The Use of Antivirals in the Treatment of Human Monkeypox Outbreaks: A Systematic Review

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Highlights

Abstract

Objectives

Human monkeypox virus infection is the recently declared public health emergency of international concern (PHEIC) by the World Health Organization. Besides, there is scanty literature available on the use of antivirals in monkeypox virus infection. This systematic review compiles all evidence of various antivirals used on their efficacy, safety and summarizes their mechanisms of action.

Methods

A review was done for all original studies mentioning individual patient data on the use of antivirals in patients with monkeypox virus infection.

Results

Of the total 487 non-duplicate studies, 18 studies with 71 individuals were included. Tecovirimat was used in 61 individuals, followed by Cidofovir (CDV) in 7 and Brincidofovir (BCV) in 3 individuals. Topical Trifluridine was used in 4 ophthalmic cases in addition to Tecovirimat. Of the total, 59 (83.1%) were reported to have complete resolution of
symptoms, 1 was experiencing waxing and waning of symptoms, only 1 (1.8%) had died, and the others were having resolution of symptoms. The death was thought unrelated to Tecovirimat. Elevated hepatic panels were reported among all individuals treated with BCV (leading to treatment discontinuation) and 5 treated with Tecovirimat.

Conclusions

Tecovirimat is the most used and has proven beneficial in several aggravating cases. No major safety concerns were detected upon its use. Topical trifluridine was used as an adjuvant treatment option along with Tecovirimat. BCV and CDV were seldom used, with the latter often being used due to the unavailability of Tecovirimat. BCV was associated with treatment discontinuation due to adverse events.

Keywords: Antiviral, Monkeypox, Tecovirimat, Brincidofovir, Cidofovir, treatment

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Introduction

The Global health emergency of the COVID-19 pandemic had worsened the situation of public health. Furthermore, as the adverse effects of this pandemic subsided, another public health threat in the form of the Monkeypox virus (MPXV) outbreak stirred nations across the globe. MPXV belongs to the same family as the smallpox virus eradicated in 1980. First reported in 1970, it has historically been largely confined to endemic regions in Western and Central Africa. However, it has spread rapidly throughout the globe in 2022.

Moreover, it has become a public health emergency of international concern, the seventh such declaration ever by WHO (World Health Organization, 2022). As of 6th November 2022, the CDC reports 78,229 confirmed cases and 41 deaths. These cases are spread across 109 countries, with most (102) countries reporting MPXV cases for the first time ever (Centers for Disease Control and Prevention, 2022). MPXV infection could lead to severe disease in certain groups, especially children, immunocompromised and pregnant (Huang et al., 2022).

MPXV belongs to the Orthopoxvirus family. Studies have revealed that poxviruses are generally large, double-stranded DNA-structured viruses and their genome size lies between 130 to 360kbp. Due to their large size, they are slow at replicating and surviving in the host body. The orthopoxviruses are surrounded by virulent genes acting as modulators against the host immune system (Okyay et al., 2022). Some in-vitro studies suggest these modulators enable the MPXV to invade the host’s immune system. On entering the human host cells, the
MPXV replicates in the nasopharyngeal and oropharyngeal mucosa. Then, the viral load spreads through the lymph nodes and various organs (Tolonen et al., 2001).

The common clinical manifestations of MPXV infection can be categorised based on the rapid spread from the site of inoculation to other lymph nodes in different stages of infection. The incubation period lasts for 7-17 days. The prodromal period includes fever, headache, and lymphadenopathy, lasting about 1-4 days. Rashes initially appear over the face and then spread centrifugally to cover other body parts like the palms, soles, and oral cavity. They stay for about 14-28 days (Kumar et al., 2022).

In various studies, supportive treatments and antivirals were used. This review will explore the use of antivirals and their mechanisms against the MPXV in clinical settings. Though antivirals and vaccines have been recommended for treatment and prevention, numerous protocols for treating poxvirus are restricted to various at-risk populations, children, pregnant women, or other immunocompromised individuals. Drugs have been selected based on the target range involved in viral replication (Baker et al., 2003). Tecovirimat is an antiviral used against poxviruses, and it is the first antiviral drug approved in the United States against orthopoxvirus (Kaler et al., 2022). In-vitro studies also indicate the effective use of cidofovir and Brincidofovir against pox viruses (Andrei & Snoeck, 2010).

Depending on how closely related the various orthopoxvirus (including MPXV) are to one another, immune responses to one orthopoxvirus can recognize other orthopoxvirus and
produce different degrees of protection. This cross-reactivity is because of shared immune epitopes and a broad extensive response covering at least two dozen structural and membrane proteins. Vaccinations against smallpox and MPXV infection can be administered pre-exposure and post-exposure (Poland et al., 2022). Prior smallpox vaccines coincidentally protected against MPV. Two live-attenuated vaccines for preventing MPXV infection have received US FDA approval: ACAM2000 and JYNNEOS. The former is of replicating type while the latter is not. Fewer complications have been reported in JYNNEOS, as compared to ACAM2000 (Abdelaal et al., 2022). Specifically for MPXV, a vaccine is currently being developed (Pruc et al., 2022).

Insufficient evidence on a particular treatment regimen hinders decision-making in the clinical setting. This ambiguity could be resolved by developing clinical guidelines enabling standardisation of care across different sites. Therefore, this study aims to summarise and give a detailed view of the use of antivirals for treating MPXV infection, including the resolution of disease and complications during treatment. It also summarises their mechanisms of action and clinical pharmacology. This study can throw light on a scenario of uncertainty regarding antiviral therapy in MPXV infection.

**Methods**

The trial protocol was submitted to the International Prospective Register of Systematic Reviews PROSPERO [CRD42022355596](Shamim et al., 2022). The preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement was complied with. The
search strategy, criteria for eligibility of studies, and variables of interest were pre-specified in the protocol. The variables of interest were chosen to keep in mind the lack of guidelines for managing human MPXV disease and the subsequently anticipated heterogeneity in managing and reporting the same. The variables of interest are the resolution of the disease and complications during treatment among individuals with MPXV disease receiving antiviral therapy.

**Search Strategy and Selection Criteria**

Following the protocol, three reviewers (M.A.S., S.D.V, C.C.) independently conducted an extensive literature search. ‘Monkeypox’ was searched along with terms like ‘management’, ‘treatment’, ‘antiviral’, ‘Tecovirimat’, ‘Cidofovir’, and ‘Brincidofovir’ in the title or abstract. A comprehensive search was carried out in Ovid-MEDLINE, Scopus, Cochrane Library, Google Scholar, and preprint servers for all the articles from the inception of each database through September 9, 2022. A search was repeated on November 1, 2022, to add new articles. For uniformity, the search was limited to studies on humans with MPXV disease. Reference lists were manually reviewed for additional relevant studies. Other details of the search strategy can be referred to in supplementary appendix 1.

Given the lack of data on this topic, all original studies on the usage of antivirals in human MPXV infections were included. Clinical trials, cohort studies, case-control studies, cross-sectional studies, case series, and case studies were eligible. Pooled fraction of recovered individuals will be calculated.
Studies performed on animals, in-vitro studies, and any study not involving human patients of MPXV infection were excluded. Studies involving related diseases like smallpox were also excluded. If a case is detected to be published more than once, it was reported only once. Studies were excluded where some individuals received antivirals while others did not, and individual patient data was unavailable in the article or the accompanying supplementary. This was done to ensure homogeneity in the review by not combining the data of those who received antivirals with those who did not.

The deduplication of studies was verified by a reviewer (M.A.S.). This was followed by three reviewers (M.A.S., S.D.V, C.C.) independently considering the eligibility of each study based on the title and abstract obtained from the literature search. The full text was screened for the eligible studies, and ineligible studies were further excluded. Disagreements were resolved by mutual consensus. In the absence of consensus, the opinion of a fourth independent reviewer (S.T.) was considered binding.

**Study Quality**

Since no validated tools are available for assessing the risk of bias in uncontrolled cohort studies or case reports and case series, a previously used and adapted iteration of the Newcastle Ottawa scale was implemented (Bazerbachi et al., 2017, 2018; Haffar et al., 2017). This tool has a good inter-rater agreement (Murad et al., 2018). For uncontrolled studies, items assessing comparability and adjustment were excluded, while those assessing selection, representativeness and ascertainment were retained. Thus, five questions were
finalised, as shown in Table 1. Studies were qualitatively assessed as good when none of the items gave a negative response, moderate when one was negative, and poor when more than one was negative.

**Data Extraction**

Using a standard form, the following data were extracted: antivirals used, dosage, number of individuals in the study, clinical features, resolution of disease, complications during antiviral therapy, and duration of hospitalisation after initiation of antiviral therapy. Data were extracted by three independent reviewers (M.A.S., S.D.V, C.C.). Disagreements were solved by consensus. In the absence of consensus, the opinion of a fourth independent reviewer (S.T.) was considered binding.

**Results**

A summary of the complete search process followed by the subsequent selection of studies is shown in Figure 1. Following a comprehensive literature search, a total of twenty-two studies that reported the use of antivirals in human individuals with MPXV infection were included. However, four studies were excluded in the final phase as not all the participants had received antivirals, and the authors presented a summarised patient data without individual data (Català et al., 2022; O’Laughlin et al., 2022; Patel et al., 2022; Thornhill et al., 2022). Efforts were made, by sending an email to them requesting individual patient data for individuals who received antivirals. We have not received the requested information to date.
and therefore we couldn’t include these studies in our review. Table 2 depicts the findings of 18 eligible studies, all of which were uncontrolled studies (Adler et al., 2022; Ajmera et al., 2022; Cash-Goldwasser et al., 2022; Desai et al., 2022; Hermanussen et al., 2022; Hernandez et al., 2022; Lucar et al., 2022; Mailhe et al., 2022; Matias et al., 2022; Mbrenga F., Nakouné E., Malaka C., Bourner J., Dunning J., Vernet G., Horby P., 2022; Moschese et al., 2022; Pastula et al., 2022; Peters et al., 2022; Raccagni et al., 2022; Rao et al., 2022; Scandale et al., 2022; Shaw et al., 2022; Viguier et al., 2022). Thus, a total of seventy-one (71) individuals have been considered. No published randomised or controlled studies were found on antiviral use for humans with MPXV infection. The heterogeneity of studies led to not all the data being included in all the studies.

A majority (58, 81.7%) of 71 participants were male. Most individuals (47, 66.2 %) were from the United States of America. Around 14 (19.7%) individuals were from the Central African Republic, while 10 (14.1%) were from Europe – Italy, the United Kingdom, and France. Of the total included individuals, 59 (83.1%) were reported to have complete resolution of symptoms, one is experiencing waxing and waning of symptoms, only 1 (1.8%) had died, and the others were having a resolution of symptoms at the study report (table 2). The death was thought not related to Tecovirimat. Elevated hepatic panels were reported among 3 of 3 individuals treated with BCV and 5 of 61 treated with Tecovirimat.

Drugs for MPXV infection are still under research. To date, only five drugs have been considered for treatment: Tecovirimat, Cidofovir (CDV), Brincidofovir (BCV), Trifluridine, and Vaccinia Immune globulin Intravenous (VIG). VIG has been used in only one individual in a
single study (Thornhill et al., 2022). However, individual patient data could not be retrieved, so we have not included this study in our review.

Tecovirimat was the most used drug in these studies. An individual had oral and facial lesions, a burning sensation in the mouth and dysphagia (Ajmera et al., 2022). The lesions were aggravating while he was initially on vancomycin, piperacillin/tazobactam, dexamethasone, acyclovir, and fluconazole. Later, penicillin was also added. Two days after Tecovirimat was started, the individual improved and was subsequently discharged. Two individuals presented with severe proctitis (Lucar et al., 2022), and both had rectal pain, and new lesions were cropping up in the trunk and limbs requiring opioids. On days 9 and 10, respectively, Tecovirimat was started for both individuals. In both cases, there was an improvement in pain within 48 hours. An individual had lesions in the tongue, later spreading to the limbs and torso (Peters et al., 2022). Tecovirimat was given, and the individual started recovering. An individual had vesicular lesions positive for both Herpes Simplex Virus - 1 and MPXV (Shaw et al., 2022). Tecovirimat was started, and lesions continued to aggravate, but the fever subsided within 72 hours, and the individual was discharged. Two individuals with encephalomyelitis started improving within days of starting Tecovirimat and other supportive therapies and were subsequently discharged (Pastula et al., 2022). The clinical condition of an immunocompromised individual living with HIV deteriorated for over a month before starting Tecovirimat, and symptoms subsided in 2 days (Viguier et al., 2022). A case series from Germany describes rapid improvement in 2 individuals. However, the third individual is slowly recovering (Hermanussen et al., 2022). Overall, Tecovirimat does indeed seem to help individuals with progressive disease.
Tecovirimat was associated with a few complications, like fatigue, headache, and nausea during treatment. However, one individual developed loose stools a few hours after each dose, while three developed transiently elevated hepatic enzymes that resolved itself (Hermanussen et al., 2022; Matias et al., 2022; Viguier et al., 2022). Treatment did not have to be paused or stopped in any case. The death and anaemia seen in one case each was deemed unrelated to Tecovirimat (Mbrenga F., Nakouné E., Malaka C., Bourné J., Dunning J., Vernet G., Horby P., 2022).

Brincidofovir and Cidofovir have been used in one and four studies, respectively. In three studies, individuals receiving CDV recovered (Moschese et al., 2022; Raccagni et al., 2022; Scandale et al., 2022). Another individual presented with severe ocular involvement (Mailhe et al., 2022). Here, two doses of CDV have been administered, and the lesions are evolving as of the last follow-up. None of the four studies reported any adverse events. As for BCV, all three individuals developed elevated hepatic enzymes (peak alanine transaminase of 127, 331, and 550 U/L, respectively), and the course of medication had to be stopped prematurely. Conjunctivitis, lower limb abscess, and neuropsychiatric symptoms were the other problems encountered (Adler et al., 2022).

Four individuals with ocular MPXV disease received Trifluridine eye drops in addition to Tecovirimat therapy. Three of them have recovered, while one has suffered marked vision impairment, and his symptoms were fluctuating. No individual reported any adverse event (Cash-Goldwasser et al., 2022).
Curating their mechanisms of action, Tecovirimat decreases the production of extracellular forms of the MPXV by inhibiting the p37 viral proteins needed for cellular localisation and formation of the viral envelope. By inhibiting the envelope on the virus, tecovirimat prevents the systemic spread of the virus by not letting out the virus from the infected cell, thereby preventing subsequent damage to the host cell. For children weighing less than 13 kg, the CDC-held Emergency Access Investigational New Protocol allows opening the capsule to mix the medicine with liquid or soft food. The Strategic National Stockpile offers Tecovirimat as an oral capsule formulation (600 mg twice daily for 14 days) or an intravenous injection. Side effects associated with tecovirimat are usually minimal such as headache, nausea, abdominal pain, and vomiting. Injections-site reactions may happen with intravenous administration. Although there are currently no known contraindications, it should be prescribed or administered with caution in individuals with renal or hepatic impairment (DrugBank, 2022; National Center for Biotechnology Information, 2022; Rizk et al., 2022).

Cidofovir (CDV) is mainly considered in cytomegalovirus retinitis, a condition commonly seen among the immunosuppressed, including people living with HIV. Cellular enzymes are required to activate CDV once it has entered the cells. CDV is converted to its monophosphoryl form (CDVp), which is then further phosphorylated to CDV-diphosphoryl (CDVpp), the active form. These reactions are catalysed by Pyrimidine nucleoside monophosphate kinase and Nucleoside 5′-diphosphate kinase, respectively. CDVpp interacts with the viral DNA polymerase, finally getting incorporated into the DNA. CDVpp can behave as a competitive inhibitor. Alternatively, it can substitute the substrate and get incorporated, leading to chain termination (Andrei & Snoeck, 2010). This has been explained
diagrammatically in Figure 2. Brincidofovir (BCV) is a pro-drug and a lipid conjugate of CDV that resembles a natural lipid. Thus, it enters infected cells by taking on the natural lipid absorption mechanisms (Chimerix, 2021). Following absorption, the lipid molecule is broken down, thereby releasing CDV for additional intracellular kinase phosphorylation to form cidofovir diphosphate, the active form of the drug used. Comparing these two drugs, in contrast to CDV, BCV does not act as a substrate for Organic Anion Transporter 1, which makes BCV less harmful to the kidneys. Therefore, compared to CDV, BCV is safer for the kidneys. CDV is less well tolerated than BCV. BCV is available in oral or suspension form, whereas CDV is in intravenous form. A dosage of 200 mg weekly for two weeks of BCV is recommended in adults weighing ≥ 48 kg, for adults and children weighing from 10 to 48 kg: 4 mg/kg weekly for two weeks are recommended and for children with body weight below 10 kg, 6 mg/kg is recommended weekly for two weeks. The recommended dosage of CDV is 5 mg/kg once weekly for 14 days, followed by 5 mg/kg IV once every other week. Those on BCV may experience minor adverse events such as diarrhoea, nausea, vomiting, and abdominal pain. In contrast, CDV presents side effects such as decreased serum bicarbonate, proteinuria, neutropenia, infection, hypotony of the eye, iritis, uveitis, nephrotoxicity, and fever. BCV is contraindicated in pregnant and lactating women. It may elevate hepatic transaminases and serum bilirubin; therefore, the individual must be assessed for liver function before and after the therapy. On the other hand, CDV may harm kidneys; dose adjustment must be made in case of renal impairment (Das & Hong, 2019; Rizk et al., 2022).
Coming to Trifluridine, there is limited data on managing ocular manifestations of MPXV disease per se (Kaufman et al., 2022). Topical trifluridine eye drops have been approved for other ophthalmological conditions like herpes simplex keratitis and vaccinia. It has also been beneficial against other viruses of the same family in-vitro (Kern, 2003; Yu & Mahendra Raj, 2019). It is being used in MPXV infection also. It is used as a 1% ophthalmic solution. It is administered as a single drop every two hours till re-epithelialisation occurs. Then, it is administered four-hourly. Long-term administration exceeding three weeks is avoided due to fear of toxicity. It is generally well-tolerated. Transient burning and oedema of eyelids are common adverse events (Milligan et al., 2022) (Carmine et al., 1982).

Vaccinia immune globulin (VIG) is prepared from the pooled blood of the recipients of the vaccine for smallpox. The main component is immune globulin G (IgG), which is involved in the human body's physiological response to infection. VIG may prevent extracellular orthopoxvirus from infecting its target cells, limiting the ability of viruses to spread from an extracellular to an intracellular location. It is administered intravenously at 6000 U/kg after symptoms appear. Another dose may be given depending on the clinical profile and treatment response. The dose may be increased to 9000 U/kg in case of lack of response. Headache, nausea, rigors, and dizziness may occur following the administration. It is contraindicated in isolated vaccinia keratitis, a history of anaphylactic response to human globulins, IgA deficiency with antibodies against IgA and a history of IgA hypersensitivity. No contraindications have been reported for this drug; however, it should be used carefully in individuals with renal insufficiency (DRUG MONOGRAPH: VACCINIA IMMUNE GLOBULIN, VIG, 2022; Rizk et al., 2022).
Discussion

In this first systematic review, we report the antiviral treatment of individuals infected with MPXV. A previous study reviewed the quality of the available guidelines (Webb et al., 2022). Many in-vitro and animal-model studies are present on this topic, and we included only reported cases/studies of therapy in humans. However, this review aimed to gather the evidence and compile the available information on the usage of antivirals in human individuals with MPXV infection.

Tecovirimat has shown promising results and has been tested earlier on non-human primates (Berhanu et al., 2015; Russo et al., 2020). It has been conditionally approved for MPXV infection by the Food and Drug Administration (FDA) and the European Medicines Agency (CDC, 2022). It has been beneficial in several cases of progressive MPXV infection among the reported cases. It also did not generate any major signal for adverse events. Hepatic dysfunction was transient, unlike in the case of Brincidofovir, where all three individuals had to discontinue treatment (Adler et al., 2022). The solitary case of death amongst those receiving Tecovirimat was also considered unrelated to the drug. Cidofovir is the next most used drug. Of the four studies, it was only used in two because of the unavailability of Tecovirimat (Mailhe et al., 2022; Moschese et al., 2022). Cidofovir has been well-tolerated in these studies which is in line with findings from other studies where intravenous Cidofovir showed a good tolerability profile when used in different indications (Caruso Brown et al., 2015; Cesaro et al., 2005; Held et al., 2000). The major concern with its use is nephrotoxicity. However, this was fortunately not seen in any of the individuals. Topical
trifluridine has been used as an adjuvant to Tecovirimat in some cases with MPXV–associated ocular lesions (Cash-Goldwasser et al., 2022). Most recovered, and no complications were reported. However, readers should be aware that even in these ocular cases, topical trifluridine has not yet been used as monotherapy.

Given the limited number of individuals in published studies who have received antivirals, there is a need for better-designed studies on the efficacy and safety of antivirals and other drugs in human MPXV disease. The promising results seen with Tecovirimat should be investigated further in well-designed research. An exploration of ClinicalTrials.gov and Cochrane Central Register of Controlled Trials shows a few results. The National Institute of Allergy and Infectious Diseases has sponsored two blinded randomised controlled trials comparing Tecovirimat to a placebo. These studies are underway (NCT05534984, NCT05559099). PLATINUM-CAN seeks to assess Tecovirimat in MPXV infection in Canada and is expected to start recruiting soon (NCT05534165).

The strength of our study is that this is the first systematic review on management, specifically the pharmacological treatment of MPXV infection in humans. All the sparsely available information was compiled. However, the study has a few limitations. Only eighteen studies could be included and were summarised in this review according to the inclusion criteria. Moreover, all were uncontrolled studies. However, no more eligible studies on the usage of antivirals in individuals with MPXV infection are present. Thus, we could not draw enough conclusions to draft guidelines or recommendations. We faced another limitation in not having individual patient data from a few studies. Important data on the use of Tecovirimat and Cidofovir could not be incorporated. We tried our best to use this data, including sending
a mail to the concerned authors, but after failing to retrieve this data, we could not include them in our systematic review. Additionally, as anticipated, the data were not amenable to performing a quantitative synthesis and meta-analysis.

This first systematic review on the usage of antivirals in humans with MPXV infection shows that antivirals - Tecovirimat, Cidofovir, Brincidofovir, Trifluridine, and Vaccinia immune globulin - have been used so far. Among these, Tecovirimat was used most often. It demonstrated promising results in individuals with progressive disease and a better safety profile than some other drugs. The data available is limited, and randomised controlled trials can add valuable evidence.
Contributors

BKP, MAS, and SDV conceptualised and designed the study. MAS, SDV, CC, ST, PS, CC and ST were involved in the screening of articles, assessment of the risk of bias, and data extraction. MAS, BKP, VKC, JAT contributed to the methodology. Software, data analysis and interpretation were done by AP, PD, AM, AJR, RS, ATA, and JAT. Project administration was done by BKP, RS and VKC. Resources were provided by BNK, VKC and RS. The original draft of various sections in the initial phase was contributed by MAS, NA, AP, and BKP. BNK, VKC and JAT provided critical comments and edited the final draft. Each author had access to all the data in the study and provided inputs to the preparation of the final manuscript. All the authors accepted the final version of the manuscript.

Data sharing

All data used in this review were obtained from studies available online. The protocol has been made publicly available at PROSPERO, CRD42022355596.

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Declaration of interests

None of the authors have any competing interests.

Ethical approval

Ethical approval is not required for this study.
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Supplementary

Appendix 1: Search strategy
Appendix 2: Outcomes of search
Appendix 3: PRISMA checklist
References


Table 1: Assessment of risk of bias of the included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Is the case definition adequate?</th>
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<th>Exclusion of other important diagnoses</th>
<th>Presence of all important data</th>
<th>Ascertainment of outcome</th>
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<td>Moderate</td>
</tr>
<tr>
<td>Mailhe et al.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
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<tr>
<td>Peters et al.</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
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<td>Shaw et al.</td>
<td>Yes</td>
<td>No</td>
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<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Mbrenge et al.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Hernandez et al.</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Moderate</td>
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<td>Cash-Goldwasser et al.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Raccagni et al.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
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<tr>
<td>Pastula et al.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
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<tr>
<td>Viguier et al.</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Moderate</td>
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<td>Hermanussen et al.</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Scandale et al.</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Moderate</td>
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</table>

* This study focused more on the public health response, rather than the management of the individual patient.
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study design</th>
<th>Antiviral</th>
<th>Dose</th>
<th>Patients</th>
<th>Clinical features (apart from MPXV lesions)</th>
<th>MPXV lesions</th>
<th>Resolution</th>
<th>Complications during treatment</th>
<th>Important details</th>
<th>Duration of hospitalisation</th>
<th>Age</th>
<th>Sex</th>
<th>Comorbidities &amp; cofactors</th>
<th>Concomitant medications</th>
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<tbody>
<tr>
<td>Adler et al., (2022)</td>
<td>USA</td>
<td>R</td>
<td>BCV</td>
<td>200mg once weekly orally</td>
<td>3</td>
<td>fever, coryzal illness, lymphadenopathy</td>
<td>Face, scalp, trunk, limbs, palms, glassy penis, soles, hands (necrotic nail bed), labia majora, penile shaft, legs and scrotum</td>
<td>Resolved</td>
<td>all had elevated transaminase and course could not be completed</td>
<td>In one patient, all skin lesions and viremia resolved except ulcerative genital lesions that were PCR positive for monkeypox virus and took longer to resolve</td>
<td>20, 21, 28</td>
<td>30 - 40</td>
<td>2 M, 1 F</td>
<td>bacterial conjunctivitis</td>
<td>antibiotics, opioid, angesics, neuropathic angesics</td>
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<tr>
<td>Rao et al., (2022)</td>
<td>USA</td>
<td>C/R</td>
<td>TPO XX</td>
<td>600 mg twice daily orally</td>
<td>1</td>
<td>fever, G6 upset, cough, fatigue</td>
<td>Face, trunk, arms, and hands</td>
<td>Resolved</td>
<td>-</td>
<td>No new lesions developed after 24 hours, and URT swab PCR came negative 48 hours later</td>
<td>7</td>
<td>30 - 40</td>
<td>F</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Manas et al., (2022)</td>
<td>USA</td>
<td>C/S</td>
<td>TPO XX</td>
<td>600 mg twice daily orally</td>
<td>3</td>
<td>fever, malaise, chills, tonsillar pain with odynophagia</td>
<td>Face, oropharynx, hands, feet (including the soles), skin of palms and lower eyelid</td>
<td>Resolved in almost all patients (only 1 out of 2 still had lesions at the last date of follow up mentioned day 7, (4))</td>
<td>All ALT rose &gt; 2 times UNL and resolved without discontinuation of drug in one, loose stool after each dose</td>
<td>2, 3, not mentioned for third</td>
<td>20, 30, 42, 50, 51</td>
<td>M</td>
<td>1 had gonococcal urethritis, 1 had HIV</td>
<td>Prophylactic HIV treatment</td>
<td></td>
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<tr>
<td>Agnera et al., (2022)</td>
<td>USA</td>
<td>C/R</td>
<td>TPO XX</td>
<td>200 mg twice daily litorially post discharge</td>
<td>1</td>
<td>sore throat, tongue swelling, burning sensation in mouth, odynophagia, lymphadenopathy</td>
<td>Mouth, tongue, and face</td>
<td>Resolving at discharge</td>
<td>Lesions were aggravating during hospitalization</td>
<td>TPOXX was started on day 3 of hospitalization, and patient started improving two days later</td>
<td>2</td>
<td>26</td>
<td>M</td>
<td>syphilis</td>
<td>temovir, acetate, stavudine, lamivudine, tenofovir/ emtricitabine for HIV pre-exposure prophylaxis (PrEP)</td>
</tr>
<tr>
<td>Desai et al., (2022)</td>
<td>USA</td>
<td>aE</td>
<td>TPO XX</td>
<td>Weight-based, twice or thrice daily orally</td>
<td>25</td>
<td>fever, lymphadenopathy, headache, fatigue, sore throat, chills, backache, myalgia, nausea, and diarrhea</td>
<td>Pernaral, genital, chest, eyelid, face, neck, arms, buttocks, back, thigh, waist, shin, throat, abdomen and forearms. I had all over the body</td>
<td>Resolved in 23 to 28 days, only one of the two developed new lesions</td>
<td>fatigue, headache, nausea, itching, and diarrhea</td>
<td>Outpatients were evaluated on day 7, 14, 21; only one of the other two developed new lesions</td>
<td>26 - 76 (mean of 40.7)</td>
<td>M</td>
<td>9 had HIV</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>C/ S</td>
<td>CDV</td>
<td>CDV</td>
<td>Dose</td>
<td>cvs</td>
<td>Symptoms</td>
<td>CDV</td>
<td>Age</td>
<td>Sex</td>
<td>Cause of Death</td>
<td>Other Medical Information</td>
<td></td>
<td></td>
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<tr>
<td>Lucar et al., (2022)</td>
<td>Italy</td>
<td>C/ S</td>
<td>CDV</td>
<td>CDV</td>
<td>5 mg/kg daily for 1 and 7 days</td>
<td></td>
<td>Fever, chills, sweating, lymphadenopathy, nausea, vomiting, diarrhea, rash</td>
<td></td>
<td>26</td>
<td>M</td>
<td></td>
<td>Malaria (confirmed by rapid diagnostic test)</td>
<td></td>
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<tr>
<td>Mailhe et al., (2022)</td>
<td>USA</td>
<td>C/ S</td>
<td>TPO</td>
<td>XX</td>
<td>600 mg twice daily orally</td>
<td></td>
<td>Fever, proctitis, lymphadenopathy, nausea, vomiting, diarrhea, rash, fatigue, rectal bleeding</td>
<td></td>
<td>40</td>
<td>M</td>
<td></td>
<td>HIV (confirmed by rapid diagnostic test)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Peters et al., (2022)</td>
<td>USA</td>
<td>C/ S</td>
<td>TPO</td>
<td>XX</td>
<td>-</td>
<td></td>
<td>Fever, myalgia, fatigue, tongue, fever, fatigue</td>
<td></td>
<td>38</td>
<td>M</td>
<td></td>
<td>Dengue fever (confirmed by rapid diagnostic test)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Shaw et al., (2022)</td>
<td>USA</td>
<td>C/ S</td>
<td>TPO</td>
<td>XX</td>
<td>600 mg twice daily orally for 14 days</td>
<td></td>
<td>Fever, chills, myalgia, fatigue, fever, back pain, and upper respiratory tract</td>
<td></td>
<td>23</td>
<td>M</td>
<td></td>
<td>Dengue fever (confirmed by rapid diagnostic test)</td>
<td></td>
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<td></td>
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<tr>
<td>Minega et al., (2022)</td>
<td>Central African Republic</td>
<td>C/ S</td>
<td>TPO</td>
<td>XX</td>
<td>-</td>
<td></td>
<td>Muscle pain, headache, lymphadenopathy, bleeding, fever, back pain, and upper respiratory tract</td>
<td></td>
<td>3</td>
<td>M</td>
<td></td>
<td>Dengue fever (confirmed by rapid diagnostic test)</td>
<td></td>
<td></td>
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<tr>
<td>Hernandez et al. (2022)</td>
<td>USA</td>
<td>C/ R</td>
<td>TPO XX</td>
<td>600 mg twice daily orally</td>
<td>1</td>
<td>fever, chills, headache, sore throat, generalised malaise, and rectal pain and discomfort</td>
<td>pulstules on the trunk, upper and lower extremities, groin, and perianal region</td>
<td>Resolved</td>
<td>-</td>
<td>37</td>
<td>M</td>
<td>metastatic Kaposis sarcoma and hypernephroma. HIV and secondary syphilis. hyerete mon.</td>
<td>etinichtocabine-tenofovir, doravirine, darunavir-cobicistat, and hydrochloro thiouride.</td>
<td></td>
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</tr>
<tr>
<td>Caso-Goldberg et al. (2022)</td>
<td>USA</td>
<td>C/ S</td>
<td>TPO XX</td>
<td>-</td>
<td>5</td>
<td>eye pain, itching, redness, swelling, discharge, foreign body sensation, photosensitivity, vision changes, rectal pain</td>
<td>Eye, facial skin, scalp, chest, abdomen, n, wrist, rectum, penis, vagina</td>
<td>Resolved in 4, one is expeirencing waxing and waning of symptoms.</td>
<td>Four patients were hospitalized, and one experienced marked vision impairment.</td>
<td>10,3,5, One patient was still admitted. One patient still admitted (day 14)</td>
<td>20</td>
<td>29, 30, 39</td>
<td>4</td>
<td>M</td>
<td>1</td>
</tr>
<tr>
<td><em>FID</em></td>
<td>-</td>
<td>48</td>
<td>eye pain, itching, redness, swelling, discharge, foreign body sensation, photosensitivity, vision changes</td>
<td>Eye, facial skin, scalp, chest, abdomen, n, wrist, rectum, penis, vagina</td>
<td>Resolved in 3, one is experiencing waxing and waning of symptoms.</td>
<td>All four patients were hospitalized, and one experienced marked vision impairment.</td>
<td>10,3,5, One patient is still admitted (day 14)</td>
<td>20</td>
<td>29, 30, 39</td>
<td>2</td>
<td>M</td>
<td>1</td>
<td>F</td>
<td>topical povidone iodine, anti retroviral therapy, antibiotics</td>
<td></td>
</tr>
<tr>
<td>Raccagni et al. (2022)</td>
<td>Italy</td>
<td>C/ S</td>
<td>CDV</td>
<td>5 mg/kg day single dose</td>
<td>4</td>
<td>aphthae, dysphagia, genital papulopapillomatosis</td>
<td>Erythema, laryngitis, tonsillitis, genitai, rectal, ocular</td>
<td>Resolved</td>
<td>-</td>
<td>8, 3, 4, 3</td>
<td>36, 36, 37, 53</td>
<td>2</td>
<td>of 4 had HIV disease. Crohn's disease in 1. Chronic gastritis in 1</td>
<td>antiinterferon 1 therapy, sulfasalazin e, testosterone, probenecid</td>
<td></td>
</tr>
<tr>
<td>Pastula et al. (2022)</td>
<td>USA</td>
<td>C/ S</td>
<td>TPO XX</td>
<td>-</td>
<td>2</td>
<td>fever, chills, malaise, hemiparesis, paraparesis, urinary retention, bladder and bowel incontinence, priapism, myalgia</td>
<td>face</td>
<td>Resolved</td>
<td>-</td>
<td>3B</td>
<td>39</td>
<td>Several tests including those for chlamydia, HIV, gonococcus, syphilis were negative</td>
<td>methyprednisolone, muscle relaxant, IV immunoglobulin, penicillin, plasma exchange, rituximab</td>
<td></td>
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<tr>
<td>Viguier et al., (2022)</td>
<td>France</td>
<td>C/ R</td>
<td>TPO XX</td>
<td>600 mg twice daily orally</td>
<td>1</td>
<td>fever, asthenia, shivers, watery diarrhea</td>
<td>face, scalp, trunk, limbs, and anal margins</td>
<td>Resolved transient rise in ALT (acme 97 IU/l) and AST activities (acme 86 IU/l)</td>
<td>His clinical condition deteriorated for 37 days, with fever, skin lesions and diarrhea before going to the infectious diseases department, where his severe, protracted infection was treated with TPOXX for 14 days</td>
<td>14</td>
<td>M</td>
<td>HIV, latent syphilis, scalp superinfections with <em>Klebsiella aerogenes</em> and <em>Staphylococcus lugdunensis</em></td>
<td>Cotrimoxazole, benzathine benzylpenicillin, antiretroviral therapy</td>
<td></td>
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<td>Hermussen et al., (2022)</td>
<td>Germany</td>
<td>C/ S</td>
<td>TPO XX</td>
<td>1200 mg daily</td>
<td>3</td>
<td>lymphadenitis, fever, malaise, fatigue</td>
<td>petus, anus, face</td>
<td>Resolved transient increase of the γ-glutamyltransferase in 1</td>
<td>Overall, the antiviral treatment with tecovirimat was well tolerated with no significant side effects</td>
<td>3</td>
<td>M</td>
<td>ulcerative colitis, syphilis, HIV positive in 1</td>
<td>Vedolizumab, HIV pre-exposure prophylaxis, penicillin</td>
<td></td>
<td></td>
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<tr>
<td>Scandale et al., (2022)</td>
<td>Italy</td>
<td>C/ R</td>
<td>CDV</td>
<td>5 mg/kg day single dose</td>
<td>1</td>
<td>ocular pain, photophobia, generalised lymphadenopathy, fever</td>
<td>conjunctivitis, oropharynx, skin, rectum</td>
<td>Resolved - unilateral ocular inflammation with multiple papules at conjunctiva, the fornix, and at the temporal limbus</td>
<td>-</td>
<td>35</td>
<td>M</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 1: Summary of the search process, screening, and selection of studies
Fig 2: Mechanism of action of Cidofovir

CDV: Cidofovir; CDV: Cidofovir monophosphoryl; CDVpp: Cidofovir diphosphoryl; BCV (CDV + L): Brincidofovir (as Cidofovir conjugated to a lipid molecule)
Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: