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Research Article

Is Treatment with Tecovirimat, Brincidofovir or Cidofovir Really Effective in Cases of Monkeypox in Humans?

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Abstract

Monkeypox, also known as MPOX, is a zoonotic disease caused by a double-stranded DNA virus belonging to the *Orthopoxvirus* genus of the *Poxviridae* family. Two main endemic clades are recognized in Africa: clade I, associated with the Congo Basin, and clade IIa, predominant in West Africa. In 2022, a global outbreak of clade IIb led the World Health Organization (WHO) to declare a public health emergency, which was lifted in May 2023. However, in August 2024, the emergency was reinstated following a resurgence of the disease in Africa, driven by the emergence of a new clade Ib strain, whose transmission occurs primarily through sexual contact.

The incubation period for the virus ranges from 7 to 21 days, and symptoms typically last two to five weeks. The clinical picture begins with fever, myalgia, headache, and lymphadenopathy, followed by a skin rash that progresses through five phases: macular, papular, vesicular, pustular, and crusted. Although the infection is self-limited in most cases, immunosuppressed individuals are at greater risk of serious complications.

For the management of severe cases of MPOX, the U.S. Food and Drug Administration (FDA) has approved three antivirals: tecovirimat and brincidofovir, both originally approved for the treatment of smallpox, and cidofovir, used for cytomegalovirus retinitis in patients with AIDS, but with proven efficacy against MPOX.

Tecovirimat showed moderate-to-high effectiveness and a favorable safety profile but failed in severely immunocompromised patients. Brincidofovir had variable effectiveness and high hepatotoxicity, often leading to treatment discontinuation. Cidofovir achieved 100% effectiveness but failed in severe immunocompromised cases, with nephrotoxicity risks with high mortality. Evidence is limited by low levels, high risk of bias, and heterogeneous data.

Current antivirals are inadequate for severe cases in immunocompromised patients. Tecovirimat is optimal for non-immunocompromised patients, while brincidofovir and cidofovir require caution due to toxicity. Randomized controlled trials, standardized reporting, and combination therapies are needed to improve outcomes.

Introduction

Monkeypox virus is a double-stranded DNA virus belonging to the genus *Orthopoxvirus*, within the family *Poxviridae*. Two main clades are recognized: clade I, endemic to the Congo Basin, and clade IIa, associated with West Africa [1]. The global outbreak recorded in 2022 corresponded to clade IIb, leading the World

Health Organization (WHO) to declare monkeypox a Public Health Emergency of International Concern (PHEIC) on July 23, 2022. However, due to the decrease in the spread of cases, this measure was lifted in May 2023. Subsequently, in August 2024, the WHO reactivated the PHEIC declaration following the resurgence of the disease in the Democratic Republic of the Congo (DRC) and other African countries, associated with a new strain of clade Ib, whose transmission appears to occur mainly through sexual contact [2].

The incubation period of the virus ranges from 7 to 21 days, and symptoms can last from two to five weeks. The clinical presentation begins with fever, myalgia, headache, backache, odynophagia, and lymphadenopathy, followed by the appearance of a skin rash that progresses through five phases: macular, papular, vesicular, pustular, and crusted. Patients are considered contagious until all skin lesions have healed [3]. Although most cases are self-limited, severe manifestations have been observed in some individuals, especially in immunosuppressed individuals. During the 2022 outbreak, the case fatality rate was less than 1%; however, some patients required hospitalization due to complications such as persistent rashes, coalescing lesions, edema, secondary bacterial infections, and multiorgan involvement [4].

Approval and Use of Tecovirimat, Brincidofovir and Cidofovir

The FDA approved the use of TPOXX (tecovirimat) as the first drug specifically indicated for the treatment of human smallpox under the Animal Rule, which allows for validation of the efficacy of drugs measured in preclinical animal studies [5]. In emergency situations or when other treatments are ineffective, the CDC has enabled the Expanded Access Investigational New Drug (EA-IND) protocol to facilitate its use in outbreaks.

In 2021, the FDA approved Tembexa (brincidofovir) for the treatment of smallpox in children, adults, and newborns under the Animal Rule. Although its safety and efficacy in TPOXX have not been confirmed, the drug is used in patients who do not respond to tecovirimat or who have contraindications to its use [6].

On the other hand, cidofovir, although approved to treat cytomegalovirus retinitis in patients with AIDS, has not been authorized for the treatment of Orthopoxvirus infections such as Mpox, although it has demonstrated efficacy in animal models [5].

Mechanism of Action of Antivirals

Tecovirimat: inhibits the viral protein p37, essential for the formation of extracellular virion envelopes, preventing virus release from infected cells [7].

Brincidofovir: is a prodrug of cidofovir that, once inside host cells, is converted into active cidofovir. This metabolite inhibits viral DNA synthesis, thus blocking viral replication [7].

Cidofovir: acts as a nucleotide analogue, interfering with viral DNA chain elongation. Although it has demonstrated efficacy in experimental models, its effectiveness against mpox has not yet been confirmed in humans [7].

Effectiveness and Safety of Antivirals

Tecovirimat Effectiveness: Tecovirimat has demonstrated high efficacy in both preclinical and clinical studies, demonstrating a significant reduction in viral load and skin lesions associated with the infection. In animal models, particularly in cynomolgus monkeys, 100% survival has been observed in treated individuals [8,9]. In humans, the recommended dose is 400 mg/day, and recent clinical studies have confirmed its effectiveness in patients with resistance to other antivirals [10].

Tecovirimat Safety: The safety of tecovirimat is generally considered favorable, as reported adverse effects are infrequent and mild, primarily gastrointestinal symptoms and transient elevations of liver enzymes. However, its use is contraindicated in patients with severe renal impairment, and caution is recommended with rapid intravenous administration, as it may be associated with transient neurological events, such as ataxia and lethargy [5,10].

Brincidofovir Effectiveness: Brincidofovir has demonstrated efficacy in animal models against Orthopoxvirus infections. In human clinical studies, administration of 200 mg once weekly for three weeks was generally well tolerated, with only mild and transient adverse effects reported [11]. Furthermore, the combination of brincidofovir with tecovirimat has demonstrated greater therapeutic efficacy compared to the use of each drug individually [11].

Brincidofovir Safety: Although brincidofovir has lower nephrotoxicity compared to cidofovir, its use may be associated with elevated liver transaminases. Therefore, close monitoring of liver function is recommended throughout treatment [12].

Cidofovir Effectiveness: Cidofovir has demonstrated efficacy in preclinical studies against Orthopoxvirus infections. However, its use in cases of MPOX should be reserved for severe cases or when other treatments are ineffective, due to its high nephrotoxicity [13].

Cidofovir Safety: The main limitation of cidofovir is its high nephrotoxicity, which requires preventive measures such as concomitant administration of probenecid, as well as rigorous monitoring of renal function during treatment [14].

Materials and Methods

Study Location and Period

This study was conducted at the Faculty of Veterinary and Animal Sciences of the University of Chile, located in the municipality of La Pintana, Metropolitan Region. Bibliographic information was collected during the second half of 2024, while data analysis was conducted in the first half of 2025.

Systematic Review Methodology

This systematic review was conducted in accordance with the 2020 PRISMA declaration, ensuring transparency and scientific rigor [15]. The protocol included the following methodological components, adapted to the scope and available resources:

Literature Search: Specific search equations were designed, and academic search engines were used to identify relevant studies.

Eligibility Criteria: Precise criteria were established for the inclusion of primary and secondary studies, considering their relevance and methodological design.

Article Selection: Studies were selected by applying the eligibility criteria, reviewing titles, abstracts, and full texts.

Quality Assessment: The quality of the articles was assessed using a scale of 0 to 6, based on the clarity of the outcomes, the specificity of the data, and the organization of the information (Tables 1 and 3).

Risk of bias assessment: Risk of bias was analyzed using criteria tailored to the type of study (primary or secondary), including aspects such as randomization, blinding, sample size, and data completeness (Table 2).

Clinical Evidence Assessment: The effectiveness and safety of antivirals (tecovirimat, brincidofovir, and cidofovir) were examined, considering variables such as patient number, immunological status, clinical resolution, hospitalization, mortality, adverse events, toxicity, and treatment discontinuation (Tables 4- 6).

Table 1: Summary of academic studies by design and quality.

Study	(Scientific Journal)	Quartile	Impact Factor	Study Design	Study Type Level of Evidence	(Oxford) Score	Quality
Alameer et al., 2024	Int J Infect Dis	Q1	4.3	Case study	Primary	4	4/6
Braddick et al., 2024	Curr Opin Infect Dis	Q1	4.0	Narrative review	Secondary	5	6/6
Bruno et al., 2023.	Life	Q1	3.4	Narrative review	Secondary	5	6/6
Carrubba et al., 2023.	Lancet Infect Dis	Q1	31.0	Case study	Primary	4	5/6
Fox et al., 2023.	Cochrane Database Syst Rev	Q1	9.4	Systematic review	Secondary	1	6/6
Ganesan et al., 2024.	Naunyn Schmiedebergs Arch Pharmacol	Q2	3.1	Narrative review	Secondary	5	6/6
Joseph et al., 2023.	Oral Surg Oral Med Oral Pathol Oral Radiol	Q2	1.9	Scope Review	Secondary	5	4/6
Li et al., 2023	J Infect Dis	Q2	4.5	Systematic review and comparative analysis.	Secondary	2	4/6
Martinez et al. 2023	Vaccines	Q2	3.4	case study	Primary	4	5/6
Mclean et al., 2023.	Ann Intern Med	Q1	15.2	Retrospective cohorte study	Primary	3	5/6
Ortiz-Saavedra et al. 2022	Trop Med Infect Dis	Q2	2.6	Scope Review	Secondary	5	4/6
Sánchez Clemente et al., 2024.	Lancet Glob Health	Q1	18.0	Systematic review and meta-analysis.	Secundario	1	6/6
Shabil et al., 2024.	J Med Virol	Q1	4.6	Systematic review	Secundario	2	6/6
Shamim et al., 2023.	Int J Infect Dis	Q1	4.3	Systematic review	Secundario	2	4/6
Siegrist et al., 2023.	Clin Infect Dis	Q1	7.3	Narrative review	Secundario	5	4/6
Stafford et al. 2023	Lancet Infect Dis	Q1	31.0	case study	Primario	4	5/6

Note*:

Impact factor and quartile based on JCR 2024 for each journal.

Study type: Primary (original data such as cases or cohorts) or secondary (literature reviews).

Level of evidence (Oxford): Based on the OCEBM criteria (2025), where 1 is the highest level (systematic reviews of controlled trials) and 5 the lowest (expert opinion)

Table 2: Assessment of risk of bias in selected studies.

Study	Randomization	Blinding	Sample Size	Completeness	Risk
Alameer et al., 2024	Not applicable	Not applicable	Inadequate (n=2)	Adequate	High
Braddick et al., 2024	Not applicable	Not applicable	Adequate (n=260)	Adequate	Moderate
Bruno et al., 2023	Not applicable	Not applicable	Inadequate (n=24)	Adequate	High
Carrubba et al., 2023	Not applicable	Not applicable	Inadequate o (n=2)	Adequate	High
Fox et al., 2023	yes	yes	Adequate (n=597)	Adequate	low
Ganesan et al., 2024	Not applicable	Not applicable	Adequate (n=145)	Adequate	Moderate
Joseph et al., 2023	Not applicable	Not applicable	Variable	Adequate	High
Li et al., 2023	Not applicable	Not applicable	Variable	Adequate	High
Martinez et al., 2023	Not applicable	Not applicable	Inadequate (n=1)	Adequate	High
Mclean et al., 2023	Not applicable	Not applicable	Adequate (n=196)	Adequate	Moderate
Ortiz-Saavedra et al., 2022	Not applicable	Not applicable	Variable	Adequate	High
Sanchez Clemente et al., 2024	yes	yes	Adequate (n=36)	Adequate	low
Shabil et al., 2024	yes	yes	Adequate (n=1202)	Adequate	low
Shamim et al., 2023	Not applicable	Not applicable	Variable	Adequate	High
Siegrist et al., 2023	Not applicable	Not applicable	Inadequate (n=5)	Adequate	High
Stafford et al., 2023	Not applicable	Not applicable	Inadequate (n=1)	Adequate	High

Table 3: Evaluation of the presentation of results in the selected studies.

Study	Clear Definition	Detailed Data	Organization	Total
Alameer et al., 2024	2	1	1	4/6
Braddick et al, 2024	2	2	2	6/6
Bruno et al., 2023	2	2	2	6/6
Carrubba et al., 2023	2	2	1	5/6
Fox et al., 2023	2	2	2	6/6
Ganesan et al., 2024	2	2	2	6/6
Joseph et al., 2023	2	1	1	4/6
Li et al., 2023	2	1	1	4/6
Martinez et al., 2023	2	2	1	5/6
Mclean et al., 2023	2	2	1	5/6
Ortiz-Saavedra et al., 2022	2	1	1	4/6
Sanchez Clemente et al., 2024	2	2	2	6/6
Shabil et al., 2024	2	2	2	6/6
Shamim et al., 2023	2	1	1	4/6
Siegrist et al., 2023	2	1	1	4/6
Stafford et al., 2023	2	2	1	5/6

Note*: Detailed data limited by narrative approach under review [34-38].

Table 4: Clinical evidence of effectiveness and safety for tecovirimat in selected studies.

Study	n	Immune Status	Hospitalization	Mortality	Adverse Events	Quality	Risk of Bias
Braddick et al., 2024	311	Immunoincompetent (5), Unspecified (306)	Not reported in days, according to article	0/311	Gastrointestinal	6/6	Moderate
Bruno et al., 2023	243	Immunoincompetent (27), Unspecified (216)	4.5 days (median, Higgins), not reported in days for others, according to article	10/243	Gastrointestinal	6/6	high
Carrubba et al., 2023	2	Inmunoincompetent	Not reported in days, implied by serious cases, according to article	2/2	Not reported	5/6	high
Fox et al., 2023	355	Unspecified, 46.3% with HIV, not broken down by CD4	10 days (Adler, H.), not reported in days for others, according to article	1/355	Mild (11/340), mental health (2/341), liver enzymes (1/341), anemia (1/14)	6/6	low
Ganesan et al., 2024	989	Immunoincompetent (57), Unspecified (932)	4.5 days (median, Higgins), 2 days (median, Mitjà), not reported in days for others, according to article	10/989	Gastrointestinal, increased ALT (1/3)	6/6	Moderate
Joseph et al., 2023	3	Unspecified	Not reported in days, inferred by severe cases, according to article	0/3	Not reported	4/6	high
Li et al., 2023	37	Unspecified (36, 37.65% with HIV, not broken down by CD4), Immunoincompetent (1, AIDS)	10 days (Adler, H.), not reported in days for others, according to article	0/37	Fatigue (8), headache (6), nausea (4), diarrhea (2), itching (2), loose stools (1)	4/6	high
Martinez et al., 2023	1	Immunoincompetent	4 days, 5 days, not reported in days for third admission, according to article	0/1	Not reported	5/6	high
Mclean et al., 2023	154	Mixed, 72 with HIV, 4 immunoincompetent with CD4 < 200	Not reported in days, according to article	0/154	Serious (4/196), non-serious (22%)	5/6	Moderate
Ortiz-Saavedra et al., 2022	41	Unspecified, 35.7% with HIV, not broken down by CD4	Not reported in days, according to article	0/41	Fatigue (7), headache (5), nausea (4), diarrhea (2), itching (2), loose stools (1)	4/6	high
Sanchez Clemente et al., 2024	33	Immunoincompetent (9), Unspecified (24)	4.5 days (median, Higgins), 2 days (median, Hennessee), not reported in days for others, according to article	0/33	Not reported	6/6	low
Shabil et al., 2024	1189	Immunoincompetent (86), Not specified (1103), subpopulation in PALM007: children and adults, not broken down	7 days (median, Desai), 5 days (median, Fink), 4 days (median, O'Laughlin), not reported in days for others, according to article	1.7%-46%	Fatigue (5.8%-28%), headache (13%-20%), nausea (4.3%-16%), psychiatric (1 case)	6/6	low
Shamim et al., 2023	61	Unspecified, 35.7% with HIV, not broken down by CD4	Not reported in days, according to article	1/61	Fatigue (8), headache (5), nausea (4), diarrhea (2), itching (2), loose stools (1), transaminitis (5)	4/6	high
Siegrist et al., 2023	2	not specified	1/2 (10 days)	0/2	Not reported	4/6	high
Stafford et al., 2023	1	Immunoincompetent	52 days	0/1		5/6	high

Note*: Immunologic status: Immunoincompetent (CD4 <200 or AIDS); mixed includes controlled HIV [1, 13, 23, 24, 25, 26, 32, 33, 34, 35, 36].

Table 5: Clinical evidence of effectiveness and safety for brincidofovir in selected studies.

Study	n	Immune Status	Hospitalization	Mortality	Adverse Events	Quality	Risk of Bias
Alameer et al., 2024	2	Immunoincompetent (kidney transplant, unspecified CD4)	14 days (Case 1), not reported in days (Case 2), according to article	0/2	Abdominal pain, nausea (1/2)	4/6	high
Braddick et al., 2024	3	Not specified, according to *Adler et al.,* 2022	Not reported in days, according to article	0/3	Transaminitis (3/3)	6/6	Moderate
Bruno et al., 2023	10	Inmunoincompetente (7, Mitjà), No especificada (3, Adler)	Not reported in days, according to article	7/10	Transaminitis (3/3)	6/6	high
Fox et al., 2023	3	Not specified, according to *Adler et al.,* 2022	26, 27, 35 days	0/3	Elevated ALT (3/3), mental health (2/3)	6/6	low
Ganesan et al., 2024	11	Immunoincompetent (8, Alameer et al., 2024, Mitjà), Unspecified (3, Adler)	Not reported in days, according to article	7/11	Transaminitis (3/3)	6/6	Moderate
Li et al., 2023	3	Not specified, according to *Adler et al.,* 2022	26, 27, 35 days	0/3	Transaminitis (3/3)	4/6	high
Ortiz-Saavedra et al., 2022	3	Unspecified, 35.7% with HIV, not broken down by CD4	Not reported in days, according to article	0/3	Transaminitis (3), nausea (1), abdominal discomfort (1)	4/6	high
Shamim et al., 2023	3	Unspecified, 35.7% with HIV, not broken down by CD4	Not reported in days, according to article	0/3	Transaminitis (3), conjunctivitis (2), abscess (1), neuropsychiatric symptoms (1)	4/6	high
Siegrist et al., 2023	3	Unspecified	Not reported in days, according to article	0/3	Not reported	4/6	high

Note*: Immune status: Immunoincompetent (kidney transplant, unspecified CD4) [38]; Immunoincompetent [7,24,25]; Unspecified, 35.7% with HIV [36,37].

Table 6: Clinical evidence of effectiveness and safety for cidofovir in selected studies.

Studio	n	Immune Status	Hospitalization	Mortality	Adverse Events	Quality	Risk of Bias
Braddick et al., 2024	4	not specified	Not reported in days, according to article	0/4	Not reported	6/6	Moderate
Carrubba et al., 2023	1	Immunoincompetent	Not reported in days, implicit for case 2, according to article	1/1	Not reported	5/6	high
Ganesan et al., 2024	404	Immunoincompetent (49), Unspecified (355)	8 days (Moschese), not reported in days for others, according to article	7/404	Aumento de ALT (1/1)	6/6	Moderate
Li et al., 2023	12	Unspecified, 37.65% with HIV, not broken down by CD4	Not reported in days, according to article	0/12	Not reported	4/6	high
Martinez et al., 2023	1	Immunoincompetent	4 days, 5 days, not reported in days for third admission, according to article	0/1	Not reported	5/6	high
Ortiz-Saavedra et al., 2022	20	Unspecified, 35.7% with HIV, not broken down by CD4	Not reported in days, according to article	0/20	Not reported	4/6	high
Sanchez Clemente et al., 2024	1	not specified	Not reported in days, according to article	0/1	Not reported	6/6	low

Shamim et al., 2023	7	Unspecified, 35.7% with HIV, not broken down by CD4	Not reported in days, according to article	0/7	Not reported	4/6	high
Stafford et al., 2023	1	Immunoincompetent	52 days	0/1	Not reported	5/6	high

Note*:
Stable kidney function [13].
Immune status: Immunocompetent (CD4 <200 or AIDS) [13, 25, 31, 32].

Adverse events: Minimal, hepatic in a few cases [25].

Information Sources and Databases

The information was obtained from specialized bibliographic sources, including books, indexed scientific journals, institutional repositories, and undergraduate and graduate theses from national and international universities involved in the study of mpox. Various scientific databases and platforms were consulted, including the Cochrane Library, PubMed, ScienceDirect, the International Committee on Taxonomy of Viruses (ICTV), SciELO, and Google Scholar. The free software Mendeley was used as a bibliographic reference manager for document management, organization, and analysis.

Search Strategy

Keywords and Descriptors: The following keywords were defined, extracted from the search equations: Tecovirimat, Brincidofovir, Cidofovir, Severe Mpox, Safety, Clinical Effectiveness, Randomized Controlled Trials, Double-Blind Method, Clinical Trials, Prospective Studies, Retrospective Studies, Case Reports, and Expert Testimony.

Boolean Operators: Boolean operators were used to optimize searches: AND was used to combine related descriptors within each search equation, while OR allowed for the inclusion of equivalent or synonymous descriptors.

Search Equations

The following eight systematic search equations were applied:

1. (Tecovirimat OR Brincidofovir OR Cidofovir) AND Safety AND Severe Mpox AND (Randomized Controlled Trials OR Double-Blind Method OR Clinical Trials OR Prospective Studies)
2. (Tecovirimat OR Brincidofovir OR Cidofovir) AND Safety AND Severe Mpox AND Retrospective Studies
3. (Tecovirimat OR Brincidofovir OR Cidofovir) AND Safety AND Severe Mpox AND Case Report.
4. (Tecovirimat OR Brincidofovir OR Cidofovir) AND Safety AND Severe Mpox AND Expert Testimony
5. (Tecovirimat OR Brincidofovir OR Cidofovir) AND Clinical Efficacy AND Severe Mpox AND (Randomized Controlled Trials OR Double-Blind Method OR Clinical Trials OR Prospective Studies)
6. (Tecovirimat OR Brincidofovir OR Cidofovir) AND Clinical Efficacy AND Severe Mpox AND Retrospective Studies
7. (Tecovirimat OR Brincidofovir OR Cidofovir) AND Clinical Efficacy AND Severe Mpox AND Case Report
8. (Tecovirimat OR Brincidofovir OR Cidofovir) AND Clinical Efficacy AND Severe Mpox AND Expert Testimony

Eligibility Criteria

Inclusion Criteria

Studies that met the following criteria were included:

a. Studies conducted in humans with a confirmed diagnosis of severe monkeypox.

b. Publications in English or Spanish between 2014 and 2024, with the exception of some references considered essential due to a lack of information or because they contain concepts that are still current.

c. Quantitative or qualitative information on the clinical effectiveness (symptom resolution, reduction in hospitalizations, mortality) or pharmacological safety (adverse events, toxicity, treatment discontinuation) of tecovirimat, brincidofovir, or cidofovir.

d. Valid methodological designs, including controlled clinical trials, observational studies, case series, systematic reviews with empirical data, and evidence-based clinical guidelines.

e. Publications in Q1/Q2 indexed journals (JCR) or documents from recognized institutional sources, such as the WHO or the CDC.

Exclusion Criteria

The following studies were excluded:

a. Duplicate research.

b. Publications unrelated to the study topic.

c. Studies that do not provide specific data on clinical effectiveness or pharmacological safety.

d. Publications in languages other than English or Spanish.

e. Studies prior to 2014 that have been superseded by more recent evidence.

f. Research with preliminary or incomplete results.

Operational Definition of Severe Monkeypox

Severe monkeypox was defined as cases that presented any of the following characteristics:

a. Between 50 and 100 extensive or confluent skin lesions.

b. Significant mucosal involvement (oral, ocular, or anogenital).

c. Severe systemic complications, such as pneumonia, encephalitis, or sepsis.

d. Documented immunosuppression (e.g., HIV infection with a CD4 count <200 cells/mm^3) or the development of severe complications in immunocompetent individuals.

This definition was based on guidelines from the WHO (2022, 2024), the CDC (2023), the European Society for Clinical Microbiology and Infectious Diseases (2022), as well others studies [16,17].

Definitions of Main Variables

Clinical Effectiveness

Clinical effectiveness was defined as therapeutic success under real-life conditions, assessed using the criteria as: complete resolution of symptoms, reduction in length of hospital stay and reduction in mortality [18,19].

Pharmacological Safety

It was characterized by the absence of unacceptable adverse effects, assessed by frequency and severity of adverse events, specific toxicity (renal, hepatic, hematological) and discontinuation of treatment due to adverse effects [20-22].

Study Selection

Study selection was carried out following a standardized protocol to minimize potential duplications. Mendeley was used for reference management, allowing for systematic identification and elimination of duplicates. The selection process was documented in a PRISMA 2020 flowchart, which included the steps of initial identification, duplicate clearance, title and abstract review, and full-text assessment.

Study Assessment

Studies were analyzed by combining detailed original data from primary studies (such as case series) with comprehensive syntheses of secondary studies (such as reviews). This maximizes the available evidence, ensures methodological rigor, and transparently acknowledges limitations, especially the lower methodological precision of secondary studies.

Assessment of Methodological Quality and Antiviral Outcomes

The characteristics, methodological quality, and risk of bias of the studies, as well as the clinical outcomes, are analyzed and organized in tables for ease of interpretation. The assessment is structured as follows: general characteristics, quality, risk of bias, and clinical outcomes, following standardized criteria to ensure a rigorous and objective analysis.

Results

Search Strategy

The literature review was conducted through a structured search of five electronic databases: Google Scholar, PubMed, Cochrane Library, ScienceDirect, and Scielo. A broad strategy was designed using combinations of English-language keywords related to the drugs of interest (tecovirimat, brincidofovir, and cidofovir), their adverse effects, and their clinical effectiveness in severe cases of Monkeypox (MPOX).

Eight search queries tailored to the type of study (clinical trials, retrospective studies, case reports, and expert opinions) were used in each database. Most records were obtained from Google Scholar, while ScienceDirect and Scielo did not provide any relevant results.

Selected studies were discarded if they did not meet the study objectives, presented basic limitations (language, access, incomplete data), were from fourth-quartile journals, or were not indexed in the JCR. All included studies came from scientific journals in the Q1 and Q2 quartiles, with an impact factor, which guarantees the methodological quality and academic relevance of the sources.

A total of 1,794 records were identified in Google Scholar, PubMed, and the Cochrane Library, of which 1,421 were duplicates. Subsequently, 359 unique records were reviewed, excluding 241 for not meeting inclusion criteria (language, topic relevance, document type, or lack of full-text access). Of the 118 reports selected for detailed review, 97 were discarded for not aligning with the study objectives. Among the 21 reports evaluated in depth, 4 were excluded for not being indexed in the Journal Citation Reports (JCR) and 1 for belonging to a journal ranked in the fourth quartile. Ultimately, 16 studies were included, of which 5 were primary research and 11 were secondary studies.

The search and study selection process was represented in a flowchart based on the PRISMA model. A total of 1,794 records were identified in the Google Scholar, Cochrane Library, and PubMed databases. Of these, 1,421 duplicate records were removed, including 14 discarded due to formatting errors during export or upload to the reference manager.

A total of 359 unique records were examined, of which 241 were excluded because they did not meet the inclusion criteria (language, subject relevance, document type, or lack of full-text access). Full-text retrieval of 118 reports was attempted, but 97 were discarded for being irrelevant to the study objectives.

Of the 21 reports evaluated, 4 were excluded because they were not indexed in the Journal Citation Reports (JCR) and 1 because it belonged to a fourth-quartile journal. Ultimately, 16 studies were included in the review.

The results are derived from the analysis of 16 articles on the use of antivirals in MPOX, focusing on severe manifestations (necrosis, multiorgan involvement, severe proctitis, cutaneous dissemination, or related complications). Data were stratified by immunosuppressed status (CD4 <200 cells/mm^3 or AIDS, equivalent to immunoincompetent in the original texts), immunocompetent (CD4 ≥500 cells/mm^3), and unspecified (no CD4 or immunity breakdown). The structure is organized by antiviral, with subsections dedicated to clinical effectiveness (complete resolution of symptoms, length of hospitalization, and mortality) and pharmacological safety (frequency and severity of adverse events, specific renal, hepatic, or hematological toxicity, and discontinuation due to adverse effects). Quantitative values are derived from Tables 4–6, based on textual analysis and limited to explicit parameters. Relevant contributions from each article are included

Table 1 summarizes a total of 16 studies published between 2022 and 2024 in prestigious journals, including The Lancet Infectious Diseases (impact factor: 31.0) and the International Journal of Infectious Diseases. According to their classification in the Journal Citation Reports (JCR 2024), ten studies correspond to a Q1 quartile (highest impact) and six to a Q2 quartile (impact factors between 1.9 and 4.5).

Regarding the methodological design, secondary research predominated, with 11 narrative or systematic reviews. According to the Oxford Levels of Evidence (OCEBM, 2025), ten studies were classified as Levels 4 (case series) or 5 (expert opinions), while six reached higher levels: Level 1 (meta-analysis) or Level 3 (cohort studies).

Six publications stood out for achieving the maximum quality rating (6/6) and all corresponding to systematic reviews. [1,17,23-27]. Overall, the evidence prioritizes the use of robust secondary sources, supported by impact indices and levels of evidence [28, 29, 17].

Table 2 analyzes the risk of bias in the 16 studies (2022–2024). Randomization and blinding are not applicable in 13 studies (reviews or observational studies), but are implemented in three [1,26,27]. Sample sizes vary: five studies have inadequate samples (n=1–5): [10,13,30,31,32], six have adequate samples (n≥30, e.g., n=597, n=1202), and five do not clearly specify the size. All studies show adequate data completeness. The risk of bias is high in 10 studies (due to small samples or lack of controls), moderate in three [23,25,33] and low in three.

Table 3 assesses the presentation of results in the 16 studies (2022–2024). All clearly define their outcomes (score 2/2). However, detailed data are partial (1/2) in five studies [30,34-37] due to incomplete reporting or confusing structures, while 11 studies present complete data (2/2). The organization of results is confusing (1/2) in nine studies and clear (2/2) in seven. The total scores are: 4/6 in five studies, 5/6 in five [10,13,31-33] and 6/6 in six [1,23-25].

Evaluation of the Effectiveness and Safety of Tecovirimat

Table 4 summarizes the findings of 15 studies published between 2022 and 2024 evaluating the use of tecovirimat in patients with various immune statuses. A total of 98 immunosuppressed patients (CD4 <200 cells/µL or AIDS diagnosis) were identified, while the remainder were unspecified cases or HIV-infected patients without detailed breakdown. One study was excluded due to the lack of specific information for this analysis [38].

Clinical Effectiveness: Table 4 summarizes the findings of 15 studies published between 2022 and 2024 evaluating the use of tecovirimat in patients with various immune statuses. A total of 98 immunosuppressed patients (CD4 <200 cells/µL or AIDS diagnosis) were identified, while the remainder were unspecified cases or HIV-infected patients without detailed breakdown. The study by *Alameer et al.* (2024) was excluded due to the lack of specific information for this analysis.

Safety: Reported adverse events were mostly mild in both populations, with the most notable being fatigue (5.8–28%), nausea, headache, and diarrhea. Liver toxicity is infrequently observed, with only two documented cases [1,27]. Treatment discontinuation was uncommon, occurring in a range from 2 of 196 to 4 of 38 patients.

Quality and Risk of Bias: The methodological quality of the evaluated studies ranged from 4 to 6 points out of 6, with seven publications achieving the maximum score (6/6): [1,23-27,37]. Regarding the risk of bias, nine studies presented a high level, mainly associated with small sample sizes and lack of randomization; three studies showed moderate risk, and only three were classified as low risk [1,26,27].

Summary. Tecovirimat, administered at doses of 600 mg orally or 200 mg intravenously for periods of 14 to 56 days, has shown moderate to high clinical effectiveness (63.8-100%) in resolving cases. Hospitalizations ranged from 2 to 52 days, with low mortality, except in patients with severe immunosuppression. Reported adverse events were mostly mild, and treatment discontinuations were rare. However, the available evidence is limited by a high risk of bias in several of the studies analyzed, necessitating cautious interpretation of the results (Table 4).

Evaluation of the Effectiveness and Safety of Brincidofovir

Table 5 summarizes the findings of nine studies published between 2022 and 2024 evaluating the use of brincidofovir in immunocompetent patients-such as transplant recipients or people with HIV infection and a CD4 count <200 cells/µL-as well as in those with unspecified immunostatus (35.7% with HIV, no CD4 data available). Seven studies were excluded due to a lack of specific information for this analysis [13,26,27,31-34]

Clinical Effectiveness: In immunosuppressed patients, clinical resolution ranged from 0% [23] to 72.7% [25]. Length of hospitalization ranged from 14 to 35 days [38] with high mortality, reaching up to 70% in severe cases [24].

In contrast, in patients with unspecified immunosuppressed status, clinical resolution reached 100% in small studies [10] with zero mortality and poorly documented hospitalizations (26–35 days. These findings suggest that the effectiveness of brincidofovir is limited in severely immunosuppressed patients, mainly due to the severity of their clinical condition.

Safety: Adverse events associated with the use of brincidofovir are frequent and primarily include transaminitis (3/3 in several studies), nausea, and neuropsychiatric manifestations. Liver toxicity was generally reported as moderate, although mild in some cases [38]. Treatment discontinuation was common, occurring in 3/3 patients across seven studies, except for two studies where no treatment interruptions were recorded [10,38].

Quality and Risk of Bias: The methodological quality of the studies evaluated ranged from 4 to 6 out of 6 points, with four studies achieving the maximum score (6/6) [1,23,24,25]. Regarding risk of bias, seven studies were classified as high, mainly due to small sample sizes and lack of randomization; two studies were classified as moderate risk [23,25] and only one was classified as low risk [1].

Summary: Brincidofovir, administered at a weekly oral dose of 200 mg, showed variable clinical effectiveness (0–72.7%), with hospitalizations ranging from 14 to 35 days and high mortality in immunosuppressed patients. Liver toxicity and the frequency of treatment discontinuation are important limitations to its use. Furthermore, the available evidence is limited by a high risk of bias in most studies, necessitating cautious interpretation of the results (Table 5).

Evaluation of the Effectiveness and Safety of Cidofovir

Table 6 summarizes the findings of nine studies published between 2022 and 2024 evaluating the use of cidofovir in immunocompetent patients—such as those with CD4 <200 cells/µL or an AIDS diagnosis—or in patients with unspecified immunostatus (35.7% with HIV, without CD4 data; e.g., 37.65% [35]. Seven were excluded due to a lack of specific information for this analysis [1,10, 24, 27, 33, 34,38].

Clinical Effectiveness: In immunosuppressed patients, clinical resolution ranges from 0% to 100% [31,36]. Hospitalization ranges from 2 to 52 days [25,31]. In patients with unspecified immunostatus, resolution is high, reaching 100% in small studies with low mortality (0-7/404) and poorly documented hospitalization. Effectiveness depends on the clinical severity of the patients [35]

Safety: Adverse events associated with cidofovir use were minimal, with only isolated cases of mild liver toxicity, such as elevated ALT in 1/1 patients and no treatment discontinuations. Although no renal events were reported in the included studies, the known risk of nephrotoxicity cannot be ruled out and requires careful clinical monitoring during drug administration [13,25].

Quality and Risk of Bias: The methodological quality of the evaluated studies on cidofovir ranged from 4 to 6 points out of 6, with three studies achieving the maximum score (6/6): [31,25,36]. Regarding risk of bias, six studies had a high level, mainly due to small sample sizes and lack of randomization; Two studies showed moderate risk [23,25] and only one was classified as low risk [26].

Summary: Cidofovir, administered at a dose of 5 mg/kg intravenously weekly or as a 3% topical formulation, showed variable clinical effectiveness (0–100%), with hospitalizations ranging from 2 to 52 days and generally low mortality. Adverse events were minimal; however, the potential risk of nephrotoxicity requires rigorous monitoring during treatment. The available evidence is limited and is constrained by a high risk of bias in several studies, which prevents definitive conclusions (Table 6).

Discussion

Monkeypox (MPOX), caused by the monkeypox virus (Orthopoxvirus, family Poxviridae), represents a significant clinical challenge, particularly in immunosuppressed patients, due to severe complications such as coalescent lesions, edema, secondary infections, and multiorgan failure [4]. This analysis evaluates the effectiveness and safety of three antivirals—tecovirimat, brincidofovir, and cidofovir-in the management of severe cases of MPOX, integrating the relevant theoretical framework and highlighting the limitations of the available evidence, including the paucity of robust data, low methodological quality, high risk of bias, and heterogeneity in reporting.

Clinical Effectiveness in the Treatment of Monkeypox

The effectiveness of antivirals used in MPOX depends on the patient's immune status and the clinical severity of the disease, showing significant variations between immunocompetent and immunosuppressed individuals.

a. **Tecovirimat:** Inhibits the p37 protein, blocking virion egress [7]. It has shown moderate to high effectiveness (63.8–100%), with symptom resolution of 90% in large cohorts [23] and up to 100% in small studies [36]. However, its effectiveness is limited in severely immunosuppressed patients [31].

b. **Brincidofovir:** A prodrug of cidofovir that inhibits viral DNA polymerase [7]. It has variable effectiveness (0–72.7%), achieving complete resolution in small studies [10], but with unfavorable results in immunosuppressed patients [23].

c. **Cidofovir:** A nucleotide analog that interrupts viral DNA elongation [7]. In some cases, it achieves high effectiveness [36], although its efficacy decreases in patients with severe disease [31].

The effectiveness of antivirals is lower in immunosuppressed patients (CD4 <200 cells/μL or AIDS), mainly due to the severity of the disease. Mortality in these cases is high: 46% for tecovirimat, 70% for brincidofovir, and up to 100% for cidofovir [25,31]. In patients with unspecified immunosuppressed status (35.7% with HIV), antivirals show greater effectiveness; however, the lack of uniform data on hospitalization makes it difficult to assess the clinical burden. [36]. Heterogeneity in reporting and the scarcity of standardized data limit conclusions, especially in immunosuppressed patients, where available antivirals appear insufficient, suggesting the need to explore combined therapeutic strategies with immunomodulators.

Methodological Limitations and Robustness of Evidence

The available evidence on the use of antivirals in the treatment of monkeypox has multiple methodological limitations that affect its robustness. These include small sample sizes, lack of randomization, heterogeneity in study designs, variability in the definition of clinical outcomes, and poor standardization in the documentation of adverse events. These limitations generate a high risk of bias and restrict the ability to extrapolate findings to clinical practice, especially in immunosuppressed patients or those with severe disease.

A total of 16 studies published between 2022 and 2024 were analyzed, of which five correspond to primary research (level 3: [33]; level 4: [13,31,32,38,39] and once to secondary studies (level 1: [1,26]; level 2: [10,27,35,36]. 62.5% of the studies (10 investigations) present low levels of evidence (levels 4–5), due to the use of uncontrolled designs, such as case series and narrative reviews, and the heterogeneity of the reported data (Table 1).

The methodological quality of the evaluated studies is moderate to high (4–6/6, Table 3), with six investigations standing out that achieved the maximum score (6/6): [1,23-27]. However, the risk of bias was shown to be high in ten studies [10,13,24,31-38] mainly due to small sample sizes, lack of randomization, and partial data reporting (Table 2). Only three studies were classified as having a low risk [1,26,27].

Heterogeneity in immune status (immunosuppressed with CD4 <200, immunocompetent, unspecified with 35.7% HIV), comorbidities (HIV, transplants), and age ranges (children, adults, undisaggregated) complicates comparisons. The absence of key data, such as CD4 count, viral load, comorbidities (e.g., diabetes, liver disease), and age, limits accurate assessment of effectiveness and safety (Tables 4–6). The lack of standardization in reporting hospitalization and toxicity (especially renal toxicity for cidofovir) reinforces the need for uniform criteria.

Clinical Implications and Emerging Challenges

The paucity of robust evidence makes it difficult to establish clear clinical recommendations:

a. **Tecovirimat:** Approved under the Animal Rule it shows moderate-to-high effectiveness and a favorable safety profile, making it a suitable option for non-immunosuppressed patients [5].

b. **Cidofovir:** Approved for cytomegalovirus retinitis it has an acceptable safety profile, but its known nephrotoxicity requires close monitoring [5].

c. **Brincidofovir:** Approved under the Animal Rule it is less suitable due to its hepatotoxicity [6].

The high mortality rate in immunosuppressed patients (46% for tecovirimat, 70% for brincidofovir, and 100% for those treated with cidofovir) demonstrates the inadequacy of available antivirals against severe forms of the disease. Furthermore, the synergy observed between brincidofovir and tecovirimat in animal models suggests that combining antivirals or incorporating immunomodulators could be a promising strategy to improve clinical outcomes [11].

Guidelines for Future Research

To overcome current limitations, the following priorities are proposed:

Clinical Standardization: Develop uniform protocols for reporting hospitalization, clinical resolution, and toxicity, with special emphasis on measures of renal (cidofovir) and hepatic (brincidofovir) effects.

Trials in Immunosuppressed Populations: Conduct randomized clinical trials with large sample sizes, incorporating detailed data on CD4 counts, viral load, comorbidities, and age.

Combination Therapies: Evaluate combinations of antivirals (e.g., tecovirimat with cidofovir) or the addition of immunomodulators to improve efficacy in severe cases.

Toxicity Monitoring: Establish rigorous monitoring of liver and kidney toxicity to identify adverse effects that may be underreported.

Conclusions

The evidence on the use of tecovirimat, brincidofovir, and cidofovir in the treatment of severe monkeypox (MPOX) is limited, with a low level of evidence (levels 4–5 in 10 of 16 studies) and a high risk of bias in 10 studies, mainly due to uncontrolled designs and data heterogeneity.

Recommendations for Future Research: Randomized controlled trials with uniform criteria, including a detailed breakdown of immune variables (e.g., CD4 count, viral load) and systematic monitoring of liver and kidney toxicity, are a priority. The efficacy of combination therapies, such as antivirals combined with immunomodulators, should also be explored to improve outcomes in critically ill patients.

Tecovirimat: It has moderate to high effectiveness (63.8–100%) and a favorable safety profile, with generally mild adverse events, such as fatigue and nausea. However, its efficacy is limited in severely immunosuppressed patients, where it fails to resolve the most severe cases.

Brincidofovir: It shows variable effectiveness (0–72.7%), and its use is restricted by significant hepatotoxicity, which often requires treatment discontinuation.

Cidofovir: It achieves 100% effectiveness in some cases (*36Ortiz-Saavedra et al.,* 2022), but fails in severely immunosuppressed patients, with 100% mortality in specific situations (*Carrubba et al.,* 2023). Its use requires caution due to the known risk of nephrotoxicity.

Variability and limitations: Diversity in immunological status (e.g., CD4 <200, 35.7% with HIV), comorbidities, and age, along with the lack of detailed data on key variables, highlights the need to standardize clinical reporting.

High mortality: In immunosuppressed patients, mortality can reach up to 70%, highlighting the inadequacy of available antivirals for severe cases.

ANNEX 1

Tables of methodological characterization of academic studies (Table 1,2,3).

ANNEX 2

Evaluation of clinical evidence for antivirals in selected studies (Table 4,5,6).

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Conflict of Interest

None.

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