

Tecovirimat and mpox: A paradigm of the opportunities and limitations of antiviral drug repurposing

Poonam Sharma* 

Department of Zoology, Gargi College, University of Delhi, New Delhi, India.

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ABSTRACT

Emerging infectious diseases, such as mpox virus, continue to be a major challenge to global public health as they arise from zoonotic spillover, are maintained via sustained human transmission and viral evolution, and possess few to no virus-specific treatments. An important clinical pathway for rapid delivery of an antiviral to an emergent outbreak is via the repurposing of established drugs, for which safety and pharmacokinetic information already exist and have been thoroughly assessed. In this review, we assess tecovirimat as a case study of antiviral drug repurposing to demonstrate the potential and challenges of this approach based on available mechanistic studies, clinical trial results, long evolutionary history, and innovative future directions. Developed initially for smallpox under a biodefense program, tecovirimat blocks the highly conserved VP37 (F13L) envelope protein and was quickly adopted for mpox based on robust mechanistic justification, animal efficacy, and an established safety history. This reflects how past biodefense investment can be used to deploy therapies quickly against novel pathogens during emerging threats. The review critically analyzes disparities between promising observational studies and subsequent randomized clinical trial evidence. PALM007, STOMP, UNITY, and PLATINUM-UK failed to demonstrate any significant clinical advantage in the trials, and a comprehensive European Medicines Agency assessment determined that tecovirimat did not expedite lesion recovery, reduce pain, or result in improved virologic results compared to placebo. Thus, the European mpox indication for tecovirimat was removed in 2026. We also summarize the recent findings on the development of VP37-associated resistance mutations and briefly discuss how best practices, including genomic surveillance, antiviral stewardship, and rational combination therapy strategies, are needed to manage the ongoing threat of resistance and improve future outbreak therapeutics.

1. INTRODUCTION

The world's most pressing public health threat is the fast spread of newly emerging and re-emerging viral diseases [1–3]. Depending on the virus, these infections may display various features that limit control, which may include rapid transmissibility, risk of zoonotic spillover, genetic mutation, high mortality, and limited availability of effective virus-targeted treatments. The recent emergence of several viral diseases, including Ebola, SARS CoV-2, Zika, mpox, SARS CoV, and MERS-CoV, has highlighted the vulnerability of the world's public health systems to new infectious diseases [4]. Several factors contribute to the rapid emergence and transmissibility of newly identified viral pathogens, including climate change, disruption and alteration of natural ecosystems, urbanization, increased migration, deforestation, and increased contact between humans and animals [1,5].

Monkeypox (mpox) is an infectious disease caused by the mpox virus (MPXV). MPXV is an encapsulated, double-stranded Deoxyribonucleic acid (DNA) virus of the genus *Orthopoxvirus* in

the family Poxviridae [4]. MPXV was initially identified in confined monkeys in Denmark in 1958, but the first human case was reported in a male infant in the Democratic Republic of the Congo in 1970. Following this, human mpox cases were predominantly recorded in Central and West Africa, regions where virulent infections were traditionally linked to zoonotic spillover and restricted human-to-human transmission [4–6]. In 2022, the epidemiological landscape of mpox underwent a substantial transformation due to the onset of a notable global outbreak [4]. The largest multi-country mpox outbreak observed outside historically endemic regions of Africa occurred from 2022 to 2023 [7]. On July 23rd, 2022, the WHO declared a mpox Public Health Emergency of International Concern (PHEIC), which was later rescinded in May 2023 due to declining global transmission; however, it was again declared a PHEIC by the WHO in August 2024 following the re-emergence of clade I mpox in Africa [4]. The 2024 mpox Public Health Emergency of International Concern was officially concluded in September 2025; yet, ongoing worldwide transmission continues as a public health issue. The WHO reported 63,692 verified mpox cases and 256 fatalities in 105 nations from January 2025 to June 2026, as the predominant MPXV clades continue to circulate [8]. The clinical signs and symptoms of mpox infection include fever, lymphadenopathy, myalgia, tiredness, and increasing vesiculopustular skin lesions. While most infections are self-limited, serious clinical

*Corresponding Author

Poonam Sharma, Department of Zoology, Gargi College, University of Delhi, New Delhi, India. E-mail: poonam.sharma@gargi.ac.in

symptoms such as encephalitis, subsequent bacterial infections, ophthalmic sequelae, sepsis and death have been identified, especially among immunocompromised hosts, children and pregnant women [9]. Moreover, recent epidemics have indicated changing patterns of transmission that include close sexual and physical contact, which further complicates standard containment techniques [4].

One of the primary challenges of increasing viral outbreaks is the lack of disease-specific treatment options. The traditional approach to identifying antiviral drugs is expensive and time-consuming and may take 10–15 years to be successfully developed, optimized, clinically evaluated, and approved by the regulatory bodies [10]. Hence, drug repurposing has emerged as a highly desirable therapeutic approach to achieving epidemic preparedness and prompt medical intervention. The pharmacokinetics, pharmacodynamics, toxicology, and safety profiles of repurposed drugs are already known, thereby greatly shortening development and regulatory processing times [10]. During recent mpox outbreaks, tecovirimat has become one of the most rapidly deployed and widely investigated orthopoxvirus-directed antivirals. Tecovirimat was developed for the U.S. government biodefense projects against smallpox but was soon repurposed during the mpox

epidemic after showing action against numerous orthopoxviruses [11]. Tecovirimat targets the highly conserved VP37 (F13L) envelope protein and inhibits the production of new extracellular viral particles and the dissemination of the virus from cell to cell [12]. Preclinical tests have shown significant antiviral efficacy of tecovirimat against orthopoxviruses, resulting in decreased disease progression and enhanced outcomes [13,14]. Nevertheless, subsequent randomized clinical trials failed to present clinical confirmation of effectiveness at the studied doses. The disparity between the rationale based on biological and preclinical facts, contrasted with outcomes from randomized clinical trials, illustrates tecovirimat as a typical case of the efficacy and limitations of antiviral therapy repurposing. The concerns regarding resistance mutations linked to VP37/F13 and ambiguity in the reported clinical efficacy of tecovirimat offer significant challenges to its prospective long-term clinical application [15,16]. This review critically assesses tecovirimat as a translation model of antiviral drug repurposing by examining the combination of mechanistic evidence, clinical results, viral genomic changes, resistance patterns, and potential for future therapeutic applications in order to derive further insights into preparing for pandemics and novel emerging virus infections (Fig. 1).

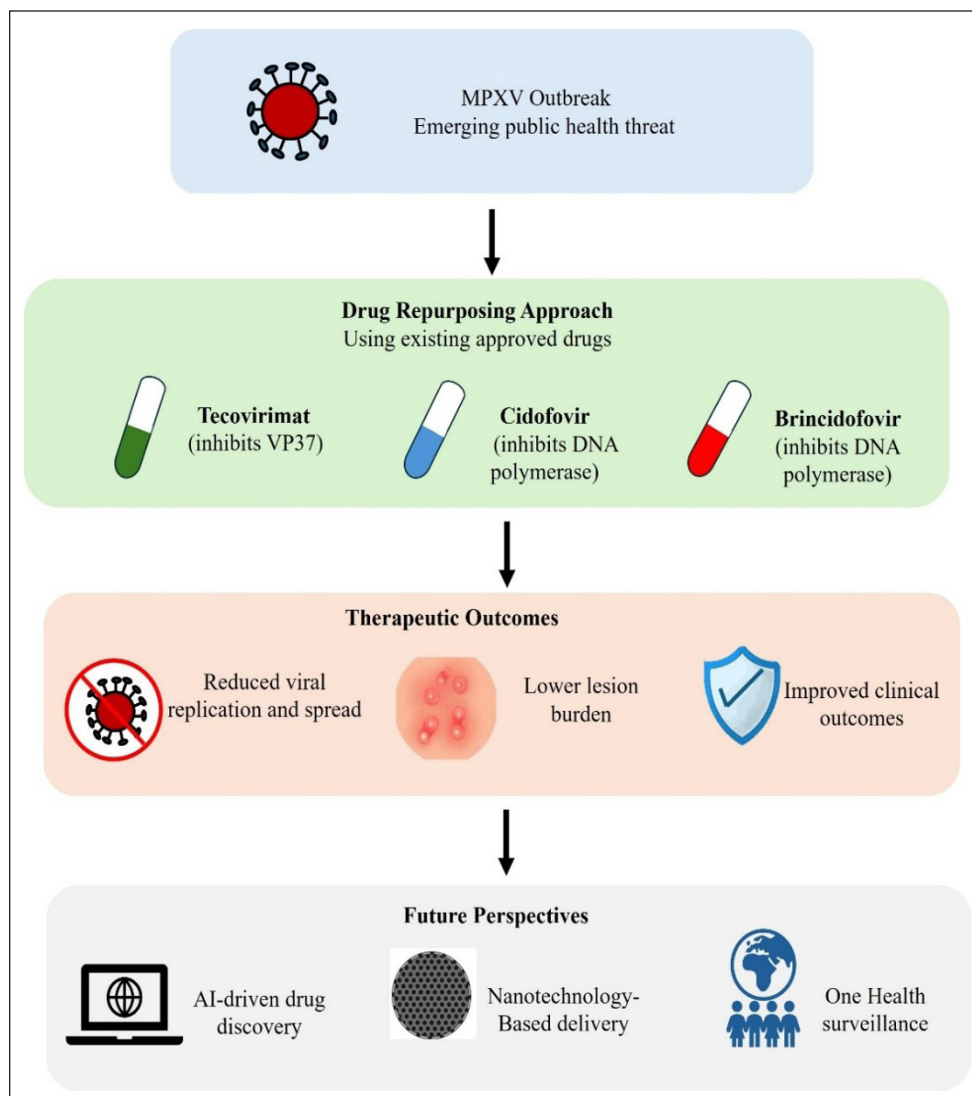


Figure 1. Antiviral repurposing strategy against monkeypox virus.

2. REVIEW METHODOLOGY

This narrative review conducted a thorough evaluation of the existing evidence regarding tecovirimat as a paradigm for the repurposing of antiviral medications in mpox and other orthopoxvirus diseases. The literature was searched on PubMed, Scopus, Web of Science, and Google Scholar from January 2003 to August 2026 using keywords including mpox, monkeypox, tecovirimat, ST-246, drug repurposing, orthopoxvirus, VP37, F13L, clinical trial, PALM007, STOMP, antiviral resistance, genomic surveillance, artificial intelligence, and One Health, using “AND” and “OR” Boolean operators to maximize search efficacy. The search included the most recent randomized clinical trials, recent regulatory reviews, and up-to-date epidemiology and genomic-surveillance news, including PALM007, STOMP, UNITY, PLATINUM-UK, the 2026 European Medicines Agency (EMA) re-assessment of tecovirimat, and WHO declarations of mpox PHEIC removal, ongoing international spread, and emergence of mpox recombinant mpXV.

A study was accepted for inclusion if it provided original data on safety or efficacy of tecovirimat or alternative treatments for mpox/orthopoxvirus infection, focusing on its mechanism of action, clinical efficacy, preclinical findings, tolerability, the virus’s capacity to develop drug resistance, evolutionary aspects, ongoing research on alternative therapies, clinical practice guidelines, and reports from significant organizations (e.g., WHO, CDC, and EMA). Original publications (e.g., articles), randomized controlled trials, observational studies, animal and *in vitro* research, as well as systematic reviews and guidelines were examined and cited, whereas abstracts from conference proceedings, non-English materials, and editorials or comments devoid of substantial data were eliminated, along with other reports that did not provide comprehensive evidence and research methodology.

3. MPOX: AN OVERVIEW

3.1. Epidemiology and Viral Evolution

Monkeypox virus is an enveloped double-stranded DNA virus belonging to the genus Orthopoxvirus within the family Poxviridae. Although originally identified in captive monkeys in 1958, ecological studies have subsequently the natural reservoir of MPXV remains unknown, although several small mammals, including squirrels and rodents, are considered potential animal hosts [17–20]. The decline in population immunity following cessation of routine smallpox vaccination has substantially increased global susceptibility to MPXV infection, contributing to the progressive rise in cases observed in endemic African regions and facilitating the unprecedented multi-country outbreak beginning in 2022 [21–23].

However, even though MPXV’s DNA genome typically limits its rate of mutations relative to most ribonucleic acid (RNA) viruses, genomic surveillance efforts recently indicated faster microevolutionary rates under sustained human-to-human transmission as a result of significant host APOBEC3-driven mutagenesis. Such evolutionary shifts carry clinical significance since continuing adaptation could potentially alter the virus’s transmission dynamics, host tropism, and sensitivity to antiviral drugs such as tecovirimat. Therefore, genome surveillance is an integral component of antiviral stewardship programs and outbreak management strategies. Another example of evolving genomic diversity within MPXV arose in 2026 when an inter-clade recombinant virus comprising parts of the genomes of clades Ib and IIb was identified. The WHO stated that, in early 2026, they detected closely related cases of recombinant infection in India and the UK. Whole-genome sequencing of those viruses showed sections that were mosaics of both ancestral clades, and the recombinant virus did not reliably produce positive results with the traditional clade-

differentiating polymerase chain reaction (PCR), highlighting the growing utility of whole-genome sequencing for MPXV evolution and surveillance [24].

3.2. Transmission and Pathogenesis

The 2022 multi-county outbreak represented a major epidemiological shift, with sustained community transmission occurring in non-endemic countries in the absence of direct zoonotic exposure. Several large observational cohorts consistently demonstrated that transmission occurred predominantly through close physical and sexual contact, particularly among men who have sex with men, while mucocutaneous, genital, and anorectal lesions emerged as characteristic clinical features of the outbreak [25–28]. Although mortality remained relatively low, hospitalization was frequently required because of severe pain, secondary bacterial infections, ocular involvement, or complications in immunocompromised individuals.

Once within a host cell through cell fusion or macropinocytosis, MPXV replicates all viral products within the cytoplasm using viral-encoded replication machinery, which differs from most other DNA viruses that rely on the host cell nucleus for viral replication [29]. Although complete replication occurs in the cytoplasm, MPXV remains susceptible to the host’s innate antiviral restriction factors, including members of the APOBEC3 family, which can access the viral DNA within the cytoplasm. Cytidine deaminations carried out by APOBEC3 enzymes can induce specific changes that are identified within the viral genome during continued human-to-human transmission [30,31]. Moreover, MPXV exhibits effective *in vivo* replication, and viral genes for immunomodulatory factors can effectively inhibit signaling and production of interferons, cytokines, and activation of complement, as well as reduce immune responses against both natural killer and T cells, thus allowing it to evade host immunity for sustained replication and dissemination [31,32] (Fig. 2).

3.3. Clinical Manifestations and Disease Burden

The incubation period of mpox generally ranges from 1 to 21 days, after which symptoms such as fever, headache, myalgia, lymphadenopathy, lethargy, and malaise may occur. Lymphadenopathy continues to be a prominent and characteristic sign of mpox in distinguishing it from smallpox. Skin lesions progress through macular, papular, vesicular, pustular, and crusted stages, which typically last 2–4 weeks [33].

Although most infections are self-limiting, severe disease may occur, particularly in young children, pregnant women, immunocompromised individuals, and people living with human immunodeficiency virus (HIV). Reported complications include secondary bacterial infections, respiratory involvement, acute sepsis, encephalitis, keratitis with vision impairment, myocarditis, and severe gastrointestinal manifestations [34]. Neurological complications, including encephalitis, together with severe systemic disease and prolonged recovery, have also been reported among hospitalized HIV-positive patients [35]. Despite relatively low mortality, the global mpox outbreak imposed a considerable healthcare burden owing to hospitalization, prolonged pain management, long-term isolation, psychosocial stigma, and increased utilization of healthcare resources [36]. Hospitalization rates for the 2022 outbreak varied depending on disease severity and the clinical setting, from 5% to 13% [26,35]. Persistent pain, fatigue, and the delayed healing of skin lesions described by some patients in both cohorts also emphasized the lasting clinical consequences of mpox beyond the acute infection [37,38].

Overall, this significant clinical burden underscores the development of rapidly deployable, virus-directed antiviral agents that will

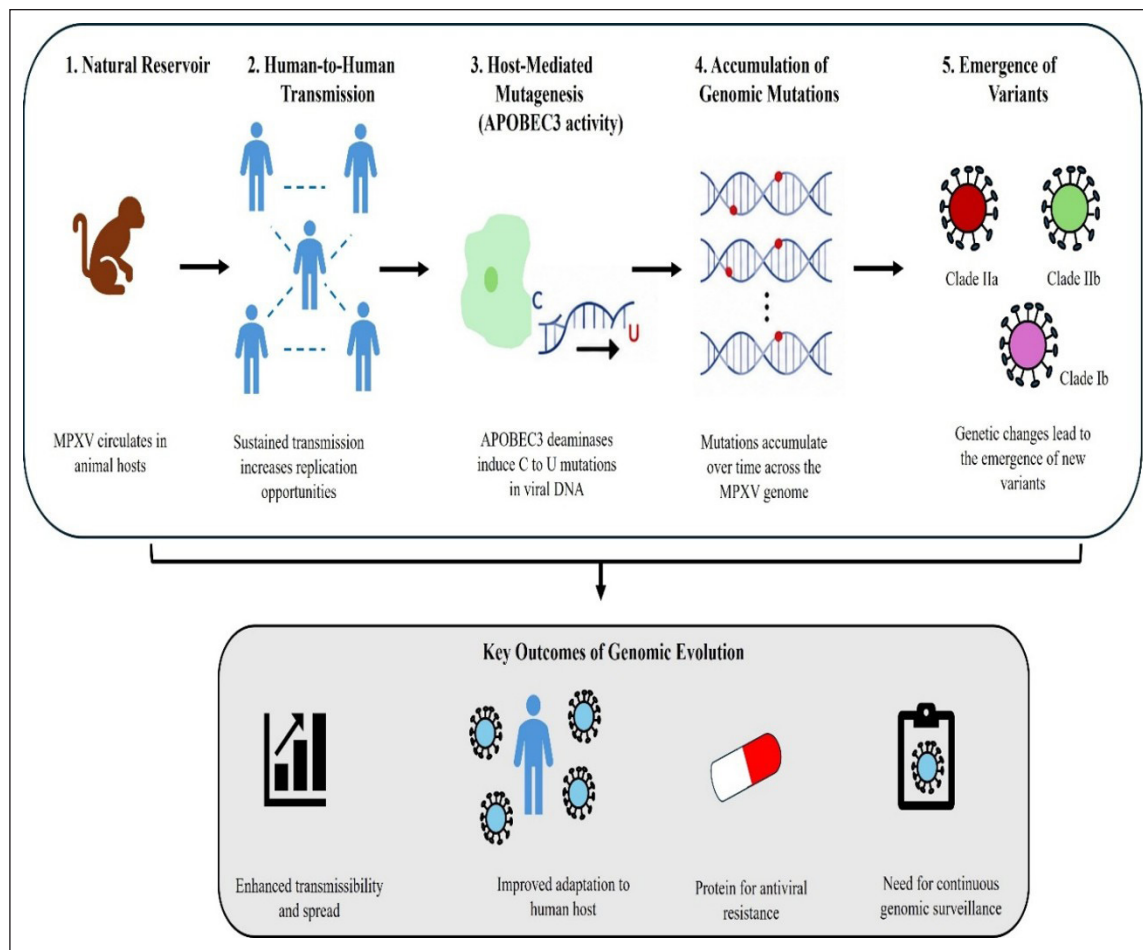


Figure 2. Genomic evolution of MPXV: (1) Possible animal host/reservoir; (2) human-to-human transmission; (3) host-mediated mutagenesis through APOBEC3 activity; (4) accumulation of genomic mutations; and (5) emergence of variants.

supplement supportive care, especially for patients likely to experience a severe or complicated illness. The significant burden of disease from mpox, even with low mortality, provided an opportunity to identify an unmet treatment need and underscored the importance of readily deployable antivirals, applicable to clinical practice, in the setting of outbreaks. Combined, these epidemiological, virologic, and clinical traits may account for the rapidity with which MPXV has become a major worldwide health problem and explain the critical requirement for quickly implementable antiviral approaches. While supportive treatment is standard practice, the lack of virus-directed medicines in the early weeks of the worldwide outbreak created demand for repurposed antiviral medications, with tecovirimat being among the most widely deployed due to its well-established safety profile, its mechanism acting only against orthopoxvirus, and its ease of implementation into clinical use during the recent mpox outbreaks (Table 1).

4. COMPARATIVE EVALUATION OF TECOVIRIMAT AND OTHER REPURPOSED ANTIVIRALS

There is currently no specific antiviral developed for the management of mpox, and treatment options have been based on supportive therapy in addition to existing approved antivirals intended for the treatment of smallpox and other orthopoxviruses [39,40]. International organizations such as the WHO, the CDC, and the EMA prepared urgent risk-based treatment guidelines for the 2022 outbreak, identifying high-risk

patients at greatest risk of severe mpox, such as immunocompromised persons, pregnant women, children, and patients with ocular or central nervous system disease [4,41]. According to Ogoina *et al.* [34], patients with complications such as bacterial skin infection, gastroenteritis, sepsis, bronchopneumonia, encephalitis, and/or keratitis may require extended hospitalization and/or interdisciplinary therapeutic strategies. The hospitalization data collected during the years of 2022 to 2024 reveal a hospitalization incidence of 8%–15% in this group, especially those with severely immunocompromised immune systems such as patients with advanced HIV [23,36]. Different repurposing therapeutic agents against moderate-to-severe mpox have been evaluated, such as tecovirimat, cidofovir, brincidofovir, vaccinia immune globulin intravenous (VIGIV), and various adjunctive treatments [42,43]. Cidofovir and brincidofovir, acting as viral DNA polymerase inhibitors, have demonstrated antiviral activity in preclinical studies; nevertheless, their therapeutic benefits for humans remain questionable, mostly limited by nephrotoxic and hepatotoxic implications [37,44]. The therapeutic and prospective uses of cidofovir are limited by its toxicity, primarily nephrotoxicity; yet, brincidofovir, an orally bioavailable derivative intended to reduce renal toxicity, has exhibited gastrointestinal and hepatic toxicities. It is essential to recognize and assess the toxicity of combinations, as the beneficial toxicity/efficacy ratios may be compromised by the emergence of adverse side effects, while the advantageous synergistic/additive mechanisms must be considered with regard to toxicity [44,45].

Table 1. Major clinical manifestations, complications, and disease burden of mpox relevant to antiviral treatment decisions.

Country/Region	Study/Period	Sample size	Key findings and significance	References
Global review	Historical–2021	Multiple outbreaks	The spread of mpox was correlated with a decline in smallpox immunity, which may cause global orthopoxvirus infections.	[22]
Nigeria	2017–2022	830 reported cases	This reappearance of mpox in 33 states throughout Nigeria has put Nigeria into a major epicenter and prime target as a global vehicle for the transmission of this virus.	[46]
United Kingdom	2018–2021	7 patients	Tecovirimat-treated patients demonstrated more rapid clinical recovery. The results show a preliminary indication of antiviral activity of the drug.	[37]
16 countries (United Kingdom, Spain, Portugal, Canada, United States, Netherlands, France, Germany, Belgium, Italy, Switzerland, Austria, Sweden, Australia, Israel, and Argentina)	2022	528 patients	About 95% of this infection was transmitted through sexual contact, and about 13% of the cases had to be hospitalized, as reflected in the epidemiological trends for the 2022 global multi-country outbreak.	[23]
Spain	2022	181 patients	Mostly genital and perianal lesions showed atypical clinical presentation compared with classic disseminated mpox disease.	[25]
United States	May–Aug 2022	549 patients	Tecovirimat was generally well tolerated, with mostly minor adverse effects, leading to its emergency clinical usage during the pandemic.	[47]
United Kingdom	2022	Hospitalized cases	Severe adverse effects, persistent disease, and hospitalization underscored the clinical burden and need for better therapeutic treatment options.	[38]
Global	2022–2023	Multi-country data	The rapid dissemination of mpox between countries prompted the WHO to declare it a Public Health Emergency of International Concern (PHEIC), a status that highlights the threat that MPXV constitutes to the health of people throughout the world, the UN agency stated.	[4]
Nigeria	2017–2022 cohort	Multicenter cases	Epidemiological data and the clinical spectrum and outcomes of disease in endemic areas have improved the characterization of severe mpox and its transmission patterns.	[34]
United States	2022–2023	Retrospective cohort	Epidemiological surveillance data with tecovirimat therapy provided essential real-world data about its safety and clinical outcomes.	[48]
Democratic Republic of Congo	2023–2024	18,922 suspected cases; 1,007 deaths	The substantial clade I epidemic that caused a high death toll triggered public and scientific concern regarding virulence, surveillance lacunae, and access to healthcare facilities in endemic settings.	[49]
United States	2023–2024	Drug-resistant cluster	The detection of tecovirimat resistance markers associated with the VP37/F13 protein demonstrates the need for continued exploration for advances in antiviral resistance in mpox.	[16]
DR Congo / Africa	2024–2025	Clade I/Ib outbreak data	The transmission and emergence of clade Ib MPXV demonstrate that the epidemiology of MPXV is changing, and it raises concerns that MPXV is being transmitted throughout the world.	[4,50]
Democratic Republic of Congo	PALM007 trial, 2025	Randomized controlled trial	Tecovirimat did not significantly reduce time to lesion resolution compared with placebo; no clinical efficacy of monotherapy was demonstrated in the studied population.	[51]
Africa	2025–2026	51,159 confirmed cases; 235 deaths	Recurrent transmissions in some African countries highlight the persisting global and regional spread of mpox despite control efforts.	[8]

In the field of passive immunotherapeutic strategy, VIGIV might benefit certain immunocompromised cases but is currently not supported by sufficient clinical evidence. More investigational strategies are being developed in order to enhance therapeutic effects and avoid the emergence of resistance to antivirals, which involve the development of monoclonal antibodies, interferon-based agents, host-directed antiviral agents, combination therapies, and so on [33,52].

To date, supportive therapy and drug repurposing for mpox remain the mainstay of treatment for patients with severe disease. Among these, tecovirimat has emerged as the most clinically advanced candidate

because of its orthopoxvirus-specific mechanism of action, favorable safety profile, and extensive preclinical efficacy. Nevertheless, inconsistent findings from recent randomized clinical trials, the emergence of VP37-associated resistance mutations, and the limited availability of high-quality clinical evidence indicate that important therapeutic challenges remain [13–16]. These strengths and limitations make tecovirimat an instructive case study for understanding both the opportunities and constraints of antiviral drug repurposing against emerging viral diseases. The repurposed anti-mpox drugs exhibit distinct mechanisms of action, supporting evidence, safety profiles, and clinical applicability. Limitations of other repurposed therapies,

Table 2. Clinical evidence and therapeutic strategies for mpox.

Therapeutic agent	Study design/Evidence base	Key findings	Clinical significance/limitations	References
Tecovirimat	Preclinical orthopoxvirus animal models	Potent antiviral activity and >90% survival in relevant animal models.	Supported FDA approval under the Animal Rule; preclinical efficacy did not translate into demonstrated benefit in subsequent human RCTs.	[14,53]
Tecovirimat	Expanded-access observational cohort ($n = 549$)	Generally well tolerated; adverse events reported in approximately 4% of patients.	Provides real-world safety data but cannot establish clinical efficacy because of the uncontrolled design.	[47]
Tecovirimat-PALM007	Randomized controlled trial; clade I mpox	No significant reduction in time to lesion resolution; favorable safety profile.	Did not demonstrate clinical efficacy of tecovirimat monotherapy in the population studied.	[51]
Tecovirimat-STOMP	Randomized controlled trial; clade II mpox	No evidence of shortened clinical resolution, reduced pain, or increased viral clearance.	Concordant with PALM007; no demonstrated clinical benefit of monotherapy in the population studied.	[45]
Cidofovir	Preclinical and limited clinical evidence	Inhibits viral DNA polymerase and has broad anti-orthopoxvirus activity.	Clinical use is limited, particularly by nephrotoxicity and requirement for IV administration.	[41,42]
Brincidofovir	Preclinical and limited clinical evidence	Lipid-conjugated cidofovir derivative with reduced renal toxicity; hepatic adverse effects reported clinically.	Human efficacy for mpox remains unestablished; gastrointestinal/hepatic toxicity requires consideration.	[37,44]
Tecovirimat+brincidofovir	Preclinical combination studies	Complementary mechanisms targeting viral egress and DNA replication; synergistic activity reported in cell culture and animal models.	Promising resistance-resilient strategy, but efficacy and safety in human mpox remain to be established.	[44,54]

including cidofovir, brincidofovir, and VIGIV, include toxicity, limited data on efficacy, or a primarily adjunctive role (Table 2). From the above comparison, it can be understood that rational combination therapy, early stratification, monitoring for resistance, and monitored trials are required.

5. TECOVRIMAT: THE PARADIGM OF ANTIVIRAL REPURPOSING

Tecovirimat serves as a paradigm for the repurposing of antiviral agents in the context of mpox and illustrates how the investment in biodefense over many years may lead to swift clinical application in the setting of a global public health crisis. The rapid clinical implementation of tecovirimat led to significant understanding of the advantages and limitations associated with the use of pathogen-selective antivirals for emerging infectious diseases (EIDs). Below, we address the underlying biologic rationale for tecovirimat, its process of translational development, and the evolving evidence base guiding its clinical use today.

5.1. Rationale for Tecovirimat Repurposing

Tecovirimat (ST-246 / TPOXX) was originally developed for the US biodefense program and is part of the efforts to strengthen preparedness efforts against smallpox outbreaks and bioterrorism. In 2018, tecovirimat was the first antiviral approved by the US Food and Drug Administration (FDA) for the treatment of smallpox under the “Animal Rule” pathway, which required approval based on efficacy studies in animal models, as human smallpox studies were not possible for ethical reasons [14]. The rationale for repurposing tecovirimat to treat mpox lies in the similarity between the various orthopox viruses, including variola virus and MPXV (both genotypically and structurally). Tecovirimat inhibits the VP37 envelope protein, which is highly conserved across the orthopoxviruses (encoded by the F13L gene). VP37 is required for producing and releasing the wrapped virions necessary for infection transmission between cells and spread

throughout the body, and thus blocking this function reduces the number of free-ranging virions being formed to limit spread within and between hosts [12,53] (Fig. 3).

5.2. From Biodefense Preparedness to Emergency Clinical Deployment

Tecovirimat exemplifies how prior biodefense funding can facilitate the rapid deployment of an antiviral in response to a developing infectious disease outbreak. Although numerous prospective therapeutic candidates for a disease typically arise only upon the identification of a pathogen, necessitating complete de novo discovery and development during a public health emergency such as the 2022 global mpox outbreak, tecovirimat had previously completed comprehensive preclinical development, human safety assessments, manufacturing advancements, and regulatory evaluations for smallpox, thus facilitating its prompt clinical application during the 2022 mpox outbreak.

Preclinical studies carried out for tecovirimat against orthopoxviruses demonstrated high effectiveness in animal models, especially enhanced survival following a lethal orthopox virus challenge [53]. Early administration in an experimental challenge setting showed decreases in lesion load, viremia, and lethality [14,53]. Taken together, these findings provided a strong preclinical rationale for its development and subsequent clinical deployment. Nonetheless, this translational preparedness must be differentiated from proven therapeutic effectiveness against human mpox. Subsequent clinical investigations demonstrate that rapid emergency intervention based on molecular rationale, animal effectiveness, and confirmed safety does not necessarily ensure clinical advantages in naturally occurring human infections. Tecovirimat must be considered as a paradigm of rapid translational repurposing accompanied by evidence-based re-evaluation, rather than as an unambiguous therapeutic breakthrough.

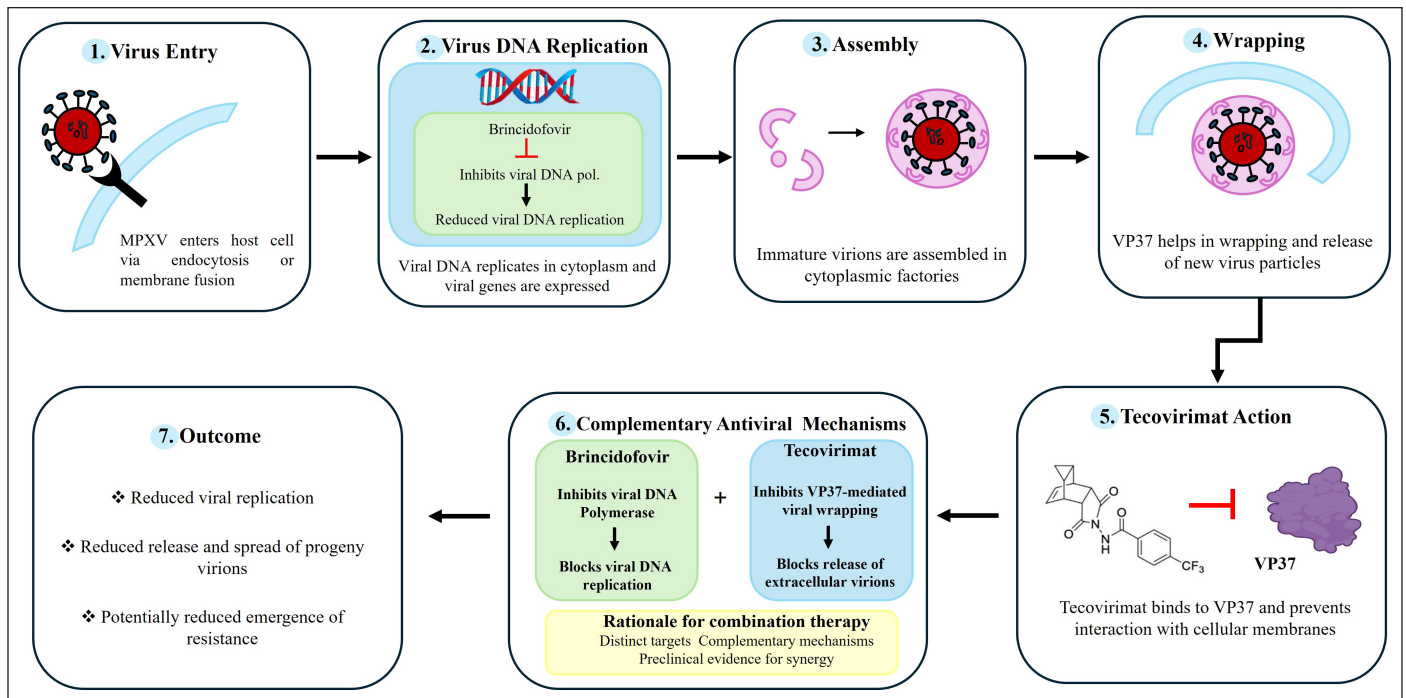


Figure 3. Mechanisms of action of tecovirimat and brincidofovir and rationale for combination therapy against MPXV: (1) virus entry; (2) viral DNA replication; (3) virion assembly; (4) virion wrapping; (5) tecovirimat action; (6) complementary antiviral mechanisms; and (7) therapeutic outcomes.

5.3. Clinical Translation: Promise Versus Reality

The apparent clinical potential illustrated by observational data was later challenged by randomized controlled studies. PALM007, carried out on individuals with clade I MPXV infection in the Democratic Republic of the Congo, failed to exhibit a substantial reduction in the duration until lesion resolution when tecovirimat was compared to placebo [51]. In the same manner, STOMP, which assessed mainly immunocompetent individuals with clade II mpox, revealed no significant increase in clinical resolution, lesion rehabilitation, pain outcomes, or clearance of the virus [45]. Furthermore, STOMP was unable to demonstrate efficacy in severely immunocompromised groups; thus, the prospective advantages for severely immunocompromised or other high-risk individuals remain unverified rather than proven.

The basis of evidence eventually grew beyond PALM007 and STOMP. The UNITY randomized trial included 480 subjects and likewise showed that tecovirimat failed to improve lesion healing or other clinical results [55]. PLATINUM-UK conducted an extra placebo-controlled assessment that yielded a similar overall effect trend [56]. In 2026, the EMA combined data from PALM007, STOMP, UNITY, and PLATINUM-UK, concluding that tecovirimat failed to attain the primary effectiveness endpoint regarding the duration to clinical efficacy of mpox lesions across all four trials conducted. Other findings, such as alleviation of pain and viral eradication, similarly showed no distinction compared to placebo. On 26 March 2026, the EMA's Committee for Medicinal Products for Human Use proposed the removal of mpox from the approved criteria for Tecovirimat SIGA, which was subsequently accepted by the European Commission on 29 May 2026. These results collectively affect the understanding of tecovirimat as a model for antiviral repurposing. Its significance is not rooted in proven clinical effectiveness against mpox, but in showing how a biologically convincing and promptly implementable

countermeasure can evolve from robust preclinical data and emergency application to thorough randomized assessment and regulatory re-evaluation. This approach demonstrates the merits and drawbacks of repurposing pharmaceuticals during epidemics of new infectious diseases.

The discrepancy between favorable observational studies and the lack of proven effectiveness in randomized clinical trials underscores the significance of evidence hierarchy in assessing antiviral treatments amid infectious disease epidemics. Preliminary experimental studies had significant challenges, such as limited sample numbers, lack of randomized controls, variations in initial disease severity, timing of therapy, and the likelihood of selection bias. Conversely, randomized studies yield more substantial evidence for evaluating therapy effectiveness. The consistent outcomes obtained in the PALM007, STOMP, UNITY, and PLATINUM-UK clinical trials indicate that the potential demonstrated in preclinical and observational studies failed to be translated into a significant therapeutic impact of monotherapy in the populations examined by the trials. The therapeutic efficacy of tecovirimat in underrepresented populations in these studies, especially among those with severe immunosuppression or critical illness, remains an unanswered research inquiry and cannot presently be regarded as a verified advantage [15].

6. GENOMIC EVOLUTION, RESISTANCE, AND ANTIVIRAL STEWARDSHIP

While the genome of monkeypox virus, which is a double-stranded DNA virus, is relatively stable compared to RNA viruses, it has a notable capability to evolve due to adaptation to persistent human-to-human transmission. Recent outbreaks in 2022–2025 in various countries have suggested faster evolution of the virus, with greater concern with regard to elevated levels of transmissibility, adaptation to new hosts, as well as antiviral resistance [20,57]. Sequencing of

genomes of present-day MPXV variants indicates that the viruses developed mutations associated with APOBEC3 deaminase enzyme activity, which demonstrated that the host defense system would have, in fact, been responsible for viral diversity following prolonged transmission [30]. APOBEC3-mediated mutation events were critical for the generation of novel variants in clade IIb and even clade Ib MPXVs [20,30,58].

The occurrence of an inter-clade Ib/IIb recombinant MPXV in 2026 clearly highlights the virus's capacity to produce genomic diversity during ongoing worldwide transmission. Due to the inconsistency of first clade-specific PCR analysis in identifying the recombinant strain, the WHO underscored the importance of whole-genome sequencing for accurate identification and characterization. Despite the absence of data indicating modified tecovirimat susceptibility in this particular recombinant lineage, its appearance underscores the necessity of combining genomic surveillance with antiviral-resistance assessment instead of presuming the genomic stability of clinically significant viral targets [24].

The ongoing evolution of MPXV has significant effects for antiviral repurposing methodologies, especially for tecovirimat, the main repurposed antiviral drug against orthopoxvirus infections. Tecovirimat targets a VP37 protein involved in virus production and virus propagation, and hence, it was previously believed that the establishment of resistance would be relatively limited. Nevertheless, mutations conferring resistance linked to VP37/F13L have been identified through genomic analysis, especially in immunocompromised patients undergoing extended tecovirimat therapy [15,16,59]. The fitness consequences associated with particular VP37/F13L resistance mutations are not fully understood and are likely to vary with mutation. Experimental data indicate certain resistance-related mutations might inhibit viral survival or replication without pharmacological pressure, whereas other resistant strains continue to replicate effectively. Consequently, long-term persistence and transmissibility of tecovirimat-resistant MPXV will rely on both the degree of resistance imparted by specific mutations and the associated fitness costs.

These findings contradict the hypothesis that blocking a highly conserved viral target would broadly prevent resistance; on the contrary, they showed that continuous treatment with an antiviral agent, even in an immunocompromised individual experiencing continuous virus replication, exerts selective pressure to promote selection of resistant viral variants. Therefore, antiviral repurposing efforts need to be supplemented with systematic genomic and resistance surveillance when used in the clinic. The emergence of antiviral resistance represents a critical limitation of monotherapy-based antiviral repurposing strategies. For example, in highly immunocompromised individuals, the ongoing replication of the virus will provide an optimal environment for both the accumulation of mutations and the selection of resistant strains. Additionally, the ever-increasing spread of MPXV globally will provide opportunities for adaptive evolution, inter-host transmission of the virus, and create reservoirs of resistant viral strains. Overall, these results underscore the significance of antiviral stewardship: tecovirimat should be strategically prescribed to appropriate patients. Just as with antibiotic stewardship, antiviral stewardship seeks to maximize clinical benefits while mitigating risks of unnecessary exposure, slowing the development of resistance, and retaining the value of an agent for use in future outbreaks. This approach should include genome surveillance, resistance monitoring, selection of the appropriate patients and, if required, combination therapy for the highest risk individuals.

In summary, these results indicate that antiviral resistance is a critical consideration in future antiviral drug repurposing decisions, as viral

resistance extends beyond a solely virological challenge. Long-term clinical utility of tecovirimat will therefore rely on integrating genomics and resistance surveillance with robust clinical evidence, antiviral stewardship, and judicious combinatorial therapies to ensure efficacy of tecovirimat against orthopox viruses in the long term.

7. FUTURE DIRECTIONS: BEYOND TECOVRIMAT

Given the clinical and resistance challenges involving tecovirimat monotherapy, forthcoming antiviral efforts aimed at mpox and other orthopoxviruses need to prioritize enhanced efficacy and resistance-resilient treatment methods. Four randomized trials with placebo controls—PALM007, STOMP, UNITY, and PLATINUM-UK—have contributed to the clinical assessment of tecovirimat monotherapy, and their combined inability to show significant efficacy in the examined conditions has shifted therapeutic research toward alternative therapies, rational combinations of drugs, and more well-defined high-risk groups [51,53,55,56]. Evidence about alternative and combination therapy approaches is predominantly confined to animal models and observational cohorts, clinically relevant information, and retrospective analysis [38,47]. Future directions of antiviral research should not just focus on the direct targeting of the virus but should be one-step ahead with the concept of integrative approaches of artificial intelligence (AI)-enabled drug discovery and repurposing, drug delivery using nanomaterial technology, host-targeted therapies, combinatorial therapeutic intervention, and personalized intervention with integrated approaches with a global surveillance program (Fig. 4) [60]. Advanced computational techniques, such as AI/machine learning, molecular docking, and omics integration, are expediting antiviral drug discovery by allowing high-throughput virtual screening, lead candidate identification, identification of drug targets (such as those interacting with the viral DNA polymerase, VP37, thymidine kinase, or viral protease), protein–ligand interaction prediction, and drug repositioning for existing drugs [61,62].

The DeepRepurpose framework has been used for MPXV through transfer learning and a combination of approaches such as convolutional neural networks, graph attention networks, XGBoost, and support vector machines, to forecast compound–viral protein interactions and rank drugs suitable for repurposing. This AI-driven methodology pinpointed possible MPXV-targeting agents, such as elvitegravir, which were later assessed using molecular docking and molecular dynamics techniques [60].

Nanotechnology drug delivery approaches (lipids, polymers, dendrimers, and nanoemulsions) used for antivirals might potentially increase cellular uptake, site-specific delivery, controlled drug release and tissue distribution, and lower cumulative antiviral exposure. When employed together, antiviral medicines that address complementary viral pathways may enhance efficacy of therapies and reduce the emergence of resistance [63]. The implementation of precision medicine principles, involving integrated genomic, immune profile, pharmacogenomics, and real-world clinical data analysis, should lead to a tailored therapeutic response depending on virus type, strain and resistance status, severity of disease, and host immunity [64,65].

Future preparedness and response for mpox and future orthopoxvirus epidemics necessitate simultaneous development of new antiviral drugs and integrated surveillance across human, animal, and environmental domains (One Health approach) [4,66]. The synergistic integration of genomic epidemiology, wildlife and

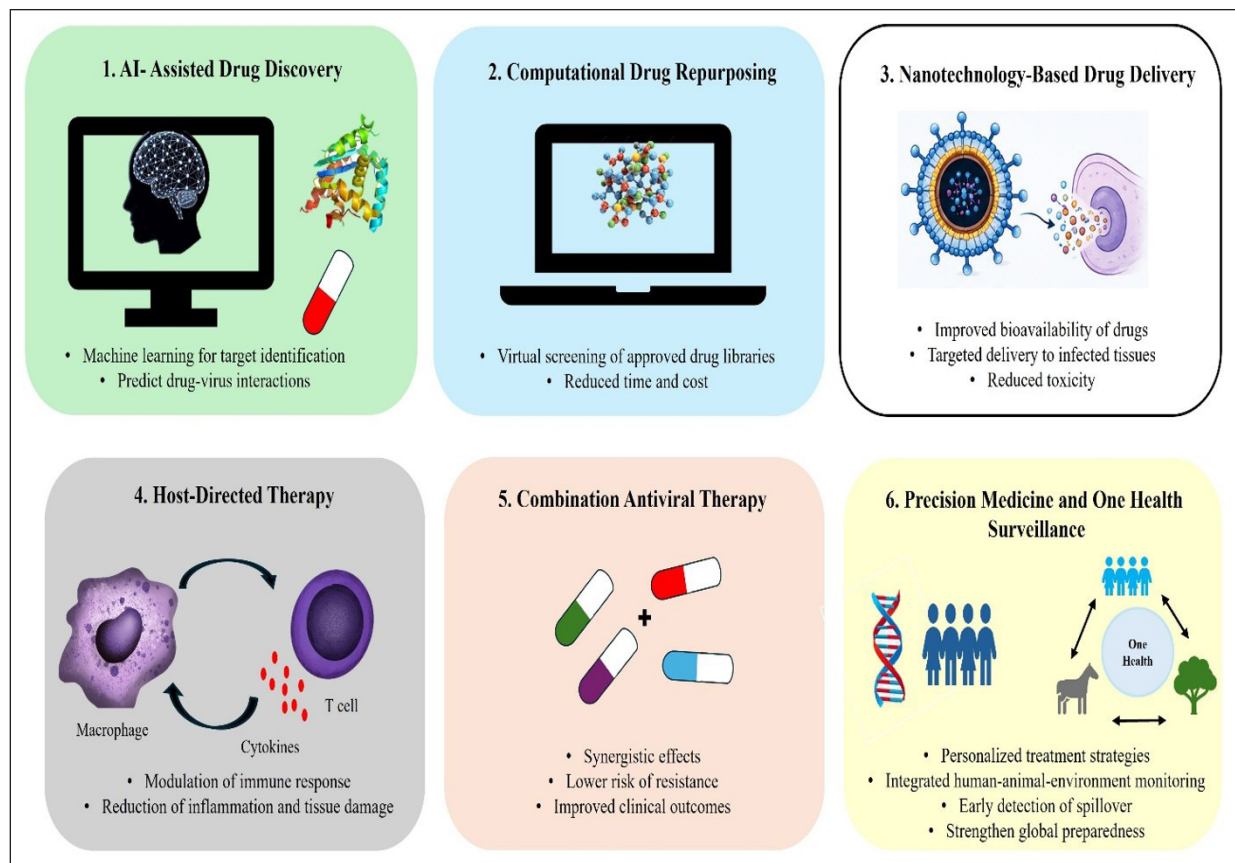


Figure 4. Emerging and future strategies for MPXV therapeutics. (1) AI-assisted drug discovery; (2) computational drug repurposing; (3) nanotechnology-based drug delivery; (4) host-directed therapy; (5) combination antiviral therapy; and (6) precision medicine and One Health surveillance.

environmental monitoring, and accelerated epidemic response might contribute to prompt identification of novel emergent viral variations and appropriate treatments for mpox. Future adaptive clinical trials may integrate prospective viral genome sequencing and resistance surveillance to detect emergent resistance mutations. Pre-established adaptive criteria may facilitate modifications to treatment regimens, encompassing the assessment of combination therapies upon the identification of virological failure or the emergence of resistance. Stratification based on host immunological status, disease severity, virus lineage, and initial resistance profile may facilitate a more insightful evaluation of therapy responses. Future mpox trials must specifically focus on populations that have been inadequately represented in earlier randomized studies, such as participants with significant immunosuppression, chronically disseminated disease, or additional predictors of severe complications, while refraining from drawing conclusions about efficacy based solely on data collected through observation [15,55]. In summary, the combination of AI, precision medicine, nanotechnology, adaptive clinical trial design, and One Health surveillance offers a translational road to antiviral drugs and robust countermeasures against current and potential orthopoxvirus threats.

8. CONCLUSION

The experience with mpox highlights the requirement for therapeutic approaches that can be rapidly implemented during outbreaks of emerging infectious diseases. Tecovirimat is an example of an interesting case of antiviral repurposing, although this has proven

to be less critical than originally anticipated. The evolution of this drug demonstrates the significant importance of biodefense readiness: a compound with a specific viral target, substantial preclinical effectiveness, established production capacity, and a positive safety record could be rapidly used during the occurrence of a worldwide mpox outbreak.

Concurrently, the following clinical trial results highlight the limitations of depending on biological plausibility, animal effectiveness, and uncontrolled observational data in order to determine therapeutic efficacy in human infections. Tecovirimat provided no benefit in lesion resolution and related clinical and viral endpoints in the PALM007, STOMP, UNITY, and PLATINUM-UK trials, prompting the EMA in 2026 to withdraw mpox from its approved indications. Its effectiveness in patients with severe immunocompromise and other specific high-risk groups is still uncertain rather than confirmed.

Tecovirimat must be viewed not as an unambiguous success of antiviral repurposing, but rather as a model of rapid emergency implementation succeeded by thorough clinical and regulatory evaluation. The path ahead underscores the necessity for future repurposing initiatives to combine mechanistic and preclinical data with sufficiently robust randomized trials, genomic and resistance monitoring, suitable patient stratification, and versatile study designs. The emergence of further MPXV lineages and inter-clade recombinant viruses underscores the need to have drug discovery supported by concurrent genome monitoring. Together, this provides a more equitable framework and adaptable strategy for antiviral response to novel emerging and re-emerging viral threats.

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10. AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

11. CONFLICT OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

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13. ETHICS APPROVAL

This study does not involve experiments on animals or human subjects.

14. DATA AVAILABILITY

All the data is available with the authors and shall be provided upon request.

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16. DECLARATION OF GENERATIVE AI USE

During manuscript preparation, the author used ChatGPT (OpenAI, San Francisco, CA, USA; <https://chatgpt.com/>) solely for language refinement and to improve the clarity and readability of the text. The tool was not used to generate scientific content, data, analyses, interpretations, references, or conclusions. All AI-assisted text was critically reviewed, edited, and verified by the author, who takes full responsibility for the accuracy, integrity, and final content of the manuscript.

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