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REVIEW

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Tecovirimat in the management of poxviruses: a narrative review of available evidence

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Abstract

Introduction Tecovirimat (TPOXX) is an effective antiviral medication recommended for treating smallpox and other *Orthopoxvirus* infections. With the rise in monkeypox (mpox) cases globally, there is an urgent need to explore therapeutic options to manage potential outbreaks.

Methodology A literature search was conducted using keywords from Scopus and ClinicalTrials.gov. English studies from 2018 to 2024 were included.

Results Ten studies assessing the effectiveness and safety of tecovirimat for poxvirus infections were evaluated, reporting diverse findings across different patient populations and study designs. Clinical trials have shown significant therapeutic potential. Various doses of tecovirimat were used in rabbit and mpox models. Early intervention slowed disease progression in vulnerable populations, such as people living with HIV (PLWHIV). Recovery times, virus eradication, and symptom relief varied among studies, but wider access and usage showed better clinical symptoms and tolerable side effects. Tecovirimat's efficacy against circulating strains has been experimentally demonstrated.

Conclusion Tecovirimat shows promise for treating poxvirus infections. Clinical trials are expected to provide more evidence-based findings to inform future therapeutic approaches and public health campaigns. Future research should explore tecovirimat's potential in managing emerging poxvirus outbreaks, such as borealpox and mpox, to strengthen and promote public health.

Keywords Tecovirimat, TPOXX, Poxviruses, Monkeypox, Smallpox, Mpox, Antiviral, *Orthopoxvirus*

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Introduction

Tecovirimat (ST-246), commercially known as TPOXX, is an antiviral agent used to treat infections caused by the variola virus (VARV). Its efficacy extends beyond cowpox, smallpox, and mpox (formerly known as monkeypox) to other orthopoxviruses and poxvirus vaccination-associated complications [1] and was the first antipox viral drug approved by the Food and Drug Administration (FDA) in the United States in 2018. Tecovirimat targets the cowpox V061 gene, which is related to the vaccinia virus F13L gene and codes for the p37 envelope protein of orthopoxviruses, an essential factor for the release and dispersion of enveloped viruses from the cell [2]. Tecovirimat functions differently from cidofovir, a nucleoside analog that inhibits viral DNA replication, by targeting the p37 protein (Fig. 1), which is expressed by all orthopoxviruses and lacks a mammalian homolog. Unlike cidofovir, which interferes with viral DNA replication, tecovirimat targets the p37 protein that plays a critical role in the formation of enveloped virions (EV), enhancing virus egress and spread within the host. It is fully active against the cidofovir-resistant cowpox virus, which demonstrates its distinct mechanism of action [3, 4]. Studies have indicated that p37 mediates the formation of EV in concert with other viral and cellular proteins, a process essential for viral release from infected cells and subsequent dissemination within the host. Viruses with defects in EV production are avirulent in vivo, underscoring the significance of targeting p37 for antiviral therapy. This evidence supports the efficacy of tecovirimat, even in strains resistant to cidofovir, due to its unique inhibition of p37, which is crucial for *Orthopoxvirus* virulence and egress [4, 5]. Extracellular enveloped viruses that spread through the circulatory system depend on this protein for their growth. Tecovirimat prevents the spread of the mpox viral envelope; however, it does not limit viral reproduction, DNA, or protein synthesis as in most antivirals. It is administered orally twice daily as capsules for a 14-day duration. With the recent development and approval of an intravenous formula by the FDA, there is a potential for more effective options. Tecovirimat is currently developing an expanded access program owing to the substantial spread of mpox in the Central African Republic [6]. Mpox, a rare and neglected disease, has become a major global health threat following epidemic outbreaks in 2022 and was recently declared a public health emergency by the World Health Organization (WHO) [7]. As of May 2023, approximately 106 nations and territories have recorded an invasion, with 65,415 confirmed cases and at least 26 documented deaths [7]. Clinical symptoms include severe headaches, fever, back discomfort, lesions, and lymphadenopathy, which self-resolves within 2–4 weeks. The disease-related mortality rate varies between 0 and 11% [7]. TPOXX's efficacy against mpox virus (MPXV) in nonhuman primates and rabbitpox in rabbits highlighted its broad-spectrum activity against various poxviruses, culminating in its approval for clinical use under the Centers for Disease Control and Prevention's (CDC) extended access policy [8]. However, given the limited number of studies conducted, a comprehensive evaluation of clinical trials employing tecovirimat for MPX is imperative to gain insights from the existing research and clinical evidence. Utilizing tecovirimat for the clinical and

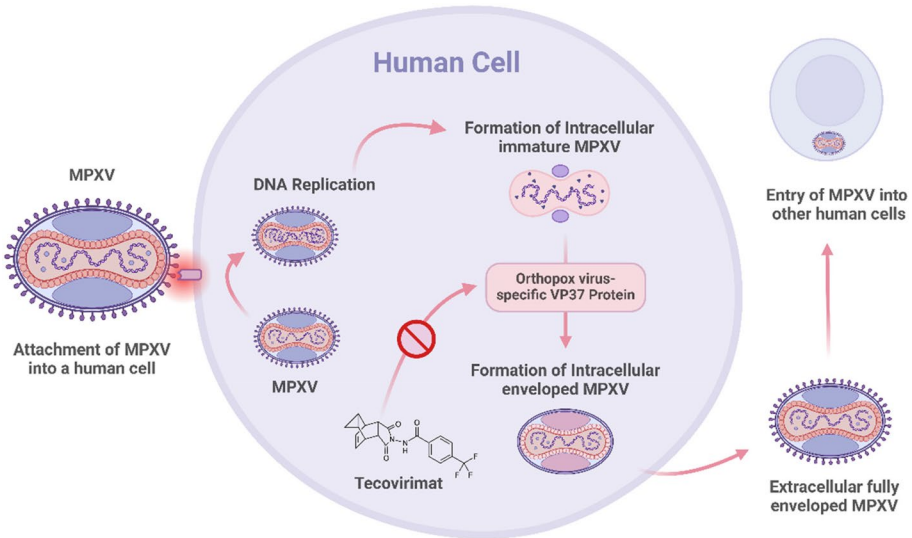

Fig. 1 Mechanism of action of tecovirimat against mpox

pharmacological management of MPXV is recommended considering its demonstrated effectiveness against orthopoxviruses. However, there are uncertainties regarding its efficacy and safety in patients with diverse demographics. This study synthesized current evidence from existing studies to assess the safety and efficacy of TPOXX in the management of poxvirus infections.

Methodology

A comprehensive literature search was undertaken, utilizing the Scopus database to identify pertinent studies and ClinicalTrials.gov for ongoing studies, using keywords such as "Tecovirimat," "Poxviruses," "Monkeypox," and "Mpox" combined with the Boolean operators "OR" and "AND." An additional bibliometric search of the included papers was conducted to gather relevant studies for the review. The search was limited to articles published between January 2018 and April 2024 to ensure the currency of information. To guarantee a systematic approach for assessing the safety and effectiveness of tecovirimat (TPOXX) in treating poxvirus infections, a standardized protocol/guide was employed in the review.

Eligibility criteria

To qualify for inclusion, studies must have investigated tecovirimat through clinical trials, cross-sectional studies, cohort studies, or experimental studies. They must have been published in English within the last 6 years (2018–2024) and reported tecovirimat's safety and efficacy with quantifiable data or qualitative safety observations. All ongoing clinical trials exploring tecovirimat in patients with MPXV or *Orthopoxvirus* were included. Case reports, reviews, editorials, letters, and commentaries were excluded.

Data extraction

Initial database searches yielded 357 outcomes that were thoroughly scrutinized against the eligibility criteria. Following full-text screening and removal of duplicates, 10 studies (including 2 clinical trials, 6 cohort studies, 1 cross-sectional study, and 1 experimental study) were included, along with 6 ongoing registered clinical trials. Data extraction encompassed the study title, author, date, aim, study type, population, intervention, and outcomes. Data extraction was conducted by two independent reviewers, and a third reviewer resolved any discrepancies. There was no specific measurement of inter-rater reliability between the two independent reviewers during the data extraction procedure. Nonetheless, attempts were made to guarantee uniformity by establishing precise criteria, and a third reviewer settled any disagreements.

Data synthesis and analysis

A rigorous qualitative synthesis method was employed to appraise and summarize the findings regarding the safety and efficacy of tecovirimat in mpox treatment and control. The analysis accounted for heterogeneity in the study designs, patient populations, and dosing regimens. Inconsistencies in the literature, particularly concerning the study outcomes, were identified, highlighted, and thoroughly discussed to ensure a comprehensive and transparent assessment.

Report of findings

A PRISMA flow chart was used to present the findings of the literature search (Fig. 2). A summary table was prepared to highlight and contextualize the salient information on the outcomes of tecovirimat as a therapeutic medication in the management of smallpox, mpox, and other ongoing clinical trials (Tables 1 and 2).

Results

Overview of findings and safety outcomes

Ten studies assessing the effectiveness and safety of tecovirimat for poxvirus infections were evaluated, with diverse findings reported across different patient populations and study designs (Suzuki et al., Grosenbach et al., Mazzotta et al., Aldred et al., Karmarkar et al., Hermanussen et al., Desai et al., Mbrenga et al., Warner et al., McLean et al.). Clinical trials have shown promising therapeutic potential, with tecovirimat effectively treating rabbitpox and mpox models at various doses (Grosenbach et al.). Early intervention has demonstrated a capacity to slow the course of the disease in vulnerable populations such as people living with HIV (PLWHIV) (Aldred et al.). Despite some inconsistencies in recovery times, virus eradication, and symptom relief reported in cross-sectional and cohort studies, broader access and usage of tecovirimat have been associated with improved clinical symptoms and tolerable side effects (Mazzotta et al., Karmarkar et al., Hermanussen et al., Desai et al., Mbrenga et al.). Furthermore, the efficacy of tecovirimat against circulating strains has been demonstrated experimentally (Warner et al.). Ongoing clinical trials are currently underway to evaluate the effectiveness of tecovirimat across different populations and disease stages. Variations in patient demographics, disease severity, and treatment regimens may have influenced the outcomes documented across studies. Safety assessments of tecovirimat have consistently reported that adverse effects are manageable and well tolerated. Common side effects associated with tecovirimat treatment include fatigue, headache, nausea, itching, and diarrhea (Desai et al., Mbrenga et al.). Mbrenga et al. reported a reduction in

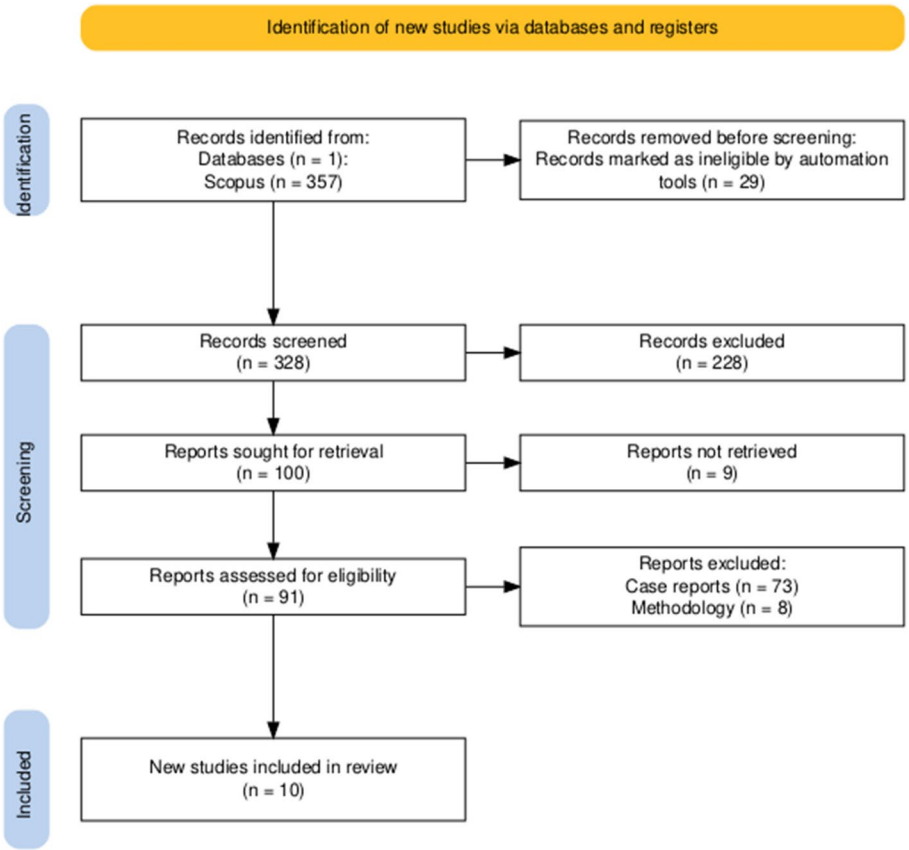

Fig. 2 PRISMA flowchart of studies included for the review [9]

active lesions during therapy, indicating a positive treatment response (Mbrenga et al.). The manageable nature of these side effects suggests that tecovirimat may be a promising treatment option for poxvirus infections, particularly during outbreaks.

Efficacy outcomes

Grosenbach et al. found that different doses of tecovirimat were required for the rabbitpox and mpox models, with the mpox model requiring a minimum dose of 10 mg per kilogram of body weight for 14 days to achieve over 90% survival (Grosenbach et al.). Mazzotta et al. did not observe any substantial improvement in healing or viral clearance time between treated and untreated individuals (Mazzotta et al.). However, Aldred et al. indicated that early tecovirimat administration within 7 days of symptom onset significantly reduced disease progression in PLWHIV compared to delayed or no treatment (Aldred et al.).

Karmarkar et al. found that early tecovirimat was not linked to faster total disease resolution but was connected with shorter time to symptom relief for participants with severe illness (Karmarkar et al.). Hermanussen et al. reported that therapy with tecovirimat was acceptable, and all patients with severe mpox exhibited improved clinical signs (Hermanussen et al.). Warner et al. demonstrated that tecovirimat was effective against MPXV strains currently circulating (Warner et al.).

Ongoing trials

Six ongoing clinical trials examining the potential of tecovirimat in the treatment of poxvirus infections have been conducted at ClinicalTrials.gov. The difficulty and urgency of treating infections associated with poxviruses are reflected in the differences in the designs, participant demographics, and phases of these studies. Ekkelenkamp (NCT06156566) is conducting a phase 4 interventional trial that seeks to register 150 persons aged 18 years or older. The trial, which is expected to be completed between 2023 and 2027, assesses the effectiveness of tecovirimat oral capsule in comparison to a placebo. Alexandra (NCT05597735) is a phase 3 interventional study that aims to treat 150 adults and adolescents aged $\geq$ 14 years. This trial compared the safety and effectiveness of tecovirimat with those of placebo. This project is anticipated to be completed between 2023 and 2025.

Table 1 An overview of research assessing tecovirimat as a treatment for smallpox and monkeypox

S/no	Title	Author and date	Aim/purpose	Study type	Participants/population	Interventions	Outcomes
1	Protocol of Tecopox study: a multicenter, open-label, double-arm trial to evaluate the efficacy and safety of oral tecovirimat therapy for patients with smallpox or monkeypox	Suzuki et al. [10]	To use oral tecovirimat in Japan and to assess its safety and efficacy in patients with monkeypox and smallpox	Clinical trial	Patients with monkeypox or smallpox	Oral tecovirimat treatment and standard supportive treatment	Yet to be completed
2	Oral tecovirimat for the treatment of smallpox	Grosenbach et al. [11]	To evaluate the efficacy of tecovirimat in models of nonhuman primates (rabbitpox) and rabbits (monkeypox)	Clinical trial	Nonhuman primates (rabbitpox) and rabbits (monkeypox)	Oral tecovirimat suspension	In the rabbitpox model, a dose of 40 mg per kilogram was equally successful; however, the monkeypox model required a minimum dose of 10 mg per kilogram of body weight for 14 days to achieve over 90% survival
3	Effect of tecovirimat on healing time and viral clearance by emulation of a target trial in patients hospitalized for mpox	Mazzotta et al. [12]	To evaluate the impact of tecovirimat on the duration of healing and the degree of viral clearance by target trial emulation	Cohort study	Hospitalized individuals with mpox	600-mg tecovirimat twice a day for 2 weeks	The study did not find any substantial improvement in healing or viral clearance times between treated and untreated individuals
4	Early tecovirimat treatment for mpox disease among people with HIV	Aldred et al. [13]	To determine whether PLWHIV with mpox who received tecovirimat treatment within 7 days of the onset of symptoms had a decreased risk of the disease progressing	Cohort study	PLWHIV suffering from mpox	Tecovirimat treatment for 7 days after mpox symptoms	Following a propensity score comparison of 112 HIV-positive individuals, early tecovirimat administration within 7 days of mpox symptom onset significantly reduced disease progression compared to late or no tecovirimat treatment. This was indicated by a paired odds ratio of 13.00 (95% *CI*, 1.71–99.40; $P = .002$)
5	Association of tecovirimat therapy with mpox symptom improvement: a cross-sectional study—King County, Washington, May–October 2022	Karmarkar et al. [14]	To conduct retrospective cross-sectional interview-based research to find correlations between the clinical course of mpox and tecovirimat medication	Cross-sectional study	Individuals with mpox diagnoses from May to October of 2022	Tecovirimat treatment	Early tecovirimat was not linked to a faster total disease resolution, although it was connected with a shorter time to symptom relief (−5.5 days, $P = .04$) for participants with severe sickness but not for those with non-severe illness

Table 1 (continued)

S/no	Title	Author and date	Aim/purpose	Study type	Participants/population	Interventions	Outcomes
6	Tecovirimat for the treatment of severe mpox in Germany	Hermanussen et al. [15]	To track down and examine every monkeypox patient in Germany who was treated with tecovirimat between May 2022 and March 2023	Cohort study	Monkeypox patient treated with tecovirimat	Tecovirimat treatment	Therapy with tecovirimat was acceptable, and all patients in this cohort with severe mpox exhibited improved clinical signs
7	Compassionate use of tecovirimat for the treatment of monkeypox infection	Desai et al. [16]	To assess side effects and clinical results in patients with monkeypox who were compassionately treated with tecovirimat	Cohort study	Patients with monkeypox	Tecovirimat	The majority of adverse effects associated with tecovirimat treatment were fatigue, headache, nausea, itching, and diarrhea. Overall, the treatment was well tolerated
8	Monkeypox treatment with tecovirimat in the Central African Republic under an Expanded Access Programme	Mbrenga et al. [17]	To provide tecovirimat to individuals diagnosed with the condition through an extended access program	Cohort study	Patients with monkeypox	Tecovirimat	Common symptoms included in the study were headache, muscle soreness, lymphadenopathy, lesions, fever, back discomfort, and symptoms related to upper respiratory tract infections. During treatment, the number of active lesions diminished, with a median of 5 days passing without any new lesions. In this cohort, there were no known deaths due to monkeypox
9	In vitro and in vivo efficacy of tecovirimat against a recently emerged 2022 monkeypox virus isolate	Warner et al. [18]	To assess TPOXX's efficacy in preventing an MPXV clade 2 Canadian isolate in vivo and in vitro during the current outbreak	Experimental study	CAST/EiJ mouse model	Tecovirimat	According to our research, TPOXX is quite effective against the MPXV strains that are now in circulation and may play a significant role in containing the outbreak

Table 1 (continued)

S/no	Title	Author and date	Aim/purpose	Study type	Participants/population	Interventions	Outcomes
10	Tecovirimat treatment of people with HIV during the 2022 mpox outbreak: a retrospective cohort study	McLean et al. [19]	To compare the clinical presentation and treatment outcomes of HIV-positive patients receiving tecovirimat for monkeypox virus (MPXV) infection with HIV-negative individuals between June and August 2022	Cohort study	PLWHIV and HIV-negative individuals receiving tecovirimat treatment for MPXV	Tecovirimat	The study found that tecovirimat treatment indications were similar between people with HIV and HIV-negative groups. Serious adverse events occurred in four participants, but none was attributed to tecovirimat. Both groups had similar rates of hospitalization and treatment indications

Table 2 Ongoing registered clinical trials on tecovirimat

S/no	Title	NCT	Stages	Study type/design	Participants/ population	Intervention	Phase	Start and proposed completion date	Funder
1	European Trial IntoMpox Infection (EPOXI)	NCT06156566	Not yet recruiting	Interventional study	150 adults of 18 years and older (both sexes)	Drug: tecovirimat oral capsule Drug: Placebo	Phase 4	2023 December to 2027 December	Miquel Ekkelenkamp
2	Assessment of the efficacy and safety of tecovirimat in patients with monkeypox virus disease (UNITY)	NCT05597735	Recruiting	Interventional	150 adolescents and adults aged 14 years and older (both sexes)	Drug: tecovirimat Drug: placebo	Phase 3	2023 March 03 to 2025 January 01	Calmy Alexandra
3	Tecovirimat for treatment of monkeypox virus	NCT05559099	Recruiting	Interventional	600 participants with no age limitation (both sexes, including children, adults, and older adults)	Tecovirimat oral capsule Drug: placebo	Phase 2	2022 October 10 to 2024 September	National Institute of Allergy and Infectious Diseases (NIAID)
4	Study of tecovirimat for human monkeypox virus (STOMP)	NCT05534984	Recruiting	Interventional	530 participants with no age limit (both sexes, including children, adults, and older adults)	Tecovirimat oral capsule Drug: placebo Drug: tecovirimat oral capsule (open label)	Phase 3	2022 September 12 to 2025 September 30	National Institute of Allergy and Infectious Diseases (NIAID)
5	Tecovirimat in non-hospitalized patients with monkeypox (PLATINUM-CAN)	NCT05534165	Recruiting	Interventional	120 participants of 18 years and older (both sexes)	Drug: tecovirimat Drug: placebo	Phase 3	2023 August 14 to 2025 march	Marina Klein
6	Tecovirimat (ST-246) treatment for orthopox virus exposure	NCT02080767	Available	Interventional	Participants with no age limit (both sexes, including children, adults, and older adults)	Tecovirimat	Not available	Not available	US Army Medical Research and Development Command

The National Institute of Allergy and Infectious Diseases (NIAID) sponsored a phase 2 interventional trial (NCT05559099) that seeks to enlist 600 people in all age categories. The trial's projected completion date is between 2022 and 2024, and it evaluates the effectiveness of tecovirimat oral capsule in comparison with placebo. NIAID is also funding a phase 3 interventional study (NCT05534984) that aims to enrol 530 individuals of all ages. This trial assessed the effectiveness of the tecovirimat oral capsule, which has an open-label arm. This project is anticipated to be completed between 2022 and 2025. Klein (NCT05534165) is conducting a phase 3 interventional study that seeks to enlist 120 people who are at least 18 years old. The goal of this experiment was to compare the effectiveness of tecovirimat and a placebo. This project is anticipated to be completed between 2023 and 2025. Finally, the US Army Medical Research and Development Command funds an open research study (NCT02080767), an interventional trial that includes individuals of all ages. This study examined the effectiveness of tecovirimat in individuals exposed to orthopox viruses. The potential of tecovirimat as a treatment for poxvirus infections has been assessed in various clinical trials. Using different study designs, participant cohorts, and phases, these trials hope to expand therapeutic choices for people with illnesses associated with the poxvirus by offering important insights into the safety and efficacy of tecovirimat.

Discussion

The findings from 10 studies investigating the efficacy of tecovirimat in treating poxvirus infections provide significant insights into the potential application of the drug. The diverse range of study designs and patient populations enable a comprehensive understanding of the effects of tecovirimat across various scenarios. Promising results from clinical trials, such as multicenter, open-label Tecopox research and Grosenbach et al.'s evaluation of oral tecovirimat solution in animal models, underscore its potential as a therapeutic alternative [11]. Additionally, a study by Merchlinsky et al. demonstrated that the ability of tecovirimat to delay illness progression in a mouse model emphasizes its dual function of directly targeting the virus while enhancing the body's immune response [20, 21]. While tecovirimat has shown broad-spectrum antiviral activity against poxviruses, the comparative effectiveness with cidofovir and brincidofovir is still an important consideration. For example, while tecovirimat's primary mechanism is the inhibition of the viral p37 envelope protein, which prevents viral spread, cidofovir and brincidofovir act through DNA polymerase inhibition, which directly targets viral replication. This mechanistic difference may account for variations in therapeutic outcomes across different studies [22]. However, regarding the impact of tecovirimat on healing time, viral clearance, and disease progression, especially in hospitalized individuals with mpox and PLWHIV, cohort studies such as those conducted by Mazzotta et al. and Aldred et al. have yielded conflicting results [12, 13].

O'Laughlin et al. noted that the majority of patients exhibited closed and healed wounds with a fresh covering of the skin behind the scar [23]. These discrepancies may stem from differences in the study methodologies, patient demographics, and disease severity. Additionally, a cross-sectional study by Karmarkar et al. elucidated the role of tecovirimat in symptom management, demonstrating quicker relief in more severe cases [14]. This complements the findings of studies on smallpox-infected animals, indicating improved clinical signs and survival rates with tecovirimat treatment [1]. In contrast, the studies on cidofovir and brincidofovir highlight their efficacy in specific settings, such as in the case of MPXV clades IIb and IIa, where brincidofovir demonstrated survival benefits despite its limited effectiveness in reducing viral titers in nasal turbinates compared to tecovirimat [13, 24, 25], suggesting that while tecovirimat may offer a broader therapeutic range, cidofovir and brincidofovir could be preferred in cases of specific viral strains or severe infections [22].

The compassionate use program by Desai et al. highlighted its general tolerability and safety profile, suggesting its potential as a treatment option, particularly in outbreak settings [14]. However, developing policies aimed at safe drug manufacturing is essential to mitigate the possible side effects of experimental medications [26]. Both cidofovir and brincidofovir, while effective, are associated with more pronounced side effects. Cidofovir's systemic toxicity and brincidofovir's potential weight loss side effects in animal models raise concerns about their tolerability in certain patient populations, which contrasts with the more favorable safety profile of tecovirimat [22, 27].

Additionally, the Central African Republic (CAF) has documented tolerance to tecovirimat among mpox-diagnosed patients, with manageable side effects and additional improvements in clinical symptoms after therapy [17], underscoring its favorable pharmacological properties as a promising therapy for poxvirus infections. Experimental investigations, such as Warner et al.'s evaluation of the effectiveness of tecovirimat in animal models, further support its potential to contain epidemics of MPXV infection [18]. These studies collectively illustrate the broad-spectrum activity of tecovirimat against poxviruses, with varying doses required for different models to achieve successful outcomes while considering patient severity and disease stage [28, 29], highlighting

the importance of considering patient population characteristics, as tecovirimat's tolerability may offer advantages over cidofovir and brincidofovir, particularly in high-risk or immunocompromised populations.

The study by Aldred et al. focused on the timing of tecovirimat administration in cases of mpox among PLWHIV cases. Findings indicated that early tecovirimat administration, within 7 days of symptom onset, significantly slowed disease progression compared to delayed or no treatment [13]. Similarly, Russo et al. emphasized the significance of initiating treatment within a short period after Mpox infection to decrease disease severity and protect against its clinical effects [30]. Comparatively, the timing of administration is also crucial for cidofovir and brincidofovir, though tecovirimat's early intervention appears to offer a more pronounced benefit in halting disease progression, especially in vulnerable populations [13]. These findings prove the potential advantages of early tecovirimat intervention in maximizing therapeutic benefits and minimizing the impact of mpox infection, especially among high-risk populations [31].

Studies evaluating the safety and efficacy of tecovirimat have consistently reported manageable and well-tolerated adverse effects. Common side effects associated with tecovirimat include fatigue, headache, nausea, itching, and diarrhea [32, 33]. However, tolerability may vary slightly across studies. For instance, the "mpox treatment with tecovirimat in the Central African Republic under an Expanded Access Programme" study noted a decrease in active lesions throughout therapy, indicating a positive treatment response [3]. The adverse effects observed in the studies by Desai et al. and Mbrenga et al. were generally manageable and did not significantly impact treatment outcomes [3]. The manageable nature of these adverse effects suggests that tecovirimat could be a promising treatment option for poxvirus infections, particularly during outbreaks. In comparison, while cidofovir and brincidofovir have shown efficacy in animal models, their adverse effect profiles, particularly the systemic toxicity associated with cidofovir, require careful consideration. This makes tecovirimat a potentially safer option for long-term use or treatment in broader populations [34].

Nonetheless, further research is necessary to comprehensively assess its safety profile and potential long-term effects. Variations in patient demographics, health status, disease severity, treatment regimens, and study designs contribute to the variability in the outcomes of studies assessing the safety and effectiveness of tecovirimat. Disease heterogeneity, particularly in cases such as mpox, further complicates the treatment response assessment, with biological and environmental factors playing significant roles [27]. Despite these differences, careful analysis of the study results and consideration of context and biases are essential to appropriately evaluate the therapeutic potential of tecovirimat [12, 27].

Clinical trials are underway to confirm the safety and efficacy of tecovirimat (ST-246) in the treatment of poxvirus infections. The European Trial of IntoMpox Infection (EPOXI) represents a phase 4 interventional study aimed at assessing the effectiveness of the drug in treating smallpox or mpox. Similarly, the "Assessment of the efficacy and safety of tecovirimat in patients with mpox disease (UNITY)" is a phase 3 study comparing the safety and effectiveness of tecovirimat versus a placebo. Sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), the "tecovirimat for treatment of MPXV" trial is a phase 2 interventional study evaluating the potential of a drug across a broad demographic. In addition, the STOMP (study of tecovirimat for human MPXV) trial is a phase 3 interventional study involving 530 participants of all ages, while the "tecovirimat in non-hospitalized patients with mpox (PLATINUM-CAN)" trial aims to recruit 120 participants aged 18 years and older to compare the effectiveness of tecovirimat versus a placebo. Lastly, the "Tecovirimat (ST-246) Treatment for Orthopox Virus Exposure" trial is crucial for understanding the potential of the drug for post-exposure prophylaxis. These ongoing trials are expected to yield valuable data that will inform future treatment strategies and public health interventions, providing promising pathways for assessing the safety and effectiveness of tecovirimat in wider patient populations [35]. By including a range of stages and participant demographics, these trials are intended to enhance our understanding of the therapeutic potential of tecovirimat and offer guidance for its possible application in combating poxviral infections.

Limitations

The safety and effectiveness of tecovirimat in the treatment of poxvirus infections have been evaluated. Heterogeneity in study designs and patient populations, including clinical trials and cohort studies, may affect the generalizability of the findings. Clinical trials, such as the Protocol of Tecopox and Oral Tecovirimat for the Treatment of Smallpox, provide valuable insights into the efficacy of tecovirimat in controlled settings but may not fully represent real-world outcomes. Cohort studies, such as those on the effect of tecovirimat on healing time and viral clearance, have inherent limitations in establishing causality and may be influenced by confounding variables. The lack of standardized protocols and outcome measures makes it difficult to compare the results and draw definitive conclusions regarding the effectiveness of tecovirimat. Additionally, ongoing clinical trials may face challenges, such as recruitment biases, dropout rates,

and unforeseen adverse events. Experimental investigations, such as the study by Warner et al., provide valuable preclinical data but may not fully translate to clinical efficacy.

Recommendations

The findings of this study highlight the potential efficacy and safety of tecovirimat for the management of poxviruses. However, there is a need to further assess the outcomes of larger ongoing clinical trials. Future trials should focus on optimal regimen dosing and treatment duration to maximize the therapeutic benefits. Patients should be stratified based on disease severity, immunocompetence, and comorbidities to understand tecovirimat's effects and possible drug interactions in the event of managing comorbid conditions. Monitoring and managing side effects, such as fatigue, headache, nausea, itching, and diarrhea, are crucial for patient safety and treatment adherence. Collaboration between researchers, healthcare providers, and regulatory agencies is essential for the timely dissemination of findings and the development of evidence-based guidelines. Continual efforts to assess the efficacy of tecovirimat in nonhospitalized patients, post-exposure prophylaxis, and orthopox virus exposure are commendable and should be continued to expand treatment options and effectively address public health needs.

Conclusion

Tecovirimat, originally developed for smallpox treatment, has demonstrated broad-spectrum activity against mpox and various orthopoxviruses. Clinical and preclinical studies reveal that tecovirimat significantly reduces viral replication, disease severity, and mortality rates in both animal models and human cases by inhibiting the p37 protein, essential for viral egress, thereby preventing the virus from spreading within the host. Key findings indicate that tecovirimat is well-tolerated with a favorable safety profile in human trials, including those conducted during the recent mpox outbreaks. Though its use in large-scale outbreaks and diverse populations is still limited, current evidence supports tecovirimat as an essential therapeutic option for poxvirus management, particularly in immunocompromised patients and severe cases.

Abbreviations

FDA	Food and Drug Administration
VARV	Variola virus
PLWHIV	People living with HIV
EV	Enveloped virions
MPXV	Monkeypox virus
ST-246	Tecovirimat code name
TPOXX	Commercial name for tecovirimat
WHO	World Health Organization
CDC	Centers for Disease Control and Prevention
MPX	Monkeypox
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
NIAID	National Institute of Allergy and Infectious Diseases
CAF	Central African Republic
EPOXI	European Trial of IntoMpox Infection
STOMP	Study of tecovirimat for human MPXV
PLATINUM-CAN	Tecovirimat in nonhospitalized patients with mpox

Authors' contributions

Conceptualization, OJO, JBO, MMA, BMU, and BOA. Methodology, OJO, JBO, BOA, and MMA. Validation, DELP III, JAD, EM, DOS, and NBI. Investigation, OJO, BOA, DOS, and WKC. Resources, JBO, BOA, OIJ, and NBI. Data curation, OJO, BOA, BMU, OA, OFJ, DOS, and WKC. Writing — original draft, OJO, JBO, OIJ, MMA, BMU, OFJ, DOS, DELP III, BOA, OA, WKC, EM, NBI, and JAD. Writing — review and editing, OJO, JBO, OIJ, MMA, BMU, OFJ, DOS, DELP III, BOA, OA, WKC, EM, NBI, and JAD. Supervision, DELP III. All authors read and approved the final manuscript.

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Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author, Mohamed Mustaf Ahmed, upon reasonable request.

Declarations

Ethics approval and consent to participate.

Ethical approval was not required for this study as it did not involve human or animal subjects.

Consent for publication.

Not Applicable.

Competing interests

The authors declare no competing interests.

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