Pharmacological Management of Monkeypox a Comprehensive Review of Current Drug Therapies

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***Abstract*—Monkeypox (mpox) has re-emerged as a significant public health concern with limited approved treatments. This review evaluates current pharmacological strategies against mpox, including antiviral agents, vaccines, immunoglobulins, and supportive therapies. Emphasis is placed on repurposing existing drugs such as Tecovirimat, cidofovir, and brincidofovir, as well as the development of vaccines like MVA-BN and LC16 for pre- and post-exposure prevention. The review also discusses potential therapeutic targets identified through computational and bioinformatics approaches, highlighting recent advances and challenges in clinical translation. Effective management of mpox requires an integrated approach involving antiviral therapy, vaccination, and supportive care, especially in vulnerable populations. The review aims to guide future research and clinical practice to optimize treatment outcomes and containment of mpox outbreaks.**

***Index Terms*—Monkeypox, Pharmacological management, Antiviraltherapy, Vaccines, Tecovirima, Cidofovir, Brincidofovir, Immunoglobulins.**

I. INTRODUCTION

1.1 Overview of Monkeypox: virology, epidemiology, and clinical significance

Monkeypox (Mpox) is a zoonotic viral infection caused by the monkeypox virus (MPXV), an enveloped double-stranded DNA virus belonging to the Orthopoxvirus genus within the Poxviridae family. This virus shares structural characteristics with other orthopoxviruses, such as variola virus, the causative agent of smallpox [1]. Originally endemic to regions in West and Central Africa, monkeypox has recently emerged as a global public health emergency with outbreaks reported across multiple non-endemic countries, driven by sustained human-to-human transmission [2]. The epidemiology has notably shifted with outbreaks such as those in 2022 and onwards, where transmission clusters occurred particularly within sexual networks among men who have sex with men, highlighting novel transmission dynamics beyond traditional zoonotic spillover[3,4]. Virologically, MPXV utilizes a complex life cycle involving genome replication and viral assembly within host cells, making it a target for antiviral interventions[2]. Diagnostic methods include PCR-based techniques, serological assays, as well as whole-genome sequencing approaches, enabling tracking of viral evolution, outbreak surveillance, and outbreak source identification[1,5]. The clinical spectrum ranges from a self-limiting febrile rash illness to more severe disease with complications such as secondary bacterial infections, ocular involvement, and urogenital manifestations[2,3,6]. Symptoms typically involve systemic features followed by characteristic pustular rash, often with genital and perianal lesions in recent outbreaks, reflecting the routes of transmission[4,7]. Epidemiological data from endemic areas, such as the Democratic Republic of Congo, illustrate continuing endemic transmission with significant case fatality rates and clinical burden, underscoring the importance of public health interventions and surveillance in affected regions [8]. The ongoing global spread of MPXV, including cases in non-endemic areas, demands heightened awareness, prompt diagnostics, and effective containment strategies. The clinical significance of monkeypox lies both in its potential for epidemic spread and in the diverse manifestations that challenge healthcare systems, especially as its epidemiology evolves in the context of waning smallpox immunity worldwide

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1.2 Importance of pharmacological management in controlling outbreaks

Pharmacological management plays a critical role in controlling monkeypox outbreaks by enabling targeted therapeutic interventions, reducing disease severity, and minimizing transmission. The re-emergence of monkeypox as a global public health threat highlights the urgent need for effective drug therapies, including antivirals such as tecovirimat, cidofovir, and brincidofovir, which have shown promising inhibitory effects against the virus. These agents provide a means to mitigate viral replication and improve clinical outcomes, especially in severe cases where supportive care alone may be insufficient[9]. Drug repurposing strategies accelerate the availability of treatments by leveraging existing medications with established safety profiles, thus offering a cost-effective and rapid response option in outbreak settings[9]. Moreover, pharmacological management is integral to reducing nosocomial transmission risks, especially in healthcare environments where monkeypox patients require surgical or anesthetic procedures, necessitating strict protocols and antiviral therapies to protect health workers and other patients[10]. Beyond direct treatment, antiviral agents and pharmacological prophylaxis contribute to outbreak containment by shortening infectious periods and reducing viral shedding, thereby lowering community transmission rates[11]. This is particularly important in vulnerable populations or settings with higher transmission risks, where early pharmacological intervention can prevent spread and complications. Additionally, pharmacological approaches complement vaccination efforts and public health measures by providing treatment options for already infected individuals, thereby enhancing overall outbreak control [11]. Comprehensive pharmacological management also includes exploring traditional medicine candidates with antiviral properties, broadening the therapeutic arsenal against monkeypox, especially in resource-limited settings[12]. Effective outbreak control ultimately depends on integrating pharmacological interventions with surveillance, early detection, and coordinated public health responses, as evidenced by lessons learned from other infectious disease outbreaks [11,13]

1.3 Objectives and scope of the review

The primary objective of this review is to comprehensively evaluate the pharmacological management options available for monkeypox, focusing on current drug therapies, including antivirals, vaccines, immunoglobulins, and repurposed agents. It aims to synthesize the latest evidence on drug repurposing strategies, molecular targets of the monkeypox virus (MPXV), and the therapeutic potential of both conventional and novel compounds identified through computational and experimental approaches[9]. The review also intends to address translational challenges such as pharmacokinetics, toxicity, and efficacy limitations, providing insights into how emerging technologies like high-throughput screening, organ-on-chip platforms, and genomic surveillance can enhance drug discovery pipelines against MPXV[9]. The scope extends to exploring pharmacological mechanisms, assessing herbal and traditional medicine candidates like Ruyi Jinhuang Powder, and evaluating microbial and host-pathogen interactions relevant to therapeutic targeting [12]. Additionally, the review covers the global patent landscape relating to monkeypox therapeutics and vaccines to understand innovation trends and barriers in medical development and access[14].

II. PATHOPHYSIOLOGY AND VIROLOGY RELEVANT TO DRUG TARGETS

2.1 Monkeypox virus structure and replication cycle

The monkeypox virus (MPXV) is a large, complex, enveloped double-stranded DNA virus belonging to the Orthopoxvirus genus within the Poxviridae family[15]. Its genome ranges from approximately 184.7 to 198 kilobases containing 143 to 214 open reading frames that encode numerous structural and regulatory proteins[15]. The virus particle consists of a core containing the linear double-stranded DNA genome tightly associated with viral enzymes essential for replication, surrounded by lateral bodies and an outer envelope derived partly from host membranes, which facilitate entry into host cells [16]. Upon infection, the monkeypox virus attaches to host cell membranes via interactions likely involving viral envelope proteins targeting host receptors. Fusion of the viral envelope and cellular membrane allows entry of the viral core into the cytoplasm. Unlike many DNA viruses, MPXV replicates exclusively in the cytoplasm, utilizing its own encoded transcriptional machinery to transcribe early genes immediately after uncoating[15]. Early gene products then mediate genome replication and late gene expression, producing structural proteins and enzymes necessary for virion assembly. Viral cores are transported along microtubules away from the cell periphery toward viral assembly sites within cytoplasmic viral factories, specialized compartments for replication and assembly. Viral assembly involves formation of immature virions that mature into intracellular mature virions and sometimes extracellular enveloped virions, enabling spread within the host[15]. Key viral proteins such as A29L play critical roles in coordinating virion assembly and host-virus interactions, with monoclonal antibodies against these proteins supporting understanding of viral structure and aiding diagnostics [17]. The life cycle includes tightly regulated gene expression with alternative transcription start and end sites, as revealed by transcriptomic analyses, contributing to viral adaptability and complexity of protein products [18]. The virus synthesizes its mRNAs and replicates DNA using virally encoded enzymes, independent of the host nucleus. By extensively encoding its own replication and transcription machinery, monkeypox virus ensures efficient replication within the cytoplasm while evading certain host defenses. This autonomous replication cycle is a target for antiviral drugs like cidofovir and tecovirimat, which inhibit viral DNA polymerase or protein function critical for virion formation [15,19]. Understanding the detailed structure and replication mechanisms is essential for the design of therapeutic interventions and tracking viral evolution during outbreaks [16].

2.2 Host-pathogen interactions influencing drug efficacy

Host-pathogen interactions significantly influence the efficacy of pharmacological treatments against monkeypox virus (MPXV) infection by shaping viral evolution, immune evasion, and drug targeting. MPXV relies on intricate interactions with human host proteins for its replication and survival. Network-based analyses have identified 160 human proteins linked to MPXV, with 39 central hub proteins that function as potential drug targets. Drugs such as Baricitinib, Infliximab, Adalimumab, and

Etanercept, originally approved for other indications, show promise against MPXV by modulating these host-pathogen interactions, thus illustrating how drug efficacy can depend on interfering with host cellular pathways co-opted by the virus[20]. Viral adaptation also plays a role in drug efficacy. Recent genomic studies have revealed unexpected mutation patterns in MPXV consistent with the activity of host immune enzymes like the APOBEC3 family, which introduces mutations from cytosine to uracil in viral DNA. This host-driven editing influences viral evolution and may affect susceptibility to antiviral drugs, as mutations in viral genes may alter drug binding or resistance profiles [21]. Moreover, the viral proteins themselves can modulate immune responses and antiviral activity of the host. For instance, MPXV encodes multiple factors that antagonize host immune defenses, such as those affecting interferon-stimulated pathways, potentially diminishing the effectiveness of immunomodulatory therapies [22]. The interplay between viral virulence factors and host immune responses creates challenges for antiviral efficacy and necessitates combination strategies that target both viral components and modulate host immunity.

2.3 Potential pharmacological targets based on viral life cycle

Potential pharmacological targets in the monkeypox virus life cycle span multiple viral proteins and host interactions critical for viral replication, assembly, and spread. Core targets identified through bioinformatics, protein modeling, and network pharmacology approaches include proteins involved in genome replication, transcription, viral assembly, and host immune evasion [9,23]. Notable viral targets include the viral DNA polymerase, responsible for replicating the viral genome, which is inhibited by known antivirals like cidofovir and brincidofovir [9]. Similarly, MPXVgp158, a viral protein essential for viral replication and virion assembly, is a validated target for the FDA-approved antiviral tecovirimat, which inhibits this protein to prevent viral spread [19]. Additional promising targets are identified through computational screening and include viral enzymes and structural proteins involved in virion morphogenesis and host cell entry[20]. Network pharmacology studies also propose targeting immunomodulatory signaling pathways such as TNF and c-type lectin receptor pathways to enhance host antiviral defenses or limit excessive inflammation[12]. Monoclonal antibodies directed against surface proteins like A29L and A27L can neutralize MPXV and block cell-to-cell spread, representing additional therapeutic strategies focused on viral entry and dissemination[24]. Moreover, AI-driven drug discovery has identified existing antiretroviral agents, such as bictegravir and etravirine, that inhibit viral DNA polymerase activity across multiple orthopoxviruses, offering rapid repurposing opportunities[25].

III. OVERVIEW OF APPROVED ANTIVIRALS WITH ACTIVITY AGAINST ORTHOPOXVIRUSES

3.1 Tecovirimat (ST-246): mechanism, clinical use, efficacy data

Tecovirimat (ST-246 or TPOXX) is an antiviral drug developed to target orthopoxvirus infections, including monkeypox virus (MPXV) and smallpox [26]. Its mechanism of action centers on inhibiting the viral F13 protein, a p37 ortholog essential for the formation of extracellular enveloped virions (EEVs). By stabilizing F13 homodimers, tecovirimat acts as a molecular glue that disrupts the viral wrapping process, preventing the transition from intracellular mature virus (IMV) to intracellular enveloped virus (IEV) and thus blocking virus spread [26]. Clinically, tecovirimat is approved for smallpox treatment and authorized under exceptional circumstances for monkeypox management, primarily based on animal model data demonstrating efficacy[27]. Human clinical efficacy data remain limited, with observational studies during the 2022 mpox epidemic showing good tolerability and adherence but mixed effects on symptom resolution. Some patients experienced initial symptom worsening despite therapy, highlighting ongoing uncertainty and the need for randomized controlled trials[28]. In vitro studies using human bronchial epithelial cell lines (Calu-3) demonstrated that tecovirimat significantly reduces MPXV replication by 77–81% intracellularly and in supernatants, with a 92% reduction in cytopathic effects. Electron microscopy showed the drug inhibits viral particle wrapping, leading to cytoplasmic vacuolation, supporting its mechanism at nanomolar concentrations[29]. This provides mechanistic insight relevant for treating severe mpox with respiratory

involvement. Advanced analytical methods such as high-resolution mass spectrometry (parallel reaction monitoring) have been developed to quantify tecovirimat plasma levels with high specificity and sensitivity, aiding pharmacokinetic studies and therapeutic drug monitoring in clinical settings[30]. In silico analyses also note that while tecovirimat primarily targets the viral p37 protein, potential off-target effects on human proteins exist, underscoring the importance of monitoring safety and off-target interactions during clinical use[31].

3.2 Cidofovir and Brincidofovir: pharmacodynamics, safety profiles, limitations

Cidofovir and brincidofovir are antiviral agents approved for smallpox and considered for monkeypox treatment due to their activity against orthopoxviruses[22,32]. Pharmacodynamically, cidofovir is a monophosphate nucleotide analog that requires intracellular phosphorylation by host kinases to its active diphosphate form. This active metabolite inhibits viral DNA polymerase, thereby preventing viral DNA synthesis and replication [15]. Brincidofovir (BCV) is an orally bioavailable lipid conjugate prodrug of cidofovir designed to improve cellular delivery and reduce nephrotoxicity. Once inside cells, brincidofovir is cleaved to release cidofovir, which then undergoes phosphorylation similarly to cidofovir [32]. Recent studies suggest certain novel derivatives of brincidofovir demonstrate superior in vitro and in vivo antiviral activity against MPXV and related viruses, with lower effective concentrations than brincidofovir itself, indicating potential for development of more potent compounds [32]. Regarding safety, cidofovir is limited by significant nephrotoxicity due to accumulation in renal proximal tubular cells, necessitating intravenous administration with hydration and probenecid co-administration to mitigate kidney damage. This limitation restricts its widespread use, especially in vulnerable populations [33]. Brincidofovir, by contrast, has a better safety profile primarily due to its improved pharmacokinetics and oral bioavailability, reducing renal toxicity concerns; however, its clinical efficacy in monkeypox remains inconclusive and under investigation [32,33].

3.3 Comparative analysis of these antivirals in monkeypox treatment

Tecovirimat, cidofovir, and brincidofovir represent the primary antiviral agents considered for monkeypox treatment, each with distinct mechanisms, efficacy profiles, and safety considerations. Tecovirimat specifically targets the viral p37 (F13) protein critical for virion envelopment and egress, thereby inhibiting extracellular virus formation and spread. It is orally bioavailable and generally well tolerated, with observational data during the 2022 mpox outbreak showing good adherence and safety. However, its clinical efficacy in humans requires further confirmation via randomized controlled trials [26,28]. In vitro, it exhibits potent nanomolar activity reducing viral replication and cytopathic effects in human cells [29]. Cidofovir and brincidofovir are nucleoside analog DNA polymerase inhibitors. Cidofovir, an intravenous drug, is effective but limited by nephrotoxicity and requires co-administration of hydration and probenecid for kidney protection [15]. Brincidofovir is an orally bioavailable lipid conjugate prodrug of cidofovir designed to improve delivery and reduce renal toxicity; however, its clinical efficacy against monkeypox remains inconclusive, and gastrointestinal adverse effects are a concern [32,33]. Comparatively, tecovirimat offers a more targeted mechanism and favorable safety profile, making it preferable for first-line use, especially in outpatient settings. Cidofovir, due to toxicity, is restricted to severe cases or special circumstances. Brincidofovir's oral availability improves convenience but with uncertain clinical benefits and potential adverse effects limiting widespread adoption. All three drugs lack extensive efficacy data in large randomized trials for mpox, underscoring the need for further research[7,9].

IV. SUPPORTIVE AND SYMPTOMATIC PHARMACOLOGICAL TREATMENTS

4.1 Management of secondary bacterial infections: antibiotic considerations

Secondary bacterial infections are important complications in monkeypox that can exacerbate illness severity and delay recovery. Skin lesions caused by monkeypox virus (MPXV) are prone to bacterial superinfection, necessitating careful

management to prevent systemic involvement [2,34]. Management of these secondary bacterial infections primarily involves supportive care with maintenance of lesion hygiene, hydration, and symptom control, alongside targeted antibiotic therapy when bacterial infection is suspected or confirmed[34]. Antibiotic selection should be guided by clinical assessment, microbiological cultures if available, local antimicrobial resistance patterns, and severity of infection. Empiric therapy usually covers common skin pathogens including Staphylococcus aureus and Streptococcus species [34]. Topical antiseptics and barrier ointments can help reduce bacterial colonization on lesions and limit spread [34]. In more severe or systemic cases, systemic antibiotics become necessary. Oral agents effective against gram-positive cocci such as cephalexin or clindamycin are frequently used. For methicillin-resistant S. aureus (MRSA) risk or confirmed MRSA, agents like trimethoprim-sulfamethoxazole, doxycycline, or linezolid may be appropriate [2]. Given that many monkeypox cases occur in immunocompromised individuals including persons living with HIV, careful monitoring for signs of bacterial superinfection and prompt initiation of antibiotics is essential to prevent complications including invasive infections and sepsis [35]. In such populations, broader spectrum and intravenous antibiotics may be warranted based on clinical judgment [35]. Importantly, differentiation between worsening viral lesions and bacterial infection should be clinically ascertained because antibiotics do not target viral replication and unnecessary use promotes antimicrobial resistance[34]. Regular wound care, infection control practices, and patient education on lesion hygiene are vital components of comprehensive management[34].

4.2 Pain management and anti-inflammatory agents

Pain management and anti-inflammatory treatment are key components of supportive care in monkeypox, especially given the significant discomfort caused by fever, skin lesions, lymphadenopathy, and associated symptoms [34]. The main goals are to reduce pain, inflammation, and pruritus to improve patient comfort and prevent complications such as secondary skin infections. Common approaches include the use of systemic analgesics such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) to alleviate fever, muscle aches, headaches, and localized pain at lesion sites [34]. NSAIDs provide both analgesic and anti-inflammatory effects and are typically used when mild to moderate pain and inflammation are present [36]. Topical agents such as petroleum jelly help maintain skin hydration and create a protective barrier to reduce lesion irritation and prevent desiccation, which can exacerbate pain. Oral antihistamines may be used to control pruritus associated with lesions, indirectly contributing to pain reduction by minimizing scratching and secondary injury [34]. Exploratory approaches with natural agents like Curcuma longa (turmeric) extracts have shown promising antioxidant and anti-inflammatory properties in computational and in vitro studies, suggesting potential for adjunctive benefits in reducing inflammation in monkeypox, though clinical evidence is pending[37].

4.3 Treatment of complications (e.g., encephalitis, respiratory distress)

Treatment of complications from monkeypox such as encephalitis and respiratory distress primarily involves supportive management alongside antiviral therapy in severe cases. Encephalitis, a rare but serious neurological complication characterized by brain inflammation, manifests with symptoms including headache, seizures, altered consciousness, and neurological deficits [38,39]. There is no specific proven antiviral treatment for monkeypox-related encephalitis; however, tecovirimat, an FDA-approved antipoxviral agent, is used in severe monkeypox infections and may provide benefit by inhibiting viral replication [19,39]. Supportive care for encephalitis includes seizure control, intracranial pressure monitoring and management, and maintaining adequate oxygenation and hydration[39]. Adjunctive therapies aiming to modulate immune responses and neuroinflammation are currently investigational but may hold future promise[40]. Respiratory complications such as pneumonia and acute respiratory distress syndrome (ARDS) can occur, particularly in immunocompromised patients or severe disease [41]. Management consists mostly of supportive respiratory care, including supplemental oxygen, mechanical ventilation if needed, and treatment of secondary bacterial infections[39]. Granulocyte-macrophage colony-stimulating factor (GM-CSF) has

shown efficacy in animal models and in human viral pneumonias by stimulating innate immunity and ameliorating respiratory inflammation, suggesting potential benefit in monkeypox-related respiratory distress, but data is limited[40]. Overall, management of serious monkeypox complications relies heavily on multidisciplinary supportive care, vigilance for secondary infections, and use of antivirals such as tecovirimat in severe cases[39,41]. Further research is needed to optimize therapeutic strategies for these life-threatening outcomes.

V. IMMUNOMODULATORY AND ADJUNCTIVE THERAPIES

5.1 Role of immune enhancers or suppressors in disease progression

Immune enhancers and suppressors play a critical role in the progression and outcome of monkeypox infection by modulating the host's antiviral response and viral pathogenesis. Immune enhancers, such as effective activation of innate and adaptive immunity, facilitate viral clearance and recovery. Key immune components involved include B-cell activation and antibody production, alongside innate immunity mediated by interferon signaling and TLR pathways [42]. Neutralizing antibodies develop post-infection and their levels correlate positively with the duration of viral detection, suggesting that prolonged antigen exposure may boost humoral immunity[43]. Vaccines utilizing orthopoxvirus antigens elicit protective immune responses, with certain antigens inducing strong neutralizing antibody titers against monkeypox virus, underscoring the importance of adaptive immune enhancements for disease prevention and control[22,44]. Conversely, immune suppressors or viral immune evasion mechanisms contribute to disease severity and prolonged replication. The monkeypox virus suppresses interferon pathway activation and reduces expression of antimicrobial peptides and chemokines, impairing innate immune detection and response [45]. This immune evasion allows enhanced viral replication and persistence, particularly evident in immunocompromised hosts. In individuals with HIV infection, immunosuppression leads to dysregulated gene expression, weakened interferon responses, and downregulated immune signaling pathways such as apoptosis and chemokine recruitment, resulting in more severe disease manifestations and delayed recovery[35,46]. At the molecular level, viral proteins such as the poly(A) polymerase catalytic subunit antagonize host antiviral proteins like guanylate-binding protein 2 (GBP2), thereby diminishing cellular antiviral capacity and facilitating viral replication[47]. Furthermore, inflammasome activation, particularly via the AIM2 sensor, triggers inflammatory cell death (pyroptosis) which is a double-edged sword it helps control infection by eliminating infected cells but excessive activation can exacerbate tissue damage and inflammation, contributing to disease severity [48]. Mitochondrial dynamics also influence antiviral immunity: an elongated mitochondrial network supports antiviral signaling (MAVS-dependent pathways) and limits viral replication, whereas fragmented mitochondria correlate with inhibited immune responses and increased viral proliferation[49].

5.2 Potential use of monoclonal antibodies or convalescent plasma

Monoclonal antibodies (mAbs) and convalescent plasma represent promising immunotherapeutic modalities with potential applications in monkeypox treatment through passive immunization strategies. Monoclonal antibodies are recombinant proteins designed to specifically bind viral proteins, neutralizing the virus and preventing cellular entry. Recent studies have isolated potent neutralizing mAbs targeting monkeypox virus (MPXV) surface proteins such as A28, A35, and H3, with anti-A28 mAbs demonstrating complement-dependent neutralization and providing modest protection in animal models[24,50]. These attributes underscore the potential for mAbs as direct antiviral agents against MPXV infection. Convalescent plasma therapy involves administration of plasma from recovered monkeypox patients containing polyclonal antibodies against multiple viral epitopes, offering an adaptive and broadly targeted immune response[51]. This approach provides rapid availability, is relatively inexpensive, and may remain efficacious despite viral mutations, as observed in experience with COVID-19[52]. Early administration in vulnerable or immunocompromised patients has been associated with improved outcomes compared to late-stage therapy[53]. However, clinical data specific to monkeypox remain limited and requires further investigation. Safety and efficacy of these therapies

depend on multiple factors including timing, antibody titer, patient immunological status, and evolving viral variants. For convalescent plasma and monoclonal antibodies, pathogen reduction technologies enhance recipient safety by eliminating potential transfusion-transmitted infections[54].

5.2 Vaccinia immune globulin: indications and limitations

Vaccinia immune globulin (VIG), also known as Vaccinia Immune Globulin Intravenous (VIGIV), is a therapeutic preparation of antibodies derived from individuals previously vaccinated with vaccinia virus (the smallpox vaccine). It is utilized as an immune-based treatment option in the management of complications arising from orthopoxvirus infections, including monkeypox.

Indications: VIGIV is primarily indicated for treating certain severe adverse reactions to vaccinia vaccination, but it is also utilized off-label for monkeypox management, especially in patients at risk of more severe disease or with complications. These include immunocompromised individuals, children, pregnant women, and those with extensive skin lesions or secondary bacterial infections that impair immune response or healing[22,55]. It can also serve as adjunctive therapy in severe monkeypox cases alongside antivirals such as tecovirimat.

Limitations: Despite its utility, VIGIV has notable constraints. It is not a specific treatment for monkeypox but rather provides passive immunity by supplying anti-vaccinia antibodies that can neutralize orthopoxviruses including monkeypox virus. Its efficacy may vary depending on timing, disease severity, and host immune status, with insufficient data available from controlled clinical trials specific to monkeypox[22]. Furthermore, supply limitations and the requirement for intravenous administration restrict its widespread use. VIGIV is also associated with potential adverse reactions inherent to blood product infusions, including hypersensitivity and transmission of infectious agents, although screening and purification minimize these risks[22]. Lastly, VIGIV does not replace the need for vaccination or antiviral agents but is part of a multifaceted approach to disease management. The development of newer monoclonal antibodies and antiviral drugs may offer more targeted and efficacious alternatives in the future[24].

VI. DRUG DEVELOPMENT AND EMERGING THERAPIES

6.1 Novel antiviral candidates in preclinical or clinical development

Novel antiviral candidates for monkeypox in preclinical and clinical development encompass both repurposed drugs and newly identified compounds targeting critical viral proteins. Tecovirimat, an FDA-approved antiviral originally developed for smallpox, remains a key agent with demonstrated binding and inhibitory potential against monkeypox virus proteins, specifically MPXVgp158[19]. Beyond tecovirimat, drug repurposing efforts have identified multiple candidate agents with antiviral properties against monkeypox. These include FDA-approved antivirals such as cidofovir, which targets viral DNA replication, as well as antibiotics like minocycline and nitroxoline, antimalarials like atovaquone and mefloquine, immunomodulators including infliximab and adalimumab, and chemotherapeutic agents such as doxorubicin; all have shown computational or experimental inhibitory activity against the virus [9]. Novel natural compounds have been investigated by in silico studies targeting the A42R profilin-like protein of monkeypox virus. Salsoline derivatives, genistein, semisynthetic kojic acid derivatives, and naringenin demonstrated stronger binding affinity and stability compared to tecovirimat, suggesting promising antiviral potential pending further validation [56]. Artificial intelligence-driven screening identified antiretroviral drugs bictegravir and etravirine as potent inhibitors of monkeypox virus clades in human organoid models, showing broad anti-orthopoxvirus activity and potential for clinical repurposing, especially in HIV co-infected patients [25]. Plant-derived compounds such as curcuminoids from Curcuma longa exhibit antioxidant and anti-inflammatory effects alongside computational evidence of stable binding to monkeypox viral proteins, highlighting their potential as multifunctional antiviral agents warranting preclinical exploration[37].

6.2Repurposing existing drugs with potential anti-monkeypox activity

Several existing drugs have been identified as potential candidates for repurposing with anti-monkeypox activity based on computational,

experimental, and AI-driven approaches. Key FDA-approved antiviral drugs like cidofovir and tecovirimat, originally developed for smallpox treatment, show inhibitory activity against monkeypox virus by targeting viral DNA replication and virion maturation[9,19]. Additional repurposed drugs include antibiotics such as minocycline and nitroxoline, antimalarial agents like atovaquone and mefloquine, immunomodulators including infliximab and adalimumab, and chemotherapeutic agents like doxorubicin, all demonstrating computational or experimental evidence of antiviral effects against monkeypox[9]. Artificial intelligence has highlighted antiretroviral drugs bictegravir and etravirine as potent inhibitors of multiple monkeypox virus clades. These drugs demonstrated broad anti-poxvirus activities in human organoid models, supporting their potential repurposing for monkeypox treatment, particularly in HIV co-infected patients [25]. In silico screening also supports natural or semi-synthetic compounds such as salsoline derivatives, genistein, semisynthetic kojic acid derivatives, and naringenin as promising inhibitors of a monkeypox viral profilin-like protein, with better binding affinity and stability than tecovirimat[56]. Additionally, curcuminoids from Curcuma longa exhibit therapeutic potential due to antiviral, antioxidant, and anti-inflammatory properties, validated through computational docking and dynamics [37]. The network-based phytochemical analysis of traditional herbal medicines such as Ruyi Jinhuang Powder highlights bioactive components like wogonin and quercetin with possible antiviral effects acting on immune-related signaling pathways[12]. A clinically used anti-HPV agent, 3-hydroxyphthalic anhydride-modified bovine β-lactoglobulin (3HP-β-LG), shows strong inhibition of monkeypox virus entry by binding viral surface proteins and exhibits synergistic effects with tecovirimat, indicating promise as a topical preventive modality[57]. In, repurposed existing drugs with potential anti-monkeypox activity include FDA-approved antivirals (cidofovir, tecovirimat), antibiotics (minocycline, nitroxoline), antimalarials (atovaquone, mefloquine), immunomodulators (infliximab, adalimumab), antiretroviral agents (bictegravir, etravirine), natural and semi-synthetic compounds, and certain biologics. These candidates warrant further preclinical and clinical evaluation to confirm efficacy and safety in monkeypox treatment[9,25,58].

VII. PHARMACOKINETICS AND PHARMACODYNAMICS CONSIDERATIONS

7.1 Absorption, distribution, metabolism, and excretion of key drugs

Key drugs used in monkeypox treatment, including tecovirimat, brincidofovir, and cidofovir, exhibit favorable pharmacokinetic profiles with respect to absorption, distribution, metabolism, and excretion (ADME), supporting their therapeutic use. Tecovirimat demonstrates good oral absorption and bioavailability, with pharmacokinetic modeling indicating adequate systemic exposure to inhibit monkeypox virus replication[59]. It shows acceptable distribution kinetics and metabolic stability conducive to clinical efficacy. Molecular dynamics simulations suggest stable interactions with monkeypox viral proteins, supporting effective pharmacodynamics. Brincidofovir, a lipid conjugate prodrug of cidofovir, offers improved oral bioavailability compared to cidofovir, which has poor gastrointestinal absorption necessitating intravenous administration[22]. Brincidofovir undergoes hepatic metabolism releasing cidofovir intracellularly to exert antiviral effects. This metabolic activation contributes to its pharmacokinetic advantage. Cidofovir, mainly renally excreted, has limited oral bioavailability and primarily administered intravenously. Its clearance relies on renal function, and dosage adjustments may be needed in renal impairment to avoid toxicity[22]. Pharmacokinetic and toxicity analyses of tecovirimat, brincidofovir, and related compounds indicate good pharmacokinetic behavior with manageable toxicity, essential for their continued investigation and use in monkeypox [59]. The balanced ADME attributes of these agents help achieve therapeutic levels while minimizing adverse events. Additional pharmacological agents identified via drug repurposing and screening demonstrate variable ADME profiles but are prioritized based on predicted oral absorption, metabolic stability, and distribution parameters to enhance clinical feasibility [20,58]. Altogether, key monkeypox therapeutics like tecovirimat and brincidofovir exhibit adequate oral absorption, systemic distribution, hepatic metabolism

for prodrug activation (in the case of brincidofovir), and renal excretion, enabling their effectiveness in inhibiting orthopoxvirus infections while maintaining manageable pharmacokinetic and toxicity profiles [22,59].

7.2 Special populations: pediatric, pregnant, immunocompromised patients

Special populations such as pediatric patients, pregnant women, and immunocompromised individuals present unique challenges and considerations in healthcare due to their specific physiological and immunological characteristics. Pediatric patients require tailored approaches in drug dosing and medical management because of their developmental differences and varied prognostic factors compared to adults. Pediatric extrapolation techniques are essential, especially when clinical trial data in children are scarce or difficult to obtain. These involve considering differences in exposure-response relationships and prognostic factors to optimize efficacy and safety in children[60]. Additionally, drug dosing in pediatrics often utilizes advanced modeling approaches such as physiologically based pharmacokinetic modeling, population pharmacokinetics, and pharmacogenetics to account for the vulnerability of preterm newborns, children with organ insufficiency, or obesity [61]. Pediatric patients with complex respiratory or neuromuscular conditions like Duchenne muscular dystrophy benefit from specialized ventilation modes such as volume assured pressure support, which requires expert management and ventilator setting adjustments[62]. Pregnant patients represent a physiologically immunocompromised group with increased cardiovascular demands and altered immune responses. Pregnancy predisposes women to more severe disease manifestations in infections like COVID-19, with higher risks of myocardial injury, cardiomyopathy, thromboembolism, pre-eclampsia, and arrhythmias compared to non-pregnant women [63]. Obstetric care during pandemics requires proactive planning and multidisciplinary strategies to manage these risks safely for both mother and fetus [64]. Multidisciplinary cardio-obstetric teams and routine cardiac testing for high-risk pregnant women hospitalized with severe infections optimize maternal and fetal outcomes[63]. Access to healthcare insurance and adequate prenatal care remains critical, as disparities and socioeconomic factors influence maternal mortality and morbidity globally [65]. Immunocompromised patients, including those with HIV, organ transplants, or malignancies, carry increased susceptibility to infections, multidrug-resistant bacteria, and secondary cancers. In pediatric intensive care units, immunosuppression is strongly associated with higher rates of healthcare-associated infections caused by multidrug-resistant organisms, often involving Gram-positive and coagulase-negative Staphylococcus species[66]. Systemic therapies such as multikinase inhibitors for advanced malignancies in immunosuppressed adults are under investigation, though data remain limited for this special population[67]. Supportive care and targeted treatment therapies are crucial for infections like monkeypox in immunocompromised patients, children, and pregnant women due to their fragile immune status and risk of severe complications[55].

VIII. RESISTANCE PATTERNS AND SURVEILLANCE

8.1 Evidence and mechanisms of antiviral resistance in orthopoxviruses

Antiviral resistance in orthopoxviruses is primarily driven by genetic mutations in viral proteins critical for replication, notably the viral DNA polymerase. Recent structural studies on the Mpox virus (an orthopoxvirus) DNA polymerase complex reveal mechanisms that underlie replication fidelity and proofreading processes, with mutations affecting these functions potentially contributing to resistance by altering the enzyme's interaction with nucleotides and antiviral drugs[68]. Similar to antiviral resistance mechanisms described in other viruses, amino acid substitutions in key viral enzymes can lead to structural changes that diminish drug binding. For example, studies on coronavirus proteases demonstrate that mutations causing the loss of hydrogen bonds or steric clashes reduce inhibitor effectiveness, a mechanism that likely parallels resistance development in orthopoxviruses targeting viral enzymes[69]. Evidence also indicates that mutations accumulate under drug pressure, affecting antiviral efficacy. This is supported by resistance mutation identification techniques such as genotypic analysis, which have been crucial in other viral infections for detecting mutations in critical genes

(e.g., polymerases or proteases) that mediate drug resistance[70,71]. While specific studies detailing orthopoxvirus antiviral resistance mutations remain limited, insights from small molecule inhibitor research show that enhanced potency compounds against orthopoxviruses, such as pyridopyrimidinones, must consider potential resistance mediated by viral mutations in their targets to maintain efficacy[72].

8.2 Strategies to monitor and mitigate resistance development

Strategies to monitor and mitigate antiviral resistance development involve a multifaceted approach combining surveillance, diagnostics, therapeutic strategies, and novel drug development. To effectively monitor resistance, establishing robust networks of laboratories capable of performing diagnostic tests for antiviral resistance is critical. These laboratories participate in surveillance programs coordinated through central reference facilities or collaborative groups, enabling early detection and tracking of resistance mutations in circulating viral populations[73]. Genotypic resistance testing databases, such as those developed for herpesviruses, provide valuable tools for identifying resistance mutations and guiding clinical management by linking specific mutations with drug susceptibility[74]. Similar infrastructures are essential for other viral pathogens, including orthopoxviruses, to prompt timely intervention when resistance emerges. Mitigating resistance development involves therapeutic strategies such as combination therapy, wherein using two or more antiviral agents with different mechanisms of action reduces the likelihood of resistance. For example, in enterovirus infections, consecutive alternating administration (CAA) of double antiviral combinations improved survival and suppressed resistance emergence more effectively than monotherapy or simultaneous administration [75]. Combination regimens can hinder the selection of resistant mutants by imposing multiple barriers to viral adaptation. Targeting host factors essential for viral replication represents an innovative strategy to circumvent direct selection pressure on the virus, thereby limiting the development of resistance. For instance, disrupting the host deubiquitinase complex OTUD4-USP7 has been shown to suppress herpesvirus replication by affecting key viral transcription factors, offering a promising host-targeted antiviral approach with potentially reduced resistance risk[76]. Additionally, understanding the evolutionary dynamics of viral populations helps predict resistance development. Using hypermutator viral mutants facilitates real-time modeling of adaptation under drug pressure, accelerating the study of resistance pathways which can inform the design of better therapeutic regimens[77]. Computational analyses of viral protein coevolution and mutational landscapes further aid in predicting compensatory mutations and resistance mechanisms that may arise during treatment [78]. Adherence to antiviral therapy and optimized dosing regimens also are critical to resistance mitigation, as inadequate drug levels can favor selection of resistant variants. In hepatitis C virus treatment, combining high-potency specifically targeted antiviral therapy with careful management has increased treatment success while reducing resistance emergence[79]. Novel antiviral development integrates insights from virus-host interactions, chemical biology, and synthetic biology to design drugs that are less susceptible to resistance, have broad-spectrum activity, and effectively target viral or host components[80]. Dietary adjuncts such as non-digestible oligosaccharides also show promise in modulating host immunity and interfering with pathogen binding, potentially complementing traditional antivirals and reducing resistance pressure[81].

IX. REGULATORY AND ACCESS ISSUES

9.1 Approval status of monkeypox therapies globally

Currently, the global approval status of monkeypox therapies includes a limited number of antiviral drugs and vaccines authorized primarily based on their prior development for related orthopoxviruses like smallpox. Two antiviral drugs, tecovirimat and brincidofovir, have been identified and are authorized in certain countries for treatment of monkeypox or orthopoxvirus infections under specific conditions. Tecovirimat is currently the only FDA-approved antiviral specifically for smallpox but has been used under expanded access or emergency use protocols for monkeypox treatment. Brincidofovir, an oral antiviral also approved for smallpox, is occasionally considered for monkeypox but has limited data and use [82]. Vaccination remains a critical preventive

strategy. The smallpox vaccine, which offers up to 85% protection against monkeypox, is considered the primary vaccine option globally. Third-generation smallpox vaccines, such as JYNNEOS (also known as Imvamune or Imvanex), are preferred due to their improved safety profile and are approved or authorized in multiple countries for monkeypox prevention, particularly for high-risk groups like healthcare workers, immunocompromised individuals, pregnant women, and those exposed to the virus[14,83]. The ACAM2000 vaccine, a second-generation live vaccinia virus vaccine, remains in use but has more adverse effects and is used more cautiously. Global health authorities, including the World Health Organization (WHO), declared monkeypox a Public Health Emergency of International Concern in 2022, emphasizing vaccination, antiviral treatment when indicated, and infection control measures to manage the outbreak [84,85]. However, availability and regulatory approvals of specific therapies vary by country, with some regions still facing challenges in access to licensed antivirals and vaccines. Research on repurposing existing drugs and developing novel antivirals against monkeypox is ongoing, aimed at expanding therapeutic options beyond those currently authorized [58]. Patent and intellectual property landscapes indicate rapid innovation but also highlight the need for collaborative efforts to ensure equitable access globally[14].

9.2 Availability and distribution challenges during outbreaks

The availability and distribution of monkeypox therapies during outbreaks face significant challenges, especially in achieving equitable access across different regions. One major issue is the global inequity in vaccine distribution, where low- and middle-income countries (LMICs), particularly in endemic regions like central and west Africa, are disadvantaged compared to high-income countries. Factors contributing to this disparity include advanced purchase agreements and vaccine stockpiling by wealthier nations, vaccine nationalism, and limited manufacturing capacity worldwide. These create supply shortages and hinder timely vaccination efforts in countries with elevated risk profiles and fewer resources[86]. Surveillance and reporting also remain insufficient, impairing targeted distribution and outbreak containment. Limited access to diagnostic testing and therapeutics further complicates public health responses in resource-constrained settings[8,87]. Healthcare systems in many affected countries face challenges such as inadequate infrastructure, high workload on frontline workers, and limited availability of protective equipment, which exacerbate difficulties in managing outbreaks and ensuring proper treatment and vaccination coverage[11,88]. For example, nurses in some regions report low preparedness and high stress during monkeypox outbreaks, highlighting the need for adequate resources, training, and safety protocols to support healthcare providers[89]. The scarcity of approved antivirals and vaccines specific for monkeypox means many countries rely on repurposed smallpox treatments and vaccines, which may not be sufficient or readily accessible everywhere. The supply limitations lead to recommendations against widespread immunization, focusing instead on targeted vaccination for high-risk populations and exposed individuals[22]. In addition to logistical and manufacturing constraints, vaccine hesitancy and lack of awareness can reduce uptake even when supplies exist, necessitating public education and community engagement to improve acceptance[86].

9.3 Ethical considerations in drug allocation and use

Ethical considerations in drug allocation and use during infectious disease outbreaks involve balancing equity, fairness, transparency, and maximizing public health benefits while respecting individual rights. One core ethical principle is distributive justice, which requires the fair and equitable allocation of scarce medical resources such as antiviral drugs. Allocation schemes that minimize overall harm at the population level while balancing individual patient needs are often preferred, especially when resources are limited[90]. Transparent, consistent decision-making processes must be established before scarcity arises to avoid panic, inequity, and moral distress among clinicians and to uphold accountability [91]. Procedural fairness entails multidisciplinary deliberation that includes clinical evidence (efficacy and safety), economic considerations (cost and opportunity cost), social justice, and disease-specific factors. Such deliberation aids in prioritizing treatments for those most likely to benefit while

minimizing discrimination and systemic bias[92,93]. Importantly, ethical frameworks emphasize the need for timely decisions to promote equitable and effective use of scarce drugs[94]. The ethical management of drug use also involves respect for patient autonomy and informed consent, even in crisis settings. Challenges arise in conflict or resource-constrained environments where surrogate decision-making, consent, and prioritization become complex, necessitating context-sensitive ethical approaches grounded in humanity, impartiality, and neutrality [95]. Applying ethical frameworks to infectious disease interventions, including antiviral use, benefits from collaboration between public health, clinical ethics, and community stakeholders. Integrating ethical values explicitly into decision models helps anticipate and mitigate unintended consequences, ensuring interventions are both scientifically sound and ethically justifiable[96].

X. REGULATORY GUIDELINES

10.1 Summary of current guidelines from WHO, CDC, and other health authorities

Current guidelines from the World Health Organization (WHO), Centers for Disease Control and Prevention (CDC), and other health authorities for monkeypox emphasize prevention, surveillance, case management, vaccination, and infection control measures. The WHO declared monkeypox a Public Health Emergency of International Concern in 2022 and recommends measures focused on early detection, isolation of cases, contact tracing, and use of personal protective equipment by healthcare workers to prevent nosocomial transmission. Vaccination with third-generation smallpox vaccines like JYNNEOS (MVA-BN) is prioritized for at-risk populations including healthcare workers, exposed contacts, and immunocompromised persons. Treatment with antivirals such as tecovirimat may be considered for severe cases, but clinical data remain limited and usage should follow careful assessment [10,84]. The CDC mirrors these recommendations focusing on prompt recognition, isolation, and supportive care. Clinical management includes symptomatic treatment and consideration of antivirals like tecovirimat under investigational or expanded access frameworks. CDC also stresses the importance of proper infection prevention in healthcare settings to reduce transmission risk and advocates vaccination of close contacts and high-risk groups, including pre- and post-exposure prophylaxis [10]. National health authorities in endemic and non-endemic countries have tailored guidelines reflecting local epidemiology and health system capacities. For example, Malaysia's five-point preparedness strategy covers early surveillance, diagnostic capacity strengthening, case management, cluster control, and public awareness raising [97]. African CDC highlights the pivotal role of community health workers for surveillance, education, myth dispelling, and vaccine acceptance to effectively mitigate mpox spread[98].

10.2 Tailoring treatment based on disease severity and patient factors

Tailoring monkeypox treatment depends significantly on disease severity and patient-specific factors such as immune status, age, pregnancy, and comorbidities. Most monkeypox cases are mild and self-limiting, requiring primarily symptomatic and supportive care, including hydration, analgesics, and treatment for secondary infections[55,99]. Patients with severe disease manifestations such as extensive rash, respiratory involvement, encephalitis, ocular complications, or systemic bacterial infections or those who are immunocompromised, pregnant, pediatric, or have comorbidities may require antiviral therapy and closer monitoring. Currently, antivirals like tecovirimat, brincidofovir, and cidofovir have demonstrated potential efficacy against orthopoxviruses and are considered for such high-risk cases, although data specific to monkeypox remains limited[41,100]. Vaccination with replication-deficient or live vaccinia virus vaccines (e.g., MVA-BN/JYNNEOS, ACAM2000) can be used prophylactically in exposed individuals and pre-exposure for healthcare workers or vulnerable populations. The choice of vaccine and timing factors into patient characteristics, with replication-deficient vaccines preferred for immunocompromised patients due to safety concerns[55]. Clinical presentations may vary, and atypical manifestations, such as limited or anogenital lesions or proctitis without visible rash, require careful evaluation and may influence management decisions further[101]. Careful assessment of risk factors, age groups (notably neonates and children), and pregnancy status guides clinicians in

deciding the intensity of monitoring, antiviral use, and supportive interventions[55].

10.3 Integration of pharmacological therapy with public health measures

The integration of pharmacological therapy with public health measures in monkeypox management is essential for an effective, coordinated response to contain virus spread and optimize outcomes. Pharmacological interventions, primarily antivirals like tecovirimat and brincidofovir, serve to reduce disease severity especially in vulnerable or high-risk patients, thus decreasing hospitalizations and complications. However, these treatments alone cannot control outbreaks without complementary public health actions[9]. Public health measures such as early detection through surveillance, prompt isolation of cases, contact tracing, and vaccination targeting exposed or high-risk groups constitute the frontline defense to limit transmission at the community level [97]. Strengthening laboratory diagnostic capacity and real-time surveillance systems further enables timely therapeutic interventions and resource allocation [11]. Healthcare settings implement infection prevention protocols including personal protective equipment usage and environmental decontamination to minimize nosocomial transmission and protect healthcare workers, who may then receive post-exposure prophylaxis or early antiviral treatment as indicated[10].

A holistic response also involves public awareness campaigns to inform communities about transmission risks, prevention strategies, and the availability of treatments and vaccines. This integration enhances compliance with isolation guidelines and encourages early healthcare seeking, improving the effectiveness of pharmacologic and non-pharmacologic interventions[97].

XI. FUTURE DIRECTIONS AND RESEARCH PRIORITIES

Significant gaps remain in the pharmacological management of monkey pox, including limited clinical evidence on antiviral efficacy and safety, insufficient understanding of optimal dosing regimens, and scarce data on drug interactions and long-term outcomes. Current antiviral treatments such as tecovirimat, cidofovir, and brincidofovir have demonstrated promise but lack robust, large-scale clinical trial data specifically for monkeypox, leaving uncertainties about their best use in diverse patient populations and disease severities[7].

To address these gaps, clinical trials are urgently needed that focus on randomized controlled designs comparing antivirals alone and in combination, assessing efficacy, safety outcomes, and impact on viral shedding and transmission. Observational cohort studies could provide real-world insights, especially for special populations such as immune-compromised, pediatric, and pregnant patients. Adaptive trial designs with stratification by disease severity and patient comorbidities would enhance the relevance of findings. Integration of virologic, immunologic, and pharmacokinetic endpoints can reveal mechanism-based efficacy and optimize treatment duration[7,102].

There is also considerable potential for combination therapies that target multiple viral pathways or combine antivirals with immunomodulatory agents to improve outcomes while reducing resistance risk. Personalized medicine approaches could tailor treatments based on patient genetic profiles, comorbidities, and immune status, potentially guided by computational tools and AI-driven decision algorithms. For instance, individualized drug and dose selection informed by patient-specific pharmacodynamics and pharmacogenomics as seen in other diseases like diabetes or cardiovascular conditions may enhance efficacy and minimize adverse effects.

XII. CONCLUSION

The ethical considerations and management of drug allocation in infectious diseases highlight the critical balance between equitable resource distribution and maximizing population health benefits. Ethical frameworks guide allocation schemes, emphasizing transparency, fairness, and multidisciplinary decision-making while respecting patient autonomy and special considerations in vulnerable populations. Current guidelines from leading health authorities like WHO and CDC focus on early detection, isolation, targeted vaccination, antiviral use in severe cases, and robust infection control measures. Treatment tailoring requires assessing disease severity and patient factors to determine supportive

care or antiviral therapy use. Integration of pharmacological therapy with public health measures ensures comprehensive outbreak control through surveillance, vaccination, community engagement, and healthcare system preparedness. Implications for clinical practice include applying ethical principles in resource allocation decisions, maintaining vigilant case identification, utilizing personalized treatment strategies amid limited pharmacological options, and incorporating public health protocols to mitigate transmission risk. Public health policies must support equitable access to therapeutics and preventive interventions while fostering transparent communication and preparedness at system levels.

Disclosure statement

The authors declare no potential conflicts of interest.

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