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Mpox and Viral Co-Infections: A Narrative Review

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ABSTRACT

Background and Aims: Monkeypox (Mpox), caused by the monkeypox virus (MPXV), has emerged as a significant global public health concern, particularly following a substantial multi-country outbreak in mid-2022. The World Health Organization (WHO) reported 109,699 laboratory-confirmed Mpox cases and 236 fatalities worldwide from January 1, 2022, to September 30, 2024. This narrative review aims to evaluate the co-infections of Mpox with various viral agents and assess their implications for public health.

Methods: We conducted a comprehensive review of the literature regarding Mpox co-infections with human immunodeficiency virus (HIV), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), hepatitis viruses (hepatitis A virus (HAV), hepatitis B virus (HBV), and hepatitis C virus (HCV)), and herpesviruses (including herpes simplex virus (HSV)-1, HSV-2, varicella-zoster virus (VZV), and cytomegalovirus (CMV)).

Results: We analyzed epidemiological trends, clinical manifestations, preventive measures, treatment guidelines, and advanced diagnostic methodologies. The review highlights the intricate dynamics of Mpox co-infections and underscores the necessity for comprehensive diagnostic approaches, including viral load assays, to evaluate active co-infections, particularly for HIV and HBV.

Conclusion: Understanding the interplay between MPXV and other viral pathogens is crucial for enhancing management strategies for co-infections. By addressing these complexities, we aim to contribute valuable insights into the public health implications of Mpox co-infections and improve response strategies.

1 | Introduction

Monkeypox (Mpox) is an infection disease caused by the monkeypox virus (MPXV), which was first identified in 1958 in laboratory cynomolgus monkeys in Copenhagen, Denmark [1–3]. In 1970, the initial confirmed case of human Mpox was reported in the Democratic Republic of Congo [4]. Since then, intermittent outbreaks of Mpox have been observed in Central and West African countries, which are considered endemic regions for MPXV [5, 6]. Over the past 50 years, Mpox cases

have been predominantly reported as sporadic outbreaks, primarily in African nations, with several thousand human cases documented to date. Additionally, isolated cases and limited outbreaks linked to the transportation or importation of animals carrying MPXV have been documented in non-endemic countries [5, 7, 8]. In mid-2022, the world witnessed a large multi-country outbreak of Mpox. In July, 2022, the World Health Organization (WHO) declared the outbreak a public health issue of international concern, as MPXV had spread across multiple countries in Southeast Asia, the Western Pacific, the Eastern Mediterranean, the Americas, and Europe (Figure 1) [9–11]. By September 30, 2024, the global epidemiological overview of Mpox indicated a total of 109,699 laboratory-confirmed cases and 236 deaths, as reported by the WHO [12].

MPXV belongs to the Poxviridae family, specifically the *Chordopoxvirinae* subfamily and the *Orthopoxvirus* genus. It has an enveloped, brick-shaped structure with a linear double-stranded DNA genome of about 190 kilobases [5, 13, 14]. MPXV was categorized into two distinct clades, clade I (formerly referred to as the Central African or Congo Basin clade) and clade II (previously known as the West African clade), based on both genetic and geographic differences, with a genomic length difference of approximately 900 bp observed between strains belonging to these lineages [15, 16]. In the most recent nomenclature, clade II has been subdivided into two distinct subclades: IIa and IIb. Phylogenetic evidence has shown that the primary cause of the latest global MPXV outbreak is subclade IIb [15].

The transmission of MPXV is well-established and occurs through direct contact with contaminated surfaces, skin lesions, bodily fluids, large respiratory droplets from infected individuals or animals, and, in certain cases, vertical transmission is also supported by evidence [17, 18]. Compelling data suggests that the current MPXV strain primarily spreads through sexual transmission, particularly among males who have sex with men (MSM). This epidemic is notable for the increased incidence of interpersonal transmission via sexual intercourse [17].

A notable healthcare concern associated with Mpox is its co-infection with other infectious agents, particularly viruses, necessitating specific considerations. Recent data highlights that co-infections involving Mpox and other viral pathogens can result in a range of consequences, including worsened symptoms, heightened severity, and complications for both diseases. Additionally, it can present challenges in patient monitoring and management, demanding the implementation of appropriate therapeutic strategies and effective clinical scenarios [19]. To the best of our knowledge, several studies have reviewed data addressing co-infection of MPXV with other viruses [19, 20]. This study aims to provide a comprehensive examination of co-infection dynamics involving MPXV and other viral agents, including human immunodeficiency virus (HIV), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), viral hepatitis pathogens (hepatitis A, B, and C viruses), and members of the Herpesviridae family, such as herpes simplex viruses type 1 and 2 (HSV-1, HSV-2), varicella-zoster virus (VZV), and cytomegalovirus (CMV).

2 | Human Immunodeficiency Virus (HIV)

MPXV has the capacity to infect individuals with HIV, regardless of their CD4+ cell count, making it one of the most significant coinfections to consider [21]. In the wake of the ongoing Mpox outbreak, the prevalence of HIV and other sexually transmitted infections (STIs) has surged. This increase is attributed to these viruses being transmitted primarily through

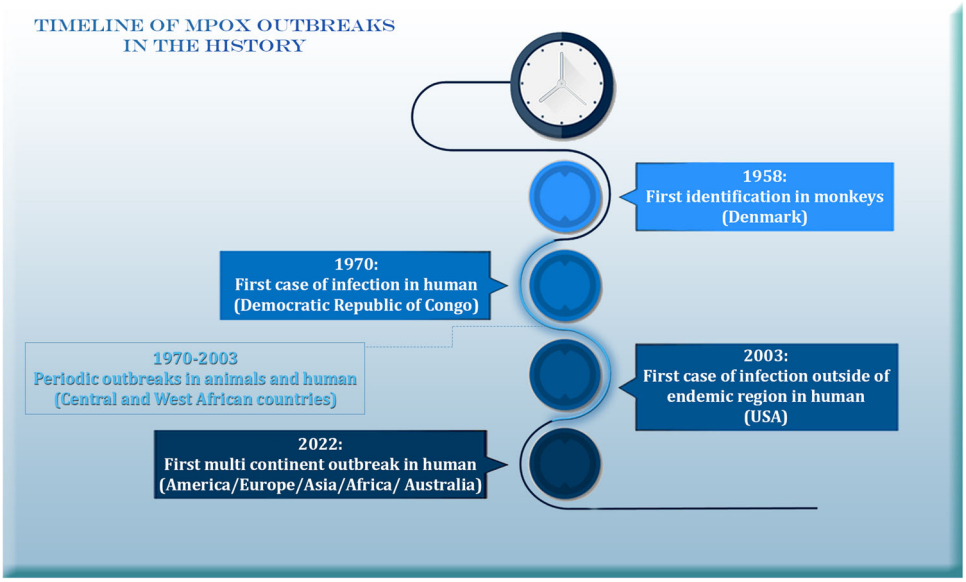

FIGURE 1 | Timeline of Mpox outbreaks: A comprehensive overview from 1958 to 2022. The timeline begins with the discovery of the MPXV in monkeys in 1958 (Denmark) and continues with the first human case reported in 1970 (Democratic Republic of Congo). Between 1970 and 2003, Central and West African countries had recurring outbreaks in both animals and humans. The timeline also contains the important first human case outside of endemic regions recorded in the United States in 2003 and culminates with the first multi-continent outbreak of mpox in 2022, affecting regions including America, Europe, Asia, Africa, and Australia.

sexual fluids and disproportionately affecting individuals who identify as gay, bisexual, and MSM [22]. The co-infection of HIV and MPXV stands at 40.3% of cases, with the majority occurring in MSM, where HIV prevalence is higher than in the general population. Additionally, a substantial 91.44% of these co-infection cases are male [2, 4, 13, 19]. Sexual behaviors among individuals living with HIV could potentially elevate their susceptibility to acquiring MPXV [13]. Furthermore, HIV-infected individuals are more likely to seek medical attention and undergo diagnostic examinations for MPXV compared to those who are HIV-uninfected [23].

The most prevalent Mpox clinical manifestations include skin lesions, fever, lymphadenopathy, and headache. Among these clinical manifestations, the most common dermatological manifestations were anogenital lesions, while the most frequent lymphadenopathy occurred in the inguinal region. Notably, there were no discernible differences in symptoms, including malaise, fever, headache, as well as genital, anal, and oropharyngeal lesions, based on HIV infection status (Figure 2) [5, 24]. HIV-infected individuals with MPXV often displayed severe skin abnormalities, as well as an increased occurrence of perioral lesions, pharyngitis, and concurrent STIs [25, 26]. If the CD4+ count falls within the normal range, the clinical characteristics of the patients resemble to those of individuals not infected with HIV [21]. Co-infection with both viruses can present substantial risks as it can exacerbate the manifestations of both illnesses and introduce significant challenges in treatment. Given that individuals with HIV have weakened immune systems, they are more susceptible to specific infections, including MPXV. Consequently, it is crucial for them to adopt preventive measures, such as refraining from contact with infected animals, avoiding high-risk behaviors, and maintaining proper hygiene practices [19]. In the endemic region, the mortality rate for individuals without HIV infection is approximately 3.6%. However, the mortality rate in individuals with HIV infection, especially those with a low CD4+ count, is notably higher. Consequently, the treatment of patients with MPXV-HIV co-infection must be approached with caution. Furthermore, individuals with compromised CD4 counts require comprehensive clinical supportive care to manage their condition effectively [21, 27].

There was a rapid stimulation and proliferation of CD4+ and CD8+ T cells, particularly effector memory cells, along with a robust and persistent T-helper 1 (Th1) cell response in individuals with Mpox, even after clinical improvement. However, it was noted that patients with mild symptoms displayed a less active T-cell response [28]. This implies a connection between the immune response and the severity of symptoms in Mpox. Furthermore, earlier reports have indicated that MPXV can induce a state of T-cell unresponsiveness through a unique major histocompatibility complex (MHC), which inhibits the activation of CD4+ and CD8+ T-cell immune responses against Mpox and the production of cytokines [29]. This connection is probably associated with the virus's transmission and the severity of symptoms in infected individuals. Consequently, immunosuppression, marked by a diminished CD4+ T-cell count and response in individuals with HIV infection, may be

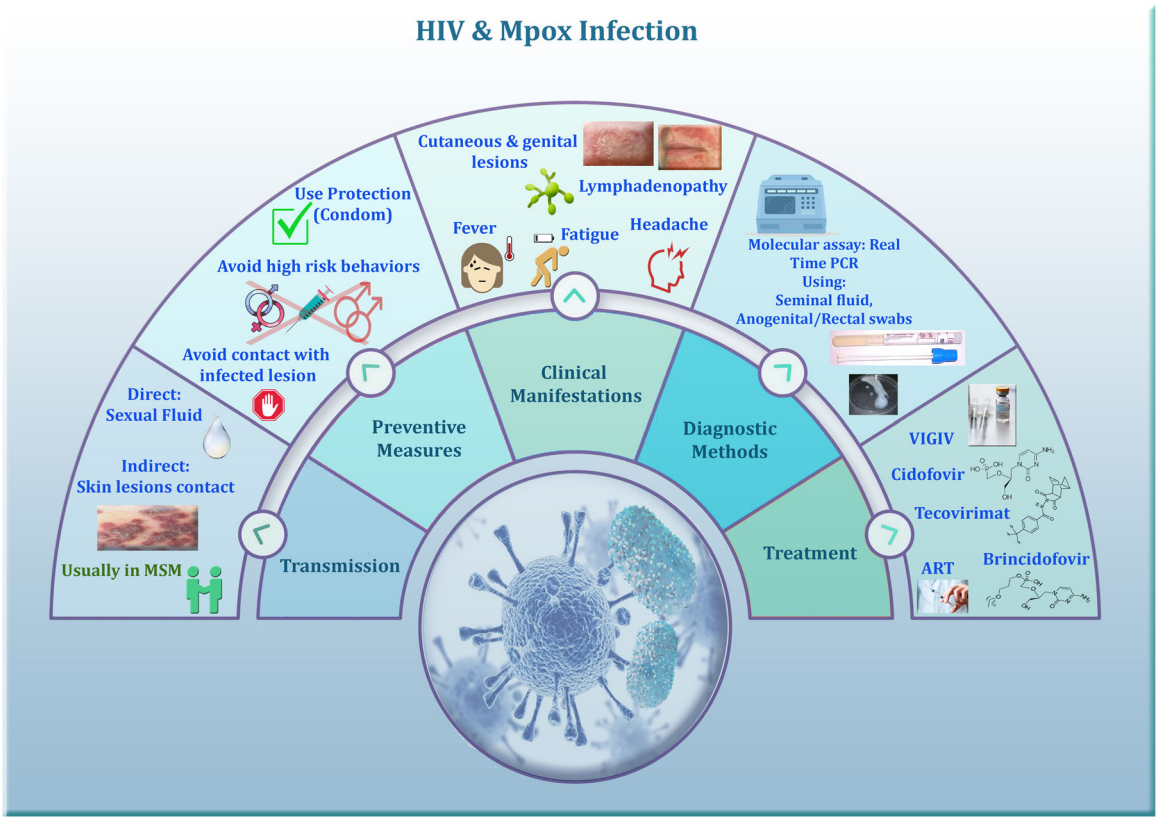

FIGURE 2 | Overview of HIV and Mpox Coinfection. Key aspects of HIV and Mpox coinfection are presented, including routes of transmission, preventive measures, clinical manifestations, diagnostic methods, and therapeutic strategies.

linked to the severity of symptoms, the spread of the infection, and the associated mortality in Mpox cases [19].

The primary diagnostic method employed for Mpox was polymerase chain reaction (PCR), emphasizing the significance of this test in accurately diagnosing MPXV [19]. In the study conducted by Reda et al., it was discovered that the samples obtained from anogenital/rectal lesions had a substantial rate of MPXV DNA positivity, slightly lower than the positivity rate observed in seminal fluid samples taken from patients infected with MPXV [13].

The advisable utilization of treatments such as vaccinia immune globulin intravenous (VIGIV) and antiviral medications like cidofovir or tecovirimat for Mpox management still lacks clear determination. These therapeutic strategies should be reserved for individuals with compromised immune systems, such as those with HIV, children, pregnant or breastfeeding women, individuals with one or multiple complications, and those with unconventional infection sites like the eyes, mouth, genitalia, or anus [30]. According to the Centers for Disease Control and Prevention (CDC) guidance, tecovirimat is recommended, considering the viroimmunological condition of the individual, to mitigate potential complications. Therefore, in individuals coinfected with Mpox and HIV, it is crucial to initiate or maintain antiretroviral therapy (ART) and, if necessary, administer targeted therapy for Mpox, such as tecovirimat. It's essential to note that the potential for drug interactions between ART and tecovirimat should not lead to discontinuing either medication. Consequently, simultaneous infection with both viruses presents a significant hazard, exacerbating the symptoms of each disease and creating challenges in their treatment [31, 32].

3 | Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

The recent outbreak of Mpox during the COVID-19 pandemic holds considerable importance and significance. The rise in cases of co-infection involving these two viruses, which was not unexpected, can potentially impact various aspects, including pathogenesis, severity, management, vaccination response, and the efficiency of diagnostic tests used in patients with either or both diseases. However, it is currently premature and complex to definitively conclude whether the ongoing Mpox outbreak is an independent phenomenon or if it has been exacerbated by the influence of the COVID-19 pandemic [33].

In a systematic review study investigating co-infection of SARS-CoV-2 and MPXV up until October 2022, only three cases of this co-infection were reported. While this study's limited number of cases prevents establishing a definitive cause-and-effect relationship between these two viruses, some common factors were observed in the three patients. These included symptoms like fever, cough, and loss of smell and taste, which are typical in COVID-19 patients. However, the presence of distinctive vesicular and ulcerative genital lesions along with enlarged lymph nodes strongly suggested a co-infection with Mpox in these individuals. Another noteworthy symptom unrelated to COVID-19 was an increase in white blood cell count (WBC), which further supported the presence of co-infections such as MPXV. Overall, the study's results indicated that these co-infections did not progress to severe outcomes, and the patients were discharged from the hospital with a satisfactory recovery [34].

The rise in co-infection cases involving these two viruses can be attributed to several contributing factors. These include issues such as leukopenia resulting from SARS-CoV-2 infection, limited access to and distribution of the SARS-CoV-2 vaccine in developing countries, which further compromised patients' immune defenses and rendered them more susceptible to additional infections, like simultaneous MPXV infection during the pandemic. Additionally, the reduction of travel restrictions and the hosting of large gatherings in Western countries, exemplified by events like the Maspalomas festival in the Canary Islands, also played a role in increasing the number of infections caused by both these viruses [35].

Identifying commonalities in transmission routes, clinical symptoms, signaling pathways, and molecular targets is imperative for understanding the surge in co-infection cases (Figure 3). Factors such as airborne transmission and shared symptoms, including fever, lymphadenopathy, headache, sore throat, and fatigue, contribute to the concurrent occurrence of these infections. However, distinguishing between them poses challenges, notably regarding the characteristic rash, which may not be a consistent feature in Mpox cases and is infrequently observed in COVID-19 patients. This disparity complicates the diagnosis and differentiation of the two infections, necessitating a more comprehensive approach by healthcare professionals. To address this diagnostic challenge, we recommend that healthcare providers in such cases employ laboratory-based detection methods for MPXV and conduct thorough patient interviews. Particular attention should be paid to anamnestic data collection and inquiries regarding sexual history, especially in relation to male-to-male sexual contact and recent travel to regions with a high incidence of Mpox. Furthermore, in cases where visible skin manifestations of Mpox are absent, it is advisable to employ a nasopharyngeal swab, as the virus may affect the oral or rectal mucosa even in the absence of skin involvement [34, 36].

Using bioinformatic analysis conducted in 2023, common aspects of key pathways between COVID-19 and Mpox infection were elucidated. Cytokine signaling in the immune system, tumor necrosis factor (TNF) signaling, and the regulation of the mitogen-activated protein kinase (MAPK) cascade were among the common molecular targets of these two infections in the analysis, and there is a possibility that in case of co-infection with these two viruses, these pathways are strengthened and lead to increased inflammation. However, due to the small amount of co-infection samples of these two viruses, it is not possible to determine the exact cause and effect relationship between the co-infection of SARS-CoV-2 and Mpox, and it is limited to the results of bioinformatic analysis [37]. Heparanase is indeed another molecular target shared by these two viruses. This endoglycosidase cleaves heparan sulfate and plays a pivotal role in extracellular matrix degradation and remodeling. Furthermore, it is known to effectively influence various cellular processes, including autophagy activation, growth factor release, and the secretion of chemokines and cytokines.

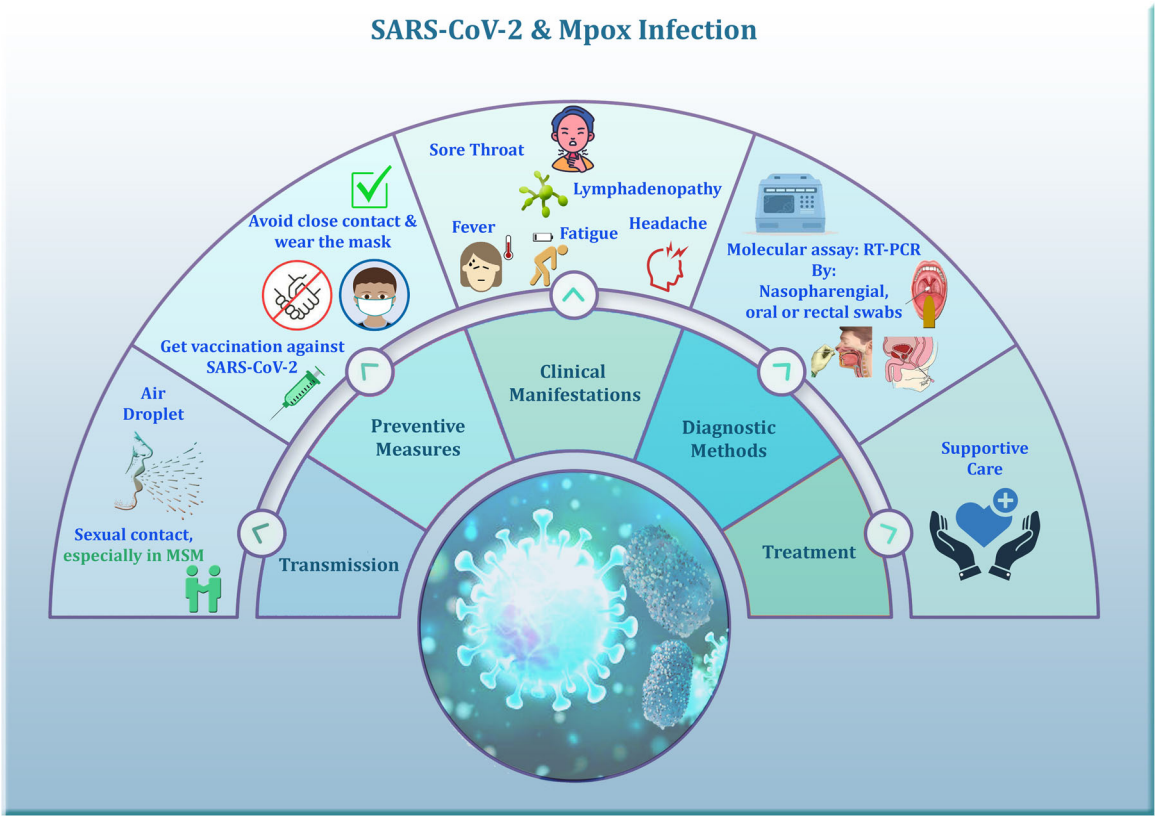

FIGURE 3 | Overview of SARS-CoV-2 and Mpox Coinfection. Primary features of SARS-CoV-2 and Mpox coinfection, covering transmission, prevention, clinical signs, diagnostics, and treatments.

Consequently, it contributes to heightened inflammatory responses and cell signaling pathways, potentially leading to severe inflammation, cytokine storms, and coagulopathy. Both SARS-CoV-2 and MPXV exploit this enzyme to enhance their infectivity, thereby increasing inflammation and the risk of thrombotic disorders. Given the occurrence of co-infections involving these two viruses, Heparanase has emerged as a potential link between Mpox and SARS-CoV-2. This connection presents an opportunity for targeted intervention using specific inhibitors such as low molecular weight heparin, which could mitigate complications associated with SARS-CoV-2 and Mpox infections [38].

Regarding prevention, there is currently no vaccine available to effectively prevent co-infection involving both SARS-CoV-2 and Mpox. However, a study utilizing bioinformatics and immunoinformatics techniques has yielded promising results in the development of a potential vaccine to combat this co-infection. This vaccine, named S7M8, is a multiepitope vaccine designed around four helper T lymphocyte (HTL) epitopes, six cytotoxic T lymphocyte (CTL) epitopes, five B cell epitopes, and Toll-like receptor (TLR) agonists. It is engineered to activate both B and T lymphocytes, inducing robust levels of Th1 cytokines and antibodies. Furthermore, S7M8 demonstrates strong binding affinity to TLR2 and TLR4, not only ensuring excellent immunogenicity but also exhibiting desirable antigenicity. Importantly, it is nontoxic and non-sensitizing, making it a potentially potent tool in the prevention of co-infection involving SARS-CoV-2 and MPXV [39]. Treatment of Mpox and COVID-19 co-infection is rarely addressed in the literature, primarily focusing on supportive care adjusted to individual clinical conditions [34].

4 | Viral Hepatitis

To our knowledge, there is limited available data concerning co-infection involving Mpox and viral hepatitis (Figure 4). In an effort to shed light on the potential influence of prior viral infections on the severity and course of Mpox, Hussain et al., in their 2023 study conducted in the United States, investigated two distinct cases of Mpox with concurrent viral infections. One case involved co-infection with HCV, while the other case featured co-infection with HIV. Both cases involved male patients, and their complications were clinically and histopathologically analyzed. Notably, Hussain et al. observed significant differences in the dermatopathology of individuals infected with Mpox who had a prior history of either HCV or HIV infections. Interestingly, when examining Mpox co-infected with HCV, the researchers noted that cutaneous manifestations were notably less severe than cases where either condition was present alone (i.e., HCV or Mpox alone). Conversely, in patients with Mpox coinfected with HIV, skin lesions were more severe than those observed in cases of either Mpox or HIV alone. In the case of HIV-positive individuals with Mpox, the authors' analysis aligns with prior research indicating that co-infection can exacerbate the inflammatory response and increase infectivity. However, in the context of HCV-MPXV co-infection, the emphasis was placed on the possibility of pro-inflammatory cytokines and their potential role as antiviral agents in the development of protective mechanisms [25].

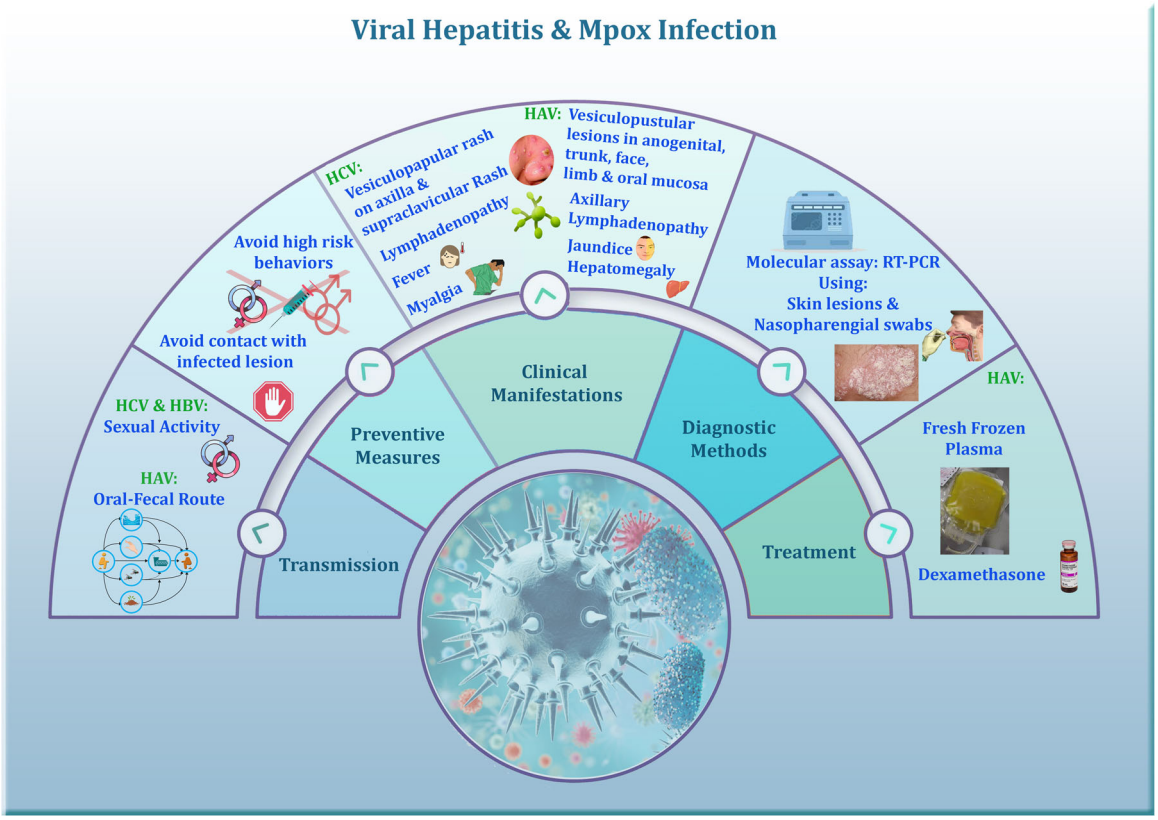

FIGURE 4 | Overview of Viral hepatitis and Mpox Coinfection. Overview of Viral Hepatitis (HAV, HBV, HCV) and Mpox Coinfection. Key factors in coinfection between Mpox and viral hepatitis (HAV, HBV, HCV), including transmission routes, prevention, clinical manifestations, diagnostics, and treatments.

In the Maldonado-Barrueco study conducted in Spain, 30 Mpox patients were assessed for STI coinfections. Among these patients, three had concurrent HBV infections, and one presented with an additional HCV infection, highlighting the relevance of monitoring and addressing multiple infections in cases within this population [40]. To evaluate active HBV co-infection and monitor the disease's status and progression, assessments included HBV viral load, serological markers such as hepatitis B surface antigen (HBsAg) and hepatitis B e-antigen (HBeAg), as well as liver function indicators—alanine aminotransferase (ALT) and aspartate aminotransferase (AST) [41, 42]. Moreover, in the Valentino study in Malta, 33 cases of Mpox were reported, and among them, 3% ($N = 1$) tested positive for HCV [43].

In a study by Oprea et al. (2023), a young male with severe hepatitis A virus (HAV) coinfected with MPOXV and a history of HIV required hospitalization in Romania. After returning from Spain, he presented with fever, malaise, jaundice, and vesiculopustular lesions. Laboratory findings showed elevated liver enzymes and positive IgM anti-HAV and acute syphilis. Despite initial treatment with intravenous glucose and arginine, his condition worsened, leading to the addition of dexamethasone, vitamin K, and fresh frozen plasma, while ART was temporarily paused due to liver failure. The patient's clinical status improved after 2 weeks, although jaundice persisted, and MPXV DNA remained detectable in nasopharyngeal swabs. The potential contribution of Mpox to liver damage is proposed, either through direct mechanisms, which are yet to be fully described, or through indirect mechanisms, possibly involving immunological processes [44].

5 | Herpesviridae Family (HSV-1, HSV-2, VZV, CMV)

Clinical assessment of Mpox includes evaluating primary skin lesions, their location, distribution, size, progression pattern, and the timing of the rash in relation to fever and other systemic symptoms. It's important to consider that conditions like HSV and VZV infections often appear as similar possibilities in this context (Figure 5) [45]. While it's essential to distinguish Mpox rashes from other infections like HSV and VZV, it's worth noting that there have been several reported cases of cutaneous Mpox co-infections with HSV and VZV [46–48].

In the Maldonado-Barrueco study, the analysis revealed the detection of a total of 36 pathogens across 30 Mpox patients. Notably, HSV-1 and HSV-2 was identified in 12 out of the 36 pathogens, accounting for 33.3% of the pathogen findings in this patient cohort [40]. In the study conducted by Tan et al., a total of 217 paired clinical samples were analyzed. Within this cohort, two patients were found to have co-infections involving Mpox and HSV. Specifically, one patient exhibited a co-infection with Mpox and HSV-1, while another patient had a co-infection with both Mpox and both HSV-1 and HSV-2. These findings highlight the potential co-occurrence of these viral infections in a limited number of cases within the study population [49].

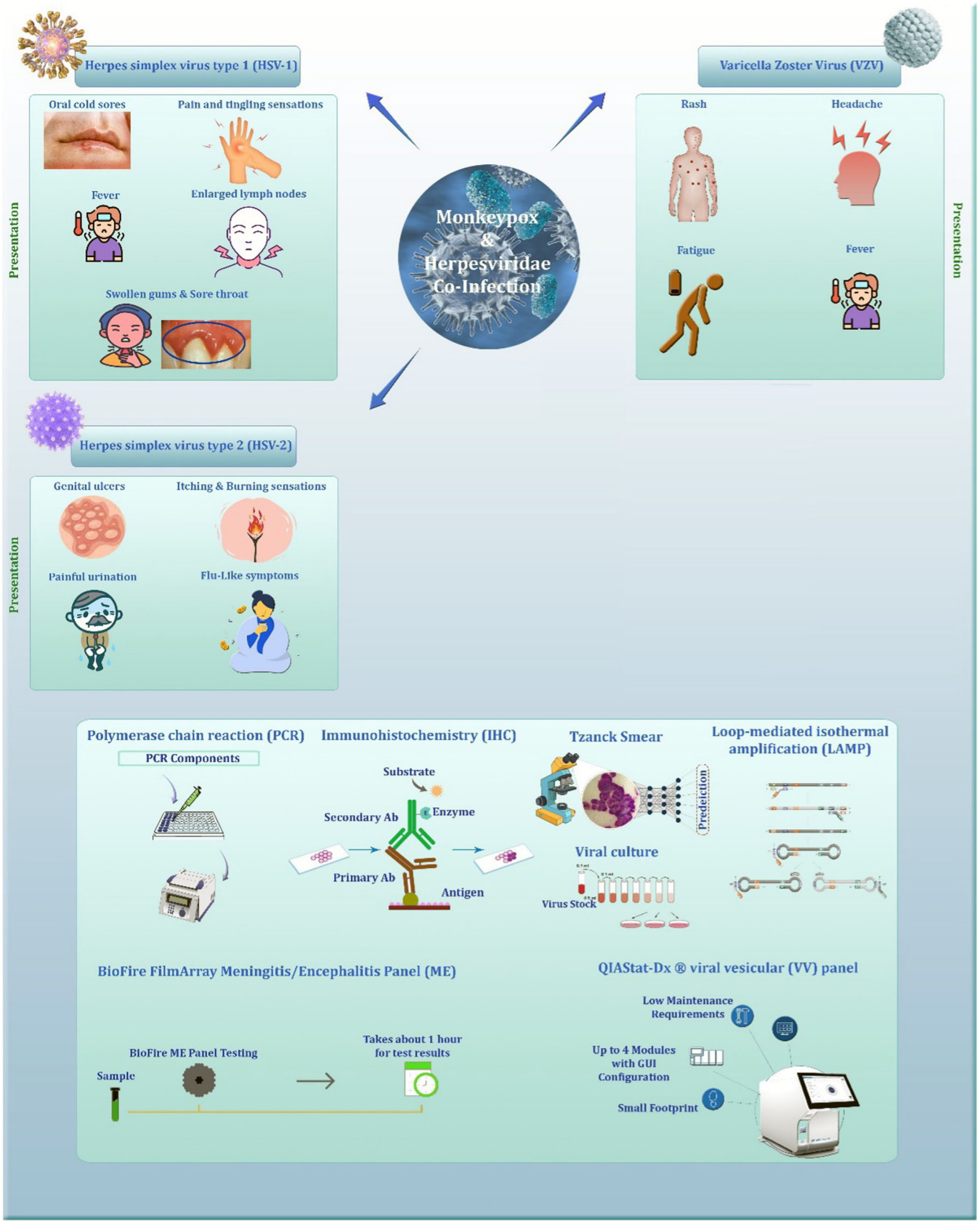

FIGURE 5 | Overview of Herpesviridae Family Members (HSV-1, HSV-2, VZV) and Mpox Coinfection. Notable aspects of Herpesviridae (HSV-1, HSV-2, VZV) and Mpox coinfection, covering clinical presentations and diagnostics.

In the study conducted by Wieder-Feinsod et al., an intriguing observation was made regarding the misidentification of MPXV infection. Among the 26 patients who received incorrect diagnoses, five of them, comprising 19.2% of this subgroup, were initially diagnosed with oral or genital herpes. However, upon closer examination, it was determined that these patients actually had Mpox. This discovery underscores the potential for Mpox infection to be easily overlooked and mistaken for other diseases, emphasizing the critical need for accurate diagnostic methods and heightened awareness to prevent such misdiagnoses [50]. A similar situation was also encountered in the study conducted by Jørgensen et al., where a patient initially exhibited symptoms resembling a primary herpes infection but later tested positive for Mpox [51].

In a case study reported by Derrick et al., a 42-year-old individual with HIV presented with a distinct skin eruption characterized by papulovesicles mainly on the face. Remarkably, this patient was diagnosed with a complex co-infection involving MPXV, HSV-1, VZV, and late latent syphilis. Subsequent biopsy results revealed viral changes consistent with both Mpox and HSV. PCR testing confirmed the presence of HSV-1 and MPXV but excluded HSV-2 and VZV. Immunohistochemistry (IHC) confirmed the presence of VZV. This case underscores the clinical challenge of distinguishing between Mpox, HSV, and VZV, particularly when they coexist. It underscores the importance of a comprehensive diagnostic approach, potentially including multiple testing methods such as PCR, histopathological examination (H&E), IHC, and Tzanck smears. Furthermore, obtaining samples from various lesions can be critical for a thorough assessment, particularly in immunocompromised patients, to ensure precise diagnosis and appropriate patient management [52].

The first documented case of Mpox in the Czech Republic, confirmed after a retrospective review of swab samples, revealed a co-infection involving MPXV, HSV-2, and HIV [53]. Umair et al.'s investigation marks the first confirmed case of MPXV in Pakistan. Furthermore, their study uncovered the co-infection of MPXV and VZV, employing a metagenome approach that provided comprehensive insights into the complete genomes of these viruses [54].

In addition to coinfection with herpesviridae, two cases of simultaneous skin infection involving MPXV, HSV, and CMV were detected in a 30-year-old Asian and a 34-year-old African man. Regrettably, the second case led to a fatal outcome attributed to CMV pneumonia and sepsis, despite receiving ganciclovir treatment [47].

The similarity in clinical presentation between Mpox and other common syndromes in MSM, coupled with the frequent occurrence of coinfections like HSV-1, HSV-2, and VZV, has prompted calls for heightened awareness among clinicians and the development of more rapidly accessible diagnostic methods [55]. A readily available multiplex PCR panel accurately detects MPXV, as well as common imitators like HSV and VZV, in clinical specimens and could be used in routine clinical, surveillance, and outbreak settings [55].

The QIAstat-Dx Viral Vesicular (VV) panel, with the ability to detect MPXV, HSV-1, HSV-2, VZV, and human herpesvirus 6 (HHV-6), combines user-friendliness, rapid results, and strong sensitivity and specificity. This amalgamation enhances diagnosis, clinical care, and public health responses [55, 56]. The emergence of nanotechnology has introduced the utilization of modified nanoparticles as potential antiviral tools for combating diseases like Mpox, HSV-1, and HSV-2 [57]. The BioFire FilmArray Meningitis/Encephalitis (ME) panel provides a rapid diagnostic tool for identifying key members of the Herpesviridae family, including HSV-1, HSV-2, VZV, and HHV-6, as well as distinguishing these viruses from Mpox and conditions that mimic it. Although the sensitivity of the BioFire ME panel may be lower than that of single-plex PCR for HSV-1 and HSV-2, its ability to detect multiple pathogens simultaneously is advantageous in clinical settings. Moreover, the use of swabs collected in universal transport media (UTM) for Mpox testing can be easily integrated with the BioFire ME panel, streamlining the diagnostic process for viral exanthems in patients being evaluated for Mpox infection [58–60]. The single-tube loop-mediated isothermal amplification (LAMP) assay is a valuable diagnostic tool for identifying suspected MPXV infection, especially in areas with limited access to laboratory resources. This test is tailored to specifically detect MPXV DNA and does not exhibit cross-reactivity with related DNA viruses, including those belonging to the herpesviridae family like HSV-1, HSV-2, and VZV [61]. Furthermore, viral culture remains an essential resource for detecting less common or newly emerging viral pathogens such as MPXV, HSV, and VZV, particularly when there are ample specimens with high viral loads accessible for analysis [62].

6 | Conclusion AND Future Trends

In summary, Mpox has evolved into a critical global public health concern, with a substantial multi-country outbreak reported by the WHO in mid-2022, resulting in over 109,699 confirmed cases and 236 fatalities by September 30, 2024. The intricate challenge of Mpox co-infections with various viral agents, including HIV, SARS-CoV-2, hepatitis viruses (HAV, HBV, HCV), as well as herpesviruses (HSV-1, HSV-2, VZV, CMV), necessitates a comprehensive examination. This study provides a thorough exploration of co-infection dynamics, addressing epidemiological aspects, clinical manifestations, preventive measures, treatment guidelines, and advanced diagnostic approaches to enhance our understanding and management of these complex interactions. Future trends in this field may involve the development of targeted therapies and vaccines to mitigate Mpox co-infections and enhance global preparedness for emerging viral outbreaks.

Author Contributions

Mohsen Nakhaie: conceptualization, writing – original draft. **Mohammad Rezaei Zadeh Rukerd:** writing – review and editing. **Niloofar Farsiu:** writing – review and editing. **Davood Bashash:** visualization. **Fatemeh Khodadadpour Mahani:** writing – review and editing. **Nasir Arefinia:** writing – original draft. **Javad Charostad:** conceptualization, supervision. **Mohammad Zarei:** supervision, writing – review and editing. **Farzane Behnezhad:** writing – original draft.

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The authors have nothing to report.

Declarations

All authors have read and approved the final version of the manuscript. Javad Charostad had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

Transparency Statement

The lead author Javad Charostad, Mohammad Zarei affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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