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Drug Repurposing for Monkeypox: An Alternative Strategy for Emergency Response

Luthfi Harbulcholizi[1], Jekmal Malau[1,2]*, Ihsan Alfiandri[1], Iqbal Zulkifli[1] and Ratika Rahmasari[3]

[1]Department of Pharmacy, Faculty of Health Sciences, Universitas Singaperbangsa Karawang, Karawang, Indonesia
[2]Biology Laboratory, UPA Laboratorium Terpadu, Universitas Singaperbangsa Karawang, Karawang, Indonesia
[3]Microbiology and Biotechnology Laboratory, Faculty of Pharmacy, Universitas Indonesia, Depok, Indonesia

*Corresponding author: jekmal.malau@fikes.unsika.ac.id

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Abstract
The global monkeypox (MPOX) outbreak, which has resulted in more than 100,000 confirmed cases across over 120 countries, underscores the urgent need for effective therapeutic strategies. MPOX, caused by a virus belonging to the Orthopoxvirus genus, poses significant clinical and public health challenges, particularly in regions with limited healthcare capacity. Although the World Health Organization declared MPOX a Public Health Emergency of International Concern in 2022, no specific antiviral treatment has yet been formally approved. While vaccination remains essential for long-term prevention, its impact is constrained by limited availability and unequal global distribution. Consequently, drug repurposing has emerged as a practical, rapid, and cost-efficient strategy to address immediate therapeutic demands during active outbreaks. This narrative review evaluates key repurposed antiviral agents including tecovirimat, brincidofovir, and cidofovir were originally developed for other Orthopoxvirus infections. A structured literature search using PubMed, ScienceDirect, and Google Scholar (2014–2024) identified studies providing clinically relevant evidence regarding their therapeutic roles in MPOX. Tecovirimat demonstrated consistent potential to improve viral clearance, shorten symptom duration, and reduce severe manifestations. Brincidofovir exhibited a more favorable safety profile, albeit with limited clinical data, whereas cidofovir showed antiviral activity but remains restricted by its nephrotoxicity. Collectively, current evidence suggests that drug repurposing offers a timely and resource-efficient option for managing MPOX and mitigating disease burden while vaccine accessibility continues to vary globally. When integrated with targeted public health interventions, repurposed drugs may serve as a crucial interim strategy to reduce transmission and enhance outbreak response capacity.

Keywords: Antiviral agents; Brincidofovir; Cidofovir; Drug repurposing; Monkeypox; Tecovirimat

1. INTRODUCTION

Viral illness has come to be viewed as a serious global public health issue. For instance, in the past two decades, the world has experienced a number of new viral outbreaks that

represent a significant danger to millions. The global spread of monkeypox (MPOX), with over 100,000 cases in more than 120 countries as of July 2024, has been a significant cause of concern (WHO 2024). First described in a laboratory setting in 1958, the virus caused illness in monkeys. The first identified human case occurred in the Democratic Republic of the Congo in 1970 (Marisah et al 2022). The disease is contracted by direct contact with infected humans or animals and contact with body fluids, breath, or contaminated materials (Amer et al 2023; Saied et al 2023; Zinnah et al 2024). The virus has the potential to spread from person to person especially in close physical contact (Duarte et al 2024). Although the disease MPOX is less contagious than other diseases such as SARS-CoV-2, its spread is especially concerning in less informed MPOX disease areas (Ullah et al 2023).

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The greatest challenge in controlling the disease MPOX is the limited access to vaccines in the non-endemic regions (Malik et al., 2023). This is where drug repurposing comes to the forefront to revolutionizing this field. This aims to utilize antiviral drugs such as tecovirimat, Brin cidofovir and cidofovir, which, although designed to combat other viral infections, are known to target orthopox viruses (Rizk et al., 2022). Drug repurposing cuts down the time line in the drug discovery process as the candidate drugs have already gone through safety and pharmacokinetics assessment and screening.

2. MATERIAL AND METHODS

For this review article, a narrative review methodology for synthesizing information from various scholarly works focusing on monkeypox (MPOX) was implemented. Evidence was gathered from reputable MPOX-focused scholarly works databases such as Google Scholar, PubMed, and ScienceDirect. Thereafter, more recent publications focusing on advancing research on MPOX were used. The selected publications were of more specialized scope and thus were those that centered on drug repurposing strategies related to MPOX.

The literature search was conducted in English using five main keywords, namely “monkeypox treatment,” “drug repurposing for monkeypox,” “antivirals for orthopoxvirus,” “repurposed drugs for orthopoxvirus,” and “efficacy of antivirals against monkeypox.” The

initial searches yielded a total of 69,889 records (PubMed = 2,981; ScienceDirect = 4,626; Google Scholar = 62,282). Inclusion criteria included articles published in the last ten years (2014-2024), studies related to MPOX treatment and drug repurposing, and articles from reputable scientific journals, along with published clinical trial reports selected as primary references to ensure data credibility. The exclusion criteria comprised articles published prior to 2014, studies that did not address MPOX treatment, case reports lacking sufficient clinical data, and articles unavailable in full text. Following the removal of duplicates and non-relevant studies, approximately 30 articles were assessed in full, and ultimately, eight articles met the inclusion criteria and were incorporated into this review.

3. RESULTS AND DISCUSSION

3.1. MPOX: from its origin into virology and pathogenesis

The most recent indicators across various epidemiological datasets locate the initial outbreak of monkeypox (MPOX) in Central and West Africa, where the virus resides in animal hosts, especially rodents and non-human primates (Ekpunobi et al., 2023). The initial MPOX cases in humans were reported in 1970 and these cases were largely in the hinterlands of the country where humans get in contact with the virus and infected hosts in activities like hunting, handling, and bushmeat consumption (Musuka et al., 2024). The virus MPOX has in recent years spread from its centers of endemicity and this has created and escalated global curiosity and concern in its potential further spread in non-endemic regions of the world outside Africa (Gao et al. 2023; Awoyomi et al. 2023). The mode of MPOX transmission and the most common symptoms are presented in Figure 1.

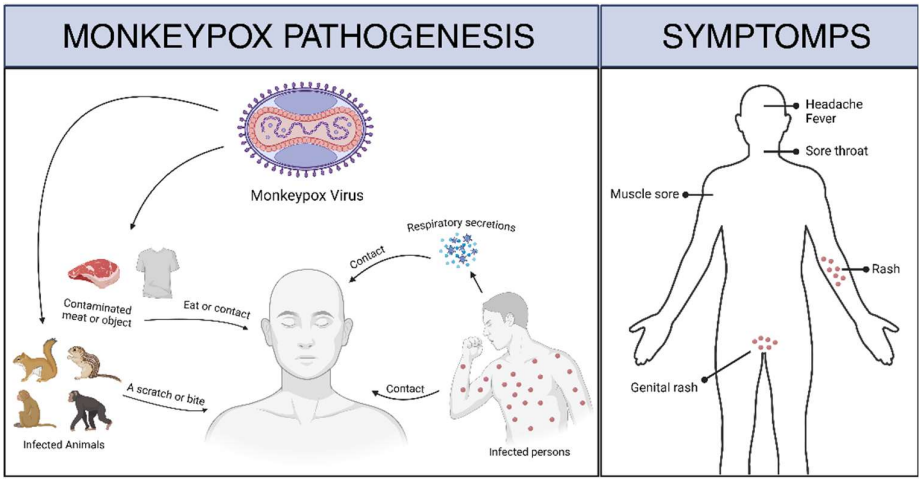

Figure 1. Monkeypox Pathogenesis and Symptomps (created with Biorender.com).

MPOX belongs to the genus Orthopoxvirus, a group of viruses that includes variola virus (which causes smallpox), cowpox, and vaccinia virus (Bhardwaj et al., 2024). Although monkeypox is generally less virulent than smallpox, it can still lead to considerable morbidity and mortality, particularly in regions with limited access to adequate healthcare services

(Reynolds et al., 2017; Petersen et al., 2019). Direct contact with body fluids, infected animals or humans' skin lesions, respiratory secretions, contaminated clothing and bedding (fomites) account for human MPOX transmission most (Amer et al. 2023; Saied et al. 2023; Zinnah et al. 2024). In contrast to common cold or flu viruses, MPOX typically needs rather prolonged and intimate contact to be transmitted (Kang & Ahmad, 2023).

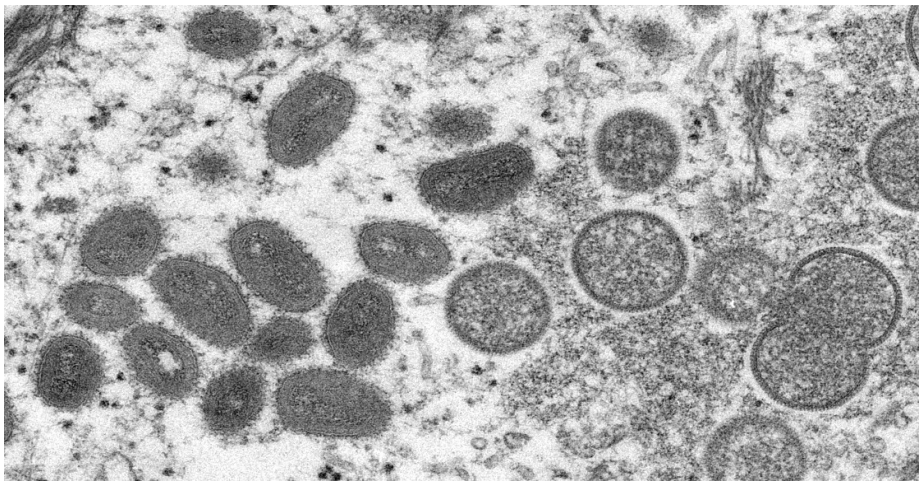

Figure 2. Electron micrograph of monkeypox virus particles. Image provided by the Centers for Disease Control and Prevention (CDC), Public Health Image Library, ID#22664.

The structure of MPOX is similar to that of other members of the Orthopoxvirus genus. MPOX is a double-stranded DNA virus with a large and complex genome covered by a virus envelope, comprising around 200,000 base pairs (Schuele et al., 2024) and this large genome encodes a number of proteina virus immune hosts and replicates efficiently (Hernaez & Alcami, 2024). The virion 200–300 nanometers in diameter, and is larger than the more common Rna viruses like the SARS-Cov 2 (Kavey & Kavey, 2024). The structural features of the virus, which are 'brick like' in nature and are also seen through an electron microscope (Figure 2) and the dens in their surfaces are proteins that act like receptors for binding entry (Zinnah et al., 2024).

In order for the Mpox virus to infect a host, the surface glycoproteins of the viron attach to the the cells of the host, allowing the virus to enter the cells of the host. While specific receptors of the mpox virus have still yet to be identified, the associated proteins of the envelopes, i.e. membrane proteins A35R, I5L, E8L, and A43R, which are hypothesized to help the virus enter cells by membrane fusion, have been identified to be possible targets for the development of drugs aimed at mpox (Lu et al., 2023; He et al., 2023; M. Li et al., 2023; Shchelkunov et al., 2022). Afterwards, the virus will be quarantined in the host cells and then the virus will replicate and create new virons by commandeering the cellular functions of the host and using them to create products that are new virons (Yu et al., 2023; Zinnah et al., 2024). In order for MPOX to replicate and disseminate through the body of the host, MPOX must initially suppress the immune system of the host. MPOX does this by using a variety of the immune system evasion techniques which allows the MPOX to replicate much more

effectively.T Cells are an important part of the adaptive immune system, but the virus can disable their functionality, which weakens the body's defense against an infection (Fang et al. 2021). Regarding the innate immune system, MPOX utilizes proteins that block caspase-1 which is vital to inflammatory responses, and is characteristically an inhibitor of viral replication (Parnian et al., 2024). Its viral envelope is also an additional layer of protection against neutralization from antibodies, avoiding the range of the complement system (Fang et al., 2024). MPOX viruses can result in an immune response that is characterized by fever, headache, muscle pain, and a unique rash. This rash goes through several stages: macules, papules, vesicles, and pustules (Shehryar et al., 2023; Estévez et al., 2023). The rash originally appears on the face before it spreads to the rest of the body, including the palms of the hands and the soles of the feet (Oiwoh et al., 2023).

Patients affected with MPOX show a broad spectrum of clinical manifestations where some forms may be self limiting and mild, and where other forms may have secondary complications, including but not limited to go bacteremia, sepsis, pneumonia, or even encephalitis (Ježek et al., 1987; Mitjà et al., 2023; Breman & Henderson, 2002).

3.2. Genome and mpox life cycle

Monkeypox virus (MPOX) is a double-stranded DNA virus with a genome size of approximately 197 kb, making it substantially larger than many other viral genomes (Monzón et al., 2024). It belongs to the genus Orthopoxvirus within the family Poxviridae and exhibits a high degree of genetic similarity to other Orthopoxviruses, including the variola virus, the causative agent of smallpox (Bhardwaj et al., 2024). However, MPOX tends to be less pathogenic than smallpox, although its genetic complexity allows it to evade the immune system and cause infections in humans and animals (Zinnah et al., 2024).

The MPOX genome is linear and contains many critical genes necessary for the functioning of the virus, including those responsible for replication, immune evasion, and spreading (Yu et al., 2023). Because of the significant genetic overlap with the smallpox virus, especially in the areas of the genome that code for the structural proteins and some of the significant proteins that drive the replication cycle, the smallpox vaccine, which is more than 2 decades old, has been proven to cross-protect against MPOX (E. Li et al., 2024). Owing to the great genetic homogeneity between smallpox and MPOX, the immune response elicited from the vaccine will be effective against smallpox, as well as MPOX (Bhardwaj et al., 2024).

MPOX binds to a certain type of receptor located in the cell`s outer membrane (Chakravarty et al., 2024). The virus enters the interior of the cell by membrane fusion or by endocytosis, depending on the type of host cell. After MPOX gets inside, it removes the membrane which encloses the virus and begins to deposit the viral double-stranded DNA into the host cell cytoplasm. It then begins to cyle (Chakravarty et al., 2024; Alakunle et al., 2024; Ezat et al., 2024). Uncharacteristically for DNA viruses, MPOX undergoes replication enzymatically only in the cytoplasm, and does not need to enter the host cell nucleus (Peng et al., 2023). This process is depicted on Figure 3, which shows the major steps in the life cycle

of MPOX, starting with the viron attached to the host cell and completed by the assembly of a new virion. MPOX is also unique in that it finishes DNA replication and transcription entirely in the cytoplasm, not relying on the nucleus of the host cell for any of the steps (Peng et al., 2023).

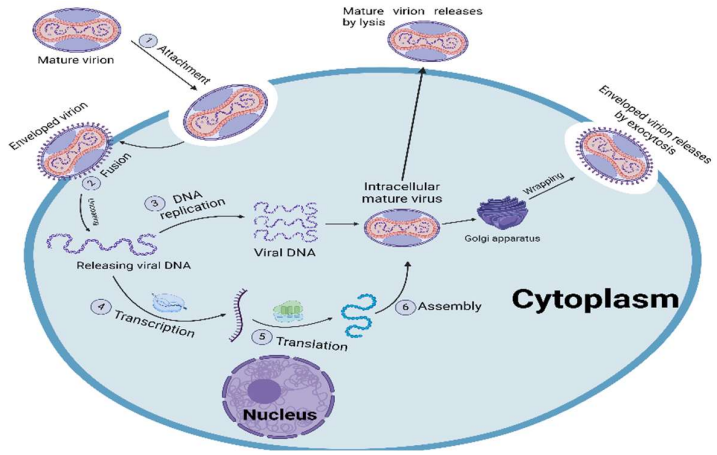

Figure 3. Monkeypox Life Cycle (Created with Biorender.com).

MPOX begins the infection process by binding to particular receptors on the host cell surfaces (Chakravarty et al., 2024). After this step, either membrane fusion or endocytosis occurs to allow the virus to gain entry, depending on host cell type. After the virus is internalized, it removes the protective layer surrounding it, and it begins to release the genetic material into the cell's cytoplasm for reproduction to begin (Y. Wang et al., 2023; Chakravarty et al., 2024; Alakunle et al., 2024; Ezat et al., 2024).

The initial stage of the MPOX replication cycle is the establishment of a 'viral factory' in the cytoplasm where the viral genome is replicated and transcribed (Karagoz et al., 2023). It is in this compartment that the viral particles are fully constructed and the viral DNA is inserted into the newly created capsids (Karagoz et al., 2023). Subsequently, the capsids obtain the envelopes that fully surround the virions from segments of the endoplasmic reticulum and Golgi membranes (Karagoz et al., 2023).

Upon completion of assembly processes, the newly formed virions utilize vesicular transport systems to migrate to the cell surface. The virions subsequently can excytose via exocytosis, or alternatively remain bound to the cell surface as cell-associated virions and facilitate the rapid infection of adjacent cells (Gu et al, 2024). The excytosis of the virions also enables the continued dissemination of the virus within the infected host and to new, uninfected hosts via direct contact body fluids, dermal lesions and/or contaminated fomites (Branda et al., 2024).

Currently, no specific antiviral treatment has been found for MPOX there is one for. However, smallpox vaccines be effective in preventing MPOX infection due to the genetic similarity between the two viruses (Zinnah et al., 2024). Understanding the replication cycle of MPOX, from virus entry into cells and genome replication to virus particle assembly, provides

important insights for finding potential therapeutic targets. Proteins involved in the process of virus entry, replication mechanism, and immune system evasion are being explored as intervention targets for antiviral development and drug reuse (Huang et al., 2022).

3.3. Drug repurposing for monkeypox

In the face of new virus threats, drug repurposing has become a crucial strategy for quickly overcoming health crises. Drug repurposing has become a popular strategy in recent years. When compared to traditional drug development strategies, it is more efficient, economical, and involves less risk (Agrawal, 2015). New drug development, particularly for antivirals, typically takes years—from initial discovery to clinical approval—and often requires substantial investments (Everts et al., 2017). However, speed is crucial in dealing with outbreaks such as MPOX, where rapid transmission and the potential for widespread infection require immediate action (Ghaseminia, 2023).

As stated by Parvathaneni et al. (2019), drug repurposing represents an unconventional therapeutic approach with significant potential. Existing drugs, which are in a developed stage, are repurposed for new indications. Existing drugs, for the most part, are safe, with a clearly established therapeutic range, which significantly reduces the time required for new drugs to enter the market (Sultana et al., 2020). Additionally, the development of new drugs requires a significant number of resources, and during events such as epidemics or other health-related crises, repurposing existing drugs is a rational approach to addressing the problem (Azvolinsky, 2017).

In the case of monkeypox, a viral zoonotic orthopox infection closely related to the smallpox virus, variola, drug repurposing becomes a viable therapeutic option. Several antiviral agents are being considered for the treatment of monkeypox that were initially designed and developed to treat other viral diseases (Rizk et al., 2022). Antivirals such as tecovirimat, cidofovir, and brincidofovir, which have shown some antiviral activity against orthopoxviruses in preliminary and earlier clinical trials, are among the most important (WHO, n.d.).

Monkeypox outbreaks in recent years have prompted various research efforts to find effective therapies for this infection. Clinical and pre-clinical studies on the treatment of monkeypox have been conducted in various countries using different antiviral agents. The findings from several key studies on the effectiveness and outcomes of repurposed drugs in various clinical contexts across multiple study sites provide an overview of recent advances in Monkeypox treatment (Table 1).

3.4. Tecovirimat

Tecovirimat is the most prominent antiviral drug in drug repurposing efforts for the treatment of monkeypox (MPOX). It was initially developed by SIGA Technologies for the treatment of smallpox and received FDA approval in 2018 (Russo et al., 2023). Tecovirimat acts through a targeted mechanism, binding to the p37 (VP37) protein—an essential component in the life cycle of orthopoxviruses, including the monkeypox virus (Hudu et al., 2023; Rabaan et al., 2023).

Table 1. Research on the use of drug repurposing in monkeypox.

Journal Title	Drugs Used	Study Location	Research Finding	As Reference
Human monkeypox outbreak: Epidemiological data and therapeutic potential of topical cidofovir in a prospective cohort study	Cidofovir (topical)	Madrid, Spain. n = 24 24 patients received symptomatic treatment, if needed and 12 of the patients were treated with topical cidofovir off label.	Topical cidofovir has been shown to accelerate the healing of skin lesions, with an average recovery time of 12 days compared to 18 days in untreated cases. By day 14, 90% of patients receiving treatment tested PCR-negative, compared to only 37.5% in the untreated group. No systemic adverse effects were reported; however, local reactions such as irritation were common, occurring in approximately 50% of cases, particularly in the anogenital region.	Sobral-Costas et al. (2023)
Early administration of tecovirimat shortens the time to mpox clearance in a model of human infection	Tecovirimat	France and Spain n = 54	Tecovirimat has been shown to accelerate MPOX viral clearance, reducing the time to virus elimination by approximately six days compared to no treatment. No indications of toxins or instability related to the use of tecovirimat were found remains under review. However, it should be noted that negative results may be more related to non-optimal timing of administration or improper dosage.	Nguyen et al. (2023)
The successful treatment of mpox with brincidofovir in renal transplant recipients - a report of 2 cases	Brincidofovir	Arab Saudi n = 2	Brincidofovir has shown effectiveness in treating MPOX in kidney transplant patients, with no major adverse effects observed during therapy. No severe side effects were reported, although one patient experienced mild transaminitis upon discharge, which may have been associated with brincidofovir use.	Alameer et al. (2024)

Table 1. Research on the use of drug repurposing in monkeypox (*Continued*).

Journal Title	Drugs Used	Study Location	Research Finding	As Reference
Tecovirimat for the treatment of severe Mpox in Germany	Tecovirimat	Germany n = 12 patient	Tecovirimat was effective in treating Monkeypox patients with severe symptoms, with all patients showing clinical improvement. No severe side effects; one patient experienced transient elevation in liver transaminase levels.	Hermanussen et al. (2023)
Efficacy and viral dynamics of tecovirimat in patients with MPOX: A multicenter open-label, double-arm trial in Japan	Tecovirimat	Japan n = 19	Tecovirimat was shown to shorten the duration of viral shedding, with 60% of patients testing PCR-negative by day 14. In contrast, patients with HIV experienced a longer period of viral persistence. No serious adverse effects were observed; however, a single case of transient liver enzyme elevation was reported, which was attributed to intense physical activity rather than the use of tecovirimat.	Akiyama et al. (2024)
Successful Outcome after Treatment with Cidofovir, Vaccinia, and Extended Course of Tecovirimat in a Newly-Diagnosed HIVPatient with Severe Mpox: A Case Report	Cidofovir, Tecovirimat, Vaccinia	Miami, AS n = 1 49-year-old man presented with 2 weeks of perianal lesions	The combination of cidofovir, tecovirimat and Vaccinia resulted in almost complete recovery in patients with severe cases of Monkeypox. Adverse effect ot reported, though concerns of tecovirimat resistance and Immune Reconstitution Inflammatory Syndrome (IRIS) risk were noted.	Martinez et al. (2023)
Treatment efficacy of cidofovir and brincidofovir against clade II Monkeypox virus isolates	Cidofovir, Brincidofovir	Canada n = not specified (animal study)	Cidofovir and brincidofovir are highly effective against Monkeypox clade II virus, significantly reducing viral replication in mouse studies. In animals, no significant adverse effects observed, though slight weight loss occurred in some groups.	Prévost et al. (2024)

Tecovirimat functions through the interaction of the VP37 protein which is essential for the formation of the extracellular viral (EV) envelope (Lee et al., 2023). Closely attached to VP37, the drug impedes the encapsidation of the virus, thus stopping the maturation of the virions and inhibiting the release of the viral particles from the infected host cells (Lu et al., 2023; Rabaan et al., 2023).

The efficacy of tecovirimat has been substantiated in several studies spanning orthopoxvirus infections and involving non human primates (NHPs) monkeypox virus models (Schmitt et al., 2014). Previous studies are limited for tecovirimat and outcomes for tecovirimat for monkeypox are in the emergency use or treating monkeypox context in appropriate outcomes for tecovirimat and monkeypox virus outcomes are encouraging. Studies demonstrated that tecovirimat lowered the viral load and improved survival and reduced the severity of the disease (Russo et al., 2018; Nguyen et al., 2023; DeLaurentis et al., 2022).

More recent clinical investigations focused on the function of tecovirimat in expediting the resolution of clinical symptomatology associated with the viral infection MPOX. For example, Nguyen et al., 2023 reported tecovirimat treatment was associated with resolution of clinical virulence approximately 6 days sooner than counterparts who did not receive the drug. In the same manner, Hermanussen et al. 2023, Germant, reported in patients with severe clinical manifestations of the disease a noticeable clinical altitude was accomplished. In the same manner, tecovirimat was noted in cases of Monkeypox associated with HIV severe clinical recovery. Some minor adverse effects were reported, with the most common being limited and temporary nausea (Lagi et al., 2024), thus suggesting the drug's usefulness in the treatment of severe cases.

The use of tecovirimat has advantages over other antiviral therapies due to its unique mechanism of action. Since VP37 is a highly conserved protein in the orthopoxvirus family and has no homolog in human host cells, tecovirimat targets a specific protein that does not interfere with normal cell function, potentially reducing toxic side effects (Lu et al., 2023; Rabaan et al., 2023). Akiyama et al. (2024) also found that in individuals living with HIV—who are typically more vulnerable to severe infections—tecovirimat was effective in shortening the duration of viral spread. Because of its targeted mechanism of action and broad activity against various orthopoxviruses, tecovirimat continues to be one of the most promising options for treating MPOX (Malik et al., 2023).

3.4. Brincidofovir and cidofovir

Brincidofovir and cidofovir are antiviral drugs used to treat infections caused by DNA viruses, including Orthopoxviruses such as monkeypox. Brincidofovir and cidofovir are prodrugs with the former designed to overcome some clinical cidofovir problems (Majewska et al., 2023). Being a derivative, brincidofovir also has a notable advantage where it has an active antiviral activity against a range of viruses, especially monkeypox, through the inhibition of viral DNA replication (Zovi et al., 2022; J. Wang et al., 2023). Most importantly, after oral administration, brincidofovir is changed to its active form, cidofovir diphosphate, in the body

(Butic et al., 2023). On the other hand, cidofovir is administered through the IV route and, like brincidofovir, is also transformed to cidofovir diphosphate after entering the cells (Andrei et al., 2015). Active/inhibitor complex of viral DNA polymerase is formed with both drugs, an enzyme important for the replication of the viral genome (Siegrist & Sassine, 2023). There are also some cases where an equally promising result was obtained for the combined use of Cidofovir with Tecovirimat. Patients with severe MPOX and the Cidofovir and Tecovirimat combination with vaccination were found to have near complete recovery as noted in the report by Martinez et al (2023). This combination is considered adequateeffective and adequate as it combines different mechanisms of action, providing a stronger, more substantial antiviral effect.

Both brincidofovir and cidofovir act through a similar mechanism. Once inside an infected cell, cidofovir is converted into cidofovir diphosphate, which then competes with the body's natural nucleotides to be incorporated into the viral DNA strand during replication (Chamberlain et al., 2019). Unlike the classic mechanism of obligate chain termination, which stops DNA synthesis completely, cidofovir diphosphate (CDVpp) works through a process called nonobligate chain termination—disrupting DNA replication without immediately halting it. In this mechanism, DNA polymerase can continue adding nucleotides after CDVpp is introduced, but the process becomes very inefficient (Chamberlain et al., 2019). At high concentrations, CDVpp is difficult for the polymerase to remove, thus progressively inhibiting DNA replication and ultimately stopping viral replication (Chamberlain et al., 2019).

Monkeypox, which belongs to the Orthopoxvirus family along with the variola virus that causes smallpox, has a DNA polymerase that is very similar to the smallpox virus (Aljabali et al., 2022). Therefore, the mechanism of DNA inhibition by brincidofovir and cidofovir, which is effective against smallpox, is also applicable to monkeypox (Zovi et al., 2022). Nonetheless, brincidofovir presents multiple benefits relative to cidofovir. Of this, brincidofovir being in oral form offers an advantage since cidofovir is in infusion form and with that, is inconvenient (Butic et al., 2023; Andrei et al., 2015). Furthermore, brincidofovir is the safer option, unlike cidofovir which is less safe for long-term administration since it has a higher renal toxicity profile. Furthermore, and unlike cidofovir which has a higher risk for renal toxicity, patients with renal impairment should be closely monitored (Faure et al., 2016).

Further studies have confirmed the effectiveness of brincidofovir in treating more complex clinical cases. For example, Alameer et al. (2024) described cases of kidney transplant patients receiving brincidofovir who had favorable clinical outcomes with no adverse effects. Thus, brincidofovir is likely the safest treatment in patients with severe immunosuppression and/or complicated kidney disease. On the other hand, while Cidofovir is potentially very effective in inhibiting the replication of the monkeypox virus by targeting its DNA polymerase, it is also limited in its use due to the availability of safer alternatives, such as brincidofovir. Therefore, it is used more frequently as a last-line treatment.

Additionally, a study by Sobral-Costas et al. (2023) demonstrated that topical Cidofovir resulted in a faster decrease in lesion size (healing) in patients with monkeypox compared to

the control group that received no treatment. Confirms the effectiveness of topical Cidofovir in treating monkeypox, especially in mild to moderate cases. It has been shown that topical Cidofovir, in the majority of mild to moderate cases of monkeypox, does not cause any systemic adverse effects. However, local adverse effects are common, and these include a burning sensation, as well as other types of ignition, which are more likely to occur in cases with a level below 50, including skin ignitions and other types of ignition. In contrast, brincidofovir has completed several clinical studies as a treatment for orthopoxvirus infections, such as monkeypox, and has received Emergency Use Authorization (EUA) for restricted use in several countries. However, there is a need for substantial clinical research on both medications to determine their long-term effects and safety, particularly in relation to the treatment of monkeypox and other infections caused by DNA viruses.

3.5. Other potential drugs

Among the antiviral; agents previosul mentioned, tecovirimat, brincidofovir, and Cidofovir, and the agents still being evaluated for treating monkeypox (MPOX). Ribavirin, which is a broad-spectrum antiviral that is also used on RNA and DNA viruses and is used for the treatment of viral hepatitis C (Byradeddy et al., 2023). The drug, through its effect on guanosine diphosphate (GDP), inhibits the replication of viruses by disrupting the virus's RNA synthesis (Beaucourt & Vignuzzi, 2014). Although this expected mechanism of action may be more applicable to RNA viruses, ribavirin is still expected to have some effect on orthopoxviruses, a condition for which limited clinical data support its efficacy. Hence, the study of monkeypox is warranted (Martínez-Fernández et al., 2023).

NIOCH-14 is an experimental antiviral agent currently under in vitro evalutation and expected to enter in vivo animal studies soon for its antiviral activity against several orthopoxviruses, including monkeypox (Shishkina et al., 2023). NIOCH-14 is also similar to tecovirimat, it targets viral proteins involved in virion assembly and release, thereby limiting intercellular spread of the virus (Hudu et al., 2023). Besides the aforementioned drugs, there is also an immunoglobulin product containing polyclonal antibodies to vaccinia, which is used in emergencies to strengthen the immune response to orthopoxviruses, specifically Vaccinia Immune Globulin Intravenous (VIGIV). VIGIV a passive immune therapy with polyclonal antibodies, is used in emergency settings to enhance immunity against orthopoxviruses, particularly in the elderly or patients with immune suppression (Harapan et al., 2022).

Methisazone, an older medication used historically for smallpox, inhibits viral protein synthesis required for a virion to replicate and release (Lee et al., 2023). Overall, while several agents are more promising than others, a more thorough understanding is necessary before the treatment of monkeypox is considered both safe and effective over an extended time.

3.6. Current state of vaccine development

Vaccine development for monkeypox currently relies on existing smallpox vaccines, given the genetic similarity between smallpox and monkeypox viruses. According to Rizk et al. (2022), the primary vaccines utilized are ACAM2000 and JYNNEOS. ACAM2000 is a

viable vaccine for the orthopoxvirus. ACAM2000 has its drawbacks. Pittman et al. (2019) state that this vaccine can cause severe adverse reactions. This is particularly true for individuals with weakened immune defenses and a history of skin problems, such as eczema. Due to this, the vaccine's use is primarily limited to specific high-risk populations, such as healthcare workers and individuals in specific laboratory settings.

On the other hand, JYNNEOS is the other vaccine. JYNNEOS is a safer, non-replicating vaccine that has been licensed for the prevention of smallpox and monkeypox in certain at-risk groups (Wang et al., 2024). JYNNEOS has fewer and milder adverse reactions. Because of this, JYNNEOS is the preferred vaccine in higher-risk populations and has been included in other vaccination strategies, even in non-endemic countries (Saadh et al., 2023).

Meanwhile, research continues to develop vaccines that are more specific and safer for the broader population, reducing side effects. Research exploring mRNA-based vaccines suggests a lower risk of side effects (Mucker et al., 2024).

3.6. Limitations

This review showcases the most important challenges and limitations. Firstly, the most published clinical cases and studies on tecovirimat, brincidofovir, cidofovir, etc. are single-case studies or small sample clinical studies. This diminishes the strength or relevance of the findings. Secondly, the long-term safety and efficacy are not documented, especially in the immunocompromised such as HIV or transplant patients, and the information for the long-term safety and efficacy of the drugs is absent. Thirdly, the majority of the available studies are not randomized controlled trials, and thus are weaker in certain areas, including confirming the strength. Additionally, the possibilities of viral resistance to the repurposed antivirals to be poorly defined support the need for mechanistic and genomic studies to deepen the understanding of resistance. Additionally, high-income countries are the principal focus of most clinical studies and thus, the findings are not accessible for low-income countries, which are the countries that most need the findings and also have high levels of monkeypox. Broadening the scope of this research to include multi-site studies and increased collaboration will be required to offer high-quality, universal, and inclusive Therapeutic options to be counter MPOX.

3.7. Future direction

The monkeypox (MPOX) outbreak highlights the importance of having the needed health resources available to deal with the possible monkeypox pandemic. Even if the COVID-19 pandemic does not seem to be a threat to national security anymore, COVID-19 taught us the importance of having public health collaboration between nations. In regards to the public health policies needed to deal with monkeypox, the most important will be having the needed laboratory facilities to diagnose monkeypox efficiently and accurately, and having adequate stockpiles available of the necessary vaccines, and antiviral therapy and other public health responsive policies needed to deal with a pandemic.

Incorporating vaccine research along with drug repositioning will provide the best foundations for future MPOX treatment. Although drug repositioning offers a solution rapidly and in the short-term, there is a need for further research into the mechanisms of viral resistance so that antiviral agents can be developed that are more precise and efficient (Saul & Einav, 2020). This is further heightened within the framework of vaccine research, which is also fundamental and most especially for mRNA (Natami et al., 2024). Stronger protection with fewer adverse effects is anticipated in more streamlined vaccine research. Furthermore, the range of vulnerable populations in which combination therapy has been studied and its potential effectiveness is known should be increased so that treatment methodologies will be complete.

Investment in global health infrastructure is vital for the ability to defend against future outbreaks. Includes the ability to spend widely on diagnostics, equitable distribution of vaccines, and the bolstering of primary healthcare systems in the most underserved areas. To defend against the global surge of viral infectious disease outbreaks, improvements in global infrastructure that defend against these outbreaks should be made. Additionally, advancements in therapeutic development, vaccines, and flexible health policies will enable a more effective and sustainable global health infrastructure to defend against diseases of zoonotic origin, including MPOX.

4. CONCLUSION

Drug repurposing is emerging as a promising strategy to address MPOX by utilizing existing antiviral agents, such as tecovirimat, Brin cidofovir, and cidofovir, which have shown efficacy against orthopox viruses. This approach offers various advantages, including faster response in situations, as these drugs already have a known safety profile and have undergone various clinical trials. In addition, drug repurposing offers a more cost-effective alternative to developing entirely new drug molecules, which often requires substantial time and financial investment.

However, there are some critical limitations to consider. One of the main drawbacks is the risk of developing viral resistance, especially with long-term use. In addition, there is limited clinical data particular on the long-term effectiveness and potential side effects in specific populations, such as patients with weakened immune systems or other comorbid conditions. While drug repurposing offers a rapid and practical response to MPOX, it should be recognized as a short-term strategy rather than a permanent solution. The development of an effective and safe vaccine remains the primary long-term option to prevent and control this outbreak more permanently.

Overall, the implementation of drug repurposing can be a practical and timely solution in dealing with health crises such as MPOX outbreaks. However, it requires careful consideration of potential side effects and efficacy. Meanwhile, the development of effective and safe vaccines should continue to be a top priority for long-term prevention and control of MPOX outbreaks.

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CONFLICT OF INTEREST

All authors declared that there was no conflict of interest.

DECLARATION OF GENERATIVE AI IN SCIENTIFIC WRITING

The authors declare that generative AI and AI-assisted technologies were used in preparing this manuscript only to improve language, grammar, and readability. The authors have reviewed and approved the final version of the manuscript and take full responsibility for its content.

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