swelling, or epistaxis. After 1–2 days of fever, the rash stage ensues, beginning on the face and neck and subsequently spreading to the trunk and extremities. Laboratory confirmation relies on rubella-specific IgM serology [71], while rubella virus RNA can also be detected by RT-PCR [72].

Table 3. Comparison of diagnostic criteria for selected viral skin diseases according to WHO and CDC guidelines.

Disease	WHO guidelines	CDC guidelines	Notes
Herpes zoster	Clinical diagnosis based on unilateral dermatomal vesicular rash with pain; PCR recommended for atypical cases	Similar clinical criteria; PCR recommended for confirmation; DFA may be used as an alternative	Both emphasize PCR as the gold standard in atypical cases
Rubella	Laboratory confirmation by detection of rubella-specific IgM or 4-fold rise in IgG; RT-PCR for viral RNA	Same serological and molecular criteria; epidemiological linkage to a confirmed case may suffice during outbreaks	Minor variations in outbreak settings
HPV-related warts	Clinical morphology; HPV DNA testing recommended for high-risk anogenital lesions	Primarily clinical diagnosis; HPV DNA or mRNA testing advised in high-risk lesions	Both emphasize molecular confirmation for high-risk HPV
Herpes simplex	Clinical diagnosis for typical lesions; PCR or virus isolation for confirmation	Similar approach; PCR preferred over viral culture	Both recognize PCR as the most sensitive and specific method

WHO, World Health Organization; CDC, United States Centers for Disease Control and Prevention; PCR, polymerase chain reaction; DFA, Direct Fluorescent Antibody.

Diagnosis of Condyloma Acuminatum

Condyloma acuminatum, typically occurring in the anogenital region, is primarily caused by HPV infection. In its early stages, it is characterized by small, reddish papules. As the disease progresses, the size and number of papules gradually increase. The papules often develop into vegetative, cockscomb-like, or papillary structures, usually gray or reddish in color, and are prone to erosion, exudation, and bleeding. Lesions are frequently accompanied by foul-smelling, purulent secretions [55]. Most patients are asymptomatic, though some may experience pruritus, a foreign body sensation, or dyspareunia. Patients with typical lesions can be diagnosed clinically, but many cases remain at the subclinical stage. Diagnosis of condyloma acuminatum is primarily based on clinical symptoms and acetic acid (vinegar) test [55]. However, the vinegar test lacks specificity for HPV infection, and false-positive results may occur in chronic inflammatory conditions. Histopathological examination provides additional diagnostic value. The presence of vacuolated cells located above the spinous layer and within the granular layer is characteristic of condyloma acuminatum. In addition, cytologic examination can be employed for the diagnosis of condyloma acuminatum. Furthermore, cytological examination can aid in diagnosis. In this approach, wart tissue is collected and stained with the Papanicolaou (Pap) stain. The presence of both poorly keratinized and vacuolated cells confirms the diagnosis [73].

Diagnosis of Herpes Simplex

Conventional laboratory diagnostic methods include virus isolation, immunofluorescence, neutralization tests, and enzyme-linked immunosorbent assay (ELISA). Virus isolation and neutralization tests have limited value in early clinical diagnosis, as they are complex, time-consuming, and impractical for processing a large number of samples during outbreaks. ELISA, although widely used, demonstrates relatively low sensitivity and may yield false-positive results [34,74]. Consequently, tissue culture of HSV is regarded as the "gold standard" for laboratory diagnosis. The Tzanck smear test, while rapid and accurate, requires fresh lesions and cannot distinguish between HSV types [75]. PCR is highly sensitive for specific HSV subtypes and is therefore widely applied in clinical diagnosis and therapeutic monitoring of herpes simplex. HSV-2 encodes more than 11 glycoproteins, several of which have been investigated as the targets for quantitative fluorescence PCR. Notably, glycoprotein G (gG) is the principal distinguishing protein between HSV-1 and HSV-2, making it the preferred marker for HSV-2 type specificity [76]. Beyond conventional PCR, recent studies have validated CRISPR-Cas-based diagnostic assays for rapid detection of HSV, HPV, and VZV, producing results within 30 minutes with high specificity [5]. Additionally, portable point-of-care nucleic acid testing platforms have been applied in outbreak settings since 2021 [77].

Treatment of Viral Skin Diseases

Interferon

Interferons (IFNs) are a family of naturally occurring cytokines with antiviral, antitumor, and immunomodulatory properties, playing a pivotal role in innate immune defense against viral infections [78]. During viral invasion, IFNs mediate diverse immune functions by activating and regulating both innate and adaptive immune cells. The IFN-mediated antiviral response is essential for controlling HSV infection, and neuronal IFN signaling may inhibit the establishment and persistence of HSV latency [79]. IFNs can be administered through various routes, including top-

ical application, intravenous injection, intramuscular injection, and subcutaneous injection. Local subcutaneous administration of recombinant IFN-α and IFN-β has proven effective in herpes simplex and condyloma acuminatum, promoting lesion regression and lowering recurrence rates. Furthermore, topical recombinant IFN-α in emulsion or gel formulations can significantly alleviate oral herpes and GH manifestations [80].

Immunotherapy

Immunotherapy is categorized into specific and nonspecific approaches. Specific immunotherapy stimulates antigen-specific immune tolerance or immune responsiveness via vaccination, thereby inducing active immune protection [81]. Current immunotherapeutic interventions include autologous wart transplantation for intractable condyloma acuminatum, verruca plana, and verruca vulgaris. Additionally, agents that enhance macrophage phagocytosis, such as levamisole, lentinan, thymosin, immune ribonucleic acid, polystictus glycopeptide, Bacillus Calmette–Guérin (BCG) vaccine, and typhoid bacillus lipopolysaccharide, may be used to correct immune dysregulation. Furthermore, interleukin-2, polyinosinic-polycytidylic acid, and tilorone enhance cellular immunity and humoral immunity, while gamma globulin provides a broad spectrum of antibodies that improve the overall host immune capacity [59]. Cimetidine, an H2 receptor antagonist primarily used for peptic ulcer disease, has also demonstrated immunomodulatory effects by restoring dendritic cell function and enhancing natural killer cell activity. Clinically, cimetidine can be employed to treat condyloma acuminatum, verruca vulgaris, molluscum contagiosum, herpes zoster, and chickenpox [60].

Antiviral Drugs

Acyclic nucleosides, including acyclovir, ganciclovir, and famciclovir, are widely used clinical antiviral agents. As important broad-spectrum antivirals, acyclic nucleosides demonstrate efficacy against HSV, GH virus, VZV, and EBV, making them first-line drugs for herpesvirus infections [58]. In addition, idoxuridine is used in the management of herpes simplex, herpes zoster, and verruca vulgaris [82]. For patients allergic to iodine, floxuridine may be considered. However, animal studies indicate that floxuridine can induce mutations or deformities. Thus, it is contraindicated in pregnant women and women of childbearing age, and for other patients, it should be applied locally for a maximum of 3 weeks. Ftibamzone also shows significant therapeutic activity against type I and II herpes simplex and herpes zoster. N-docosanol is effective for oral herpes simplex, with minimal adverse effects limited to transient local tingling or burning sensations [83].

In July 2023, the U.S. Food and Drug Administration approved Ycanth® (cantharidin 0.7% topical solution) as the first FDA-approved therapy for molluscum contagiosum in adults and children aged $\geq$2 years. Its efficacy was confirmed through two randomized, double-blinded, placebo-controlled Phase III trials (NCT03377790 and NCT03377803), showing significantly higher rates of complete lesion clearance by Day 84 compared with placebo [84].

Cytotoxic Agents

Podophyllum resin exhibits strong anti-HPV properties and is commonly employed in the treatment of condyloma acuminatum, verruca vulgaris and verruca plana [85]. Topical application of podophyllotoxin induces necrosis and shedding of HPV-infected epidermal cells, making it a mainstay in condyloma acuminatum therapy. Expected local reactions include mild burning at the application site, superficial erosion, or temporary erythema at the site of wart tissue detachment [86].

Overall, the skin is a frequent target organ for viral infections. Viral skin diseases may arise as primary epidermal infections or as secondary manifestations of systemic viral infection. Some viral skin conditions, such as herpes zoster and molluscum contagiosum, present with characteristic clinical features including erythema, papules, itching, and blisters. However, others, such as condyloma acuminatum, often present with subtle early symptoms, leading to frequent misdiagnosis. With advances in medical technology, alterations in human lifestyle, and an ageing population, the spectrum of viral skin diseases remains a serious public health concern. Consequently, there is an urgent need for more effective strategies for prevention, early detection, and treatment.

The therapeutic options for viral skin diseases, including interferons, immunotherapies, antiviral drugs, and cytotoxic agents, are summarized in Table 4.

Clinical Practice Recommendations

Based on the epidemiological characteristics, pathophysiological mechanisms, diagnostic strategies, and therapeutic approaches discussed above, the following recommendations are proposed to guide clinical practice in the management of viral skin diseases:

(1) Early and precise diagnosis: Lesion-based molecular amplification assays (e.g., PCR) should be prioritized for laboratory confirmation in atypical cases or high-risk populations, consistent with WHO and CDC guidelines [64,65,87,88].

(2) Integrating molecular insights into therapy: Understanding viral immune evasion and latency mechanisms should guide the development and clinical application of targeted immunomodulatory strategies, such as STING pathway agonists for HSV or therapeutic vaccines for HPV [31,38,53].

(3) Preventive strategies: Vaccination against preventable viral skin diseases (e.g., HPV, varicella-zoster)

Table 4. Therapeutic options for viral skin diseases.

Drug class	Representative drugs	Main mechanism/indications	Key notes
Interferon	IFN-α, IFN-β	Induces antiviral protein expression and enhances immune cell activity; used for HPV, HBV, HCV, HSV	Reduce viral load; adverse effects include flu-like symptoms
Immunotherapies	Imiquimod, therapeutic vaccines	Stimulates innate and adaptive immune responses; applied for HPV-related warts, molluscum contagiosum	Promote lesion regression; local irritation possible
Antiviral agents	Acyclovir, valacyclovir, foscarnet	Inhibits viral DNA polymerase; used for HSV, VZV, CMV	Shorten disease course and reduce recurrence; risk of renal toxicity
Cytotoxic agents	Podophyllotoxin, 5-fluorouracil	Disrupts DNA synthesis and mitosis; indicated for HPV-related warts	Induce lesion necrosis; potential for local ulceration

IFN, Interferon; CMV, Cytomegalovirus.

should be strengthened, with emphasis on high coverage and catch-up programs for under-vaccinated populations [87].

(4) Tailored patient management: Diagnostic and therapeutic approaches should be adapted for vulnerable populations, including pregnant women, immunocompromised individuals, and elderly patients, with careful assessment of risks and benefits [89,90].

(5) Surveillance and outbreak control: Robust reporting systems and genomic surveillance should be maintained to detect viral variants promptly and guide timely public health interventions [64,87,88].

(6) Multidisciplinary care: Collaboration among dermatologists, infectious disease specialists, virologists, and public health professionals is recommended to ensure comprehensive patient management and effective outbreak control [91].

Conclusion

Viral skin diseases remain a significant global public health challenge, characterized by diverse etiologies, clinical manifestations, and substantial impacts on patient quality of life. Advances in molecular diagnostics, antiviral therapies, and vaccination programs have markedly improved early detection and clinical management. However, critical challenges persist, including drug resistance, latent viral infections, and incomplete preventive coverage for specific pathogens.

This review integrates the latest domestic and international research, summarizing the classification, epidemiology, molecular mechanisms, and clinical interventions of viral skin diseases, while providing comprehensive figures and tables to enhance understanding. Looking forward, future studies should prioritize elucidating the molecular basis of viral pathogenesis, optimizing therapeutic regimens, developing broad-spectrum and virus-specific antivirals, and strengthening preventive measures through global collaboration.

Availability of Data and Materials

Not applicable.

Author Contributions

XQY, ZJL, and ZTL contributed to the conception and design of the manuscript. ZJL and ZTL were involved in drafting the manuscript. All authors critically revised the manuscript for important intellectual content and gave final approval of the version to be published. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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