Canada's Drug and
Health Technology Agency

CADTH Health Technology Review

Tecovirimat (Tpoxx): Update

Sponsor: SIGA Technologies, Inc.

Indication: Treatment of human monkeypox

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Drug Implementation Advice

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Questions or requests for information about this report can be directed to **Requests@CADTH.ca**.

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What Is the Unmet Need for the Treatment of Monkeypox?

With rapid growth and detection outside of endemic areas,[1] there is a need to develop a public health strategy for the management of human monkeypox. Vaccination is currently the primary measure to reduce risk of monkeypox disease and transmission. In Canada, per the National Advisory Committee on Immunization (NACI) Interim guidance on the use of Imvamune,[2] vaccination has been recommended in specific populations as post-exposure prophylaxis (PEP) to reduce disease risk in individuals exposed to a case, and pre-exposure prophylaxis (PrEP) to reduce acquisition in groups at high risk of occupational exposure in a research setting.

In Canada, tecovirimat has been used as a treatment for monkeypox in specific populations that meet eligibility criteria, as part of the strategy to address the global health emergency. A previous version of this CADTH Implementation Advice Report was published in July 2022. However, this guidance is currently being revisited. An unmet need remains for consideration of treatment of progressive infection, particularly for those with severe disease or at highest risk of progressing to severe disease.

What Is Tecovirimat (Tpoxx)?

Tecovirimat (sold under the brand name Tpoxx) is an antiviral therapy that is approved in Canada for the treatment of human smallpox disease in adults and pediatric patients who weigh at least 13 kg based on laboratory data demonstrating effectiveness against orthopoxvirus in animal studies, as well as human safety studies. The mechanism of action of tecovirimat is to inhibit maturation and to prevent the release and spread of viral particles to other cells. Tecovirimat inhibits the activity of the orthopoxvirus VP37 protein and blocks the interaction of VP37 with cellular Rab9 GTPase and TIP47, which prevents the formation of the egress-competent enveloped virions necessary for cell-to-cell and long-range dissemination of a virus.[3] Tecovirimat is available as a 200 mg oral capsule. For individuals weighing more than 40 kg, the treatment dose approved for smallpox is 600 mg (offered as three 200 mg capsules) taken twice daily orally for 14 days. Weight-based dose adjustment is also available for individuals who weigh less than 40 kg but more than 13 kg.[3] Some jurisdictions are considering alternative dosing and duration.

How Did CADTH Approach This Review?

The aim of this CADTH review was to inform decision-making on the appropriate use of tecovirimat for the treatment of human monkeypox infection. CADTH convened an implementation advice panel (the panel) that spanned various disciplines and clinical settings with geographical representation across Canada. The panel captured expert advice through consensus and prioritized patient populations that were most likely to

benefit from pharmaceutical management for monkeypox infection. It was not the intent of the panel to address whether tecovirimat should be made available in Canada for the treatment of monkeypox.

What Is the Implementation Advice?

The panel suggests prioritizing the treatment of individuals who have a documented laboratory-confirmed diagnosis of monkeypox infection into 3 groups, as outlined in Table 1. Use of tecovirimat should be targeted to those with severe monkeypox virus related disease, in line with usual ethical standards where potentially serious consequences to the individual are judged to outweigh the lack of clinical trial data for the use of this antiviral medication. All patients considered for therapy should be receiving optimized medical care (pain medication and attention to hydration) for the indirect consequences of infection. Outside of these limited categories use of this medication should preferably be in the context of randomized controlled trials designed to demonstrate efficacy and safety of this therapy.

The panel issued initial advice on the use of tecovirimat in monkeypox infection on July 12, 2022, based on the premise that supply was limited at the time. However, the panel reconvened in August 2022 to discuss the use of tecovirimat in the case of additional supply and whether this can be used to manage patients whose quality of life is heavily affected. However, the benefit of tecovirimat in this context remains unknown.

What Are the Limitations of the Review?

Important gaps in the available evidence include the absence of phase II and III clinical studies in humans. Given the lack of experience with tecovirimat use, beyond the evolving case series, the efficacy and safety in humans, particularly in specific subpopulations of interest (i.e., pediatric individuals weighing less than 13 kg, pregnant and lactating individuals who lack pharmacokinetic and safety data, and those who are immunocompromised), remains to be fully understood. The available evidence is limited to animal studies via the FDA Animal Rule, information from Health Canada's Extraordinary Use New Drug (EUND), and published case reports in humans.

Table 1: Prioritization of Tecovirimat Treatment Based on A Tiered Risk Group Approach

Tier	Group
1	Treatment in individuals who have a documented laboratory-confirmed diagnosis and who have severe monkeypox disease requiring care in an intensive care setting (for example, those who have monkeypox encephalitis, hypovolemic shock and/or threat to critical organ functions)
2	Treatment in individuals who have a documented laboratory-confirmed diagnosis and have progressive infection with severe disease that require hospitalization for monkeypox disease **OR** Patients with a documented laboratory-confirmed diagnosis who are in the outpatient setting and: • are pregnant (due to higher risk of adverse pregnancy outcomes) • have progressive infection and are severely[a] immunocompromised[b] • have keratitis due to the concern of blindness or visual impairment
3	Treatment in individuals who have a documented laboratory-confirmed diagnosis, have progressive infection in the outpatient setting, and are at very high risk of severe disease, which includes those who: • are moderately[a] immunocompromised[b] • are infants and young children (≤ 10 years of age) • have atopic dermatitis with significant skin lesions

[a] Defining moderately versus severely immunocompromised is at the discretion of the treating physician based on the following definition.

[b] Definition from COVID-19 vaccine – Canadian Immunization Guide: "Moderately to severely immunocompromised includes individuals with the following conditions: Immunocompromised due to solid tumour or hematologic malignancies or treatments for these conditions; solid-organ transplant and taking immunosuppressive therapy; hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy); immunocompromise due to chimeric antigen receptor (CAR)-T-cell therapy targeting lymphocytes; Moderate to severe primary immunodeficiency with associated humoral and/or cell-mediated immunodeficiency or immune dysregulation; HIV with AIDS-defining illness or tuberculosis diagnosis in last 12 months before starting vaccine series, or severe immune compromise with CD4<200 cells/uL or CD4%<15%, or without HIV viral suppression; recent treatment with the following categories of immunosuppressive therapies: anti-B cell therapies (monoclonal antibodies targeting CD19, CD20 and CD22), high-dose systemic corticosteroids (prednisone equivalent of ≥ 2 mg/kg/day or 20 mg/day if weight > 10 kg, for ≥ 14 days), alkylating agents, antimetabolites, or tumor-necrosis factor (TNF) inhibitors and other biologic agents that are significantly immunosuppressive; Chronic kidney disease on dialysis."[4]

Rationale for the Decision

The lack of efficacy and safety data, including randomized clinical trials for the use of tecovirimat for monkeypox infections in humans is a significant evidence gap. In addition, there is even a paucity of pharmacokinetic data in some subpopulations of interest of those who are at higher risk of severe disease. Evidence used to support the implementation advice included the limited number of case reports of individuals treated with tecovirimat for orthopoxvirus, including vaccinia and monkeypox cases. The panel therefore relied more heavily on expert opinion where gaps in evidence have persisted. As such, based on the available data, tecovirimat has been advised by the panel to be reserved for use as outlined in Table 1, where the panel felt that the potential benefits may outweigh the potential risks. The opinion of the panel is that the use of tecovirimat beyond very severe or very high-risk cases is not suggested based on available evidence,

and iterative data review is required as is support for appropriate trials that can be accessed by patients in Canada who do not meet current criteria.

Given that monkeypox is a self-limiting and mild infection in most cases, the goals of treatment with tecovirimat were to avoid outcomes associated with severe disease, such as death and major supportive care (e.g., intensive care hospitalization, encephalitis). The panel agreed that tecovirimat should be reserved for treatment in patients who have progressive infection with severe disease that requires hospitalization or those in the outpatient or community setting who are at extreme risk of severe disease or complications (i.e., those who are pregnant or immunocompromised; those who have keratitis; infants and young children; and those with active atopic dermatitis at risk of widespread cutaneous disease).

For those at high risk of severe disease, the panel prioritized those who are pregnant, severely immunocompromised, and/or have keratitis due to the risk of blindness or visual impairment. Given the paucity of evidence, the panel could not comment on safety and efficacy in these subpopulations but concluded that the benefits of treatment in these subpopulations may outweigh the risks given the poor outcomes seen in practice. The panel determined it was important to differentiate between moderately and severely immunocompromised, as it was posited, for example, that those being actively treated with certain categories of immunosuppressive therapies would not be at the same level of risk as patients who have undergone organ transplants. Children ages 10 and under were prioritized as the risk of more severe outcomes is thought to be higher in small children based on limited data from endemic countries and 2 case reports in monkeypox for children aged 6 and 10.[5] Those with pre-existing skin lesions from atopic dermatitis were prioritized given their higher risk of requiring supportive care, as analogous to eczema vaccinatum from vaccinia virus.

Panel Deliberation

The panel comprised 8 members representing internal medicine, critical care medicine, infectious diseases, medical microbiology, emergency medicine, pediatrics, clinical immunology and allergy, geriatrics, ethics, pharmacy, and nursing from urban and rural clinical settings across Canada. The panel met originally on June 23, 2022, to inform decision-making on the appropriate use of tecovirimat for the management of human monkeypox. Particularly, CADTH was seeking feedback from the panel regarding the prioritization of patient populations to receive treatment, with consideration for situations when supply may be limited. The panel subsequently reconvened on August 30, 2022, to discuss populations eligible to receive treatment in the case of sufficient supply, with a review of emerging evidence.

The clinical value of tecovirimat was deliberated in the context of the increasing cases within Canada, as a disease of global public health importance. The implementation advice reflects the consensus of the panel based on the best available evidence for the use of tecovirimat. Given the lack of human clinical trials, and that most evidence is in the form of case reports, important gaps in the available evidence led the panel to use expert opinion to inform decision-making for the use of tecovirimat in the management

of monkeypox. The panel also discussed ethical considerations for the judicious use of tecovirimat, particularly in scenarios of high demand for treatment. Drug costs or a health economic analysis were not considered.

Place of Therapy

Goals of Treatment

The primary goal of therapy in the context of the currently limited safety and efficacy evidence is to avoid outcomes from severe disease, such as death and intensive care admissions. Examples of individuals with severe disease include, but are not limited to, hemorrhagic disease, confluent skin and mucous membrane lesions with functional implications, sepsis, pneumonitis, encephalitis, or other conditions requiring hospitalization. Tecovirimat should not be considered an alternative to supportive care, but as an adjunct in those whose disease is progressing despite the use of optimal supportive care measures.

Although there is a lack of clinical outcome evidence to support that the use of tecovirimat meets the primary goal, the potential risks to the individual were judged to support its use. The panel suggested that potential secondary goals of antiviral treatment of monkeypox infection could include shortened duration or severity of symptomatic disease, reduction of viral shedding and consequently transmission, and reduction of long-term scarring. However, there is no high-quality evidence supporting the utility of tecovirimat for these indications, either. These are seen as areas where further safety and efficacy data are required to inform goals of therapy and place in therapy. As more evidence becomes available, such as currently planned and established clinical trials, this guidance will be reviewed to reflect the new evidence.

Unmet Needs

Vaccination is recognized as an effective measure in protecting against monkeypox virus infection and transmission and has been recommended in specific populations as PEP and PrEP, per NACI's interim guidance on the use of Imvamune in the context of monkeypox outbreaks in Canada.[2]

The panel members agreed that the greatest unmet need is for treatment of individuals who have a documented laboratory-confirmed diagnosis; who have severe disease that requires significant supportive care and has resulted, or may soon result, in hospitalization; or who have progressive infection and are at high risk of severe disease (e.g., those who are severely immunocompromised).

The panel also identified an unmet need in individuals who are pregnant due to the increased risk to the fetus. Reported outcomes on the fetus of those diagnosed with monkeypox virus have included stillbirths or pregnancy loss.[6]

The panel noted that the majority of those infected thus far are healthy individuals with self-limiting disease, and that current data are insufficient to support the use of this medication in this lower-risk population.

There are currently ongoing clinical trials to evaluate the use of tecovirimat in different places in therapy (e.g., PEP); therefore, the use of tecovirimat may evolve with studies that provide a higher level of evidence.

The panel agreed that there may be additional populations for whom there is an unmet need for antiviral treatment with tecovirimat based on epidemiological data, and who could theoretically benefit from the use of tecovirimat — if demonstrated in well-designed clinical trials; however, given the lack of available human data to assess the safety and impact on outcomes, including subgroup analyses, it remains unknown whether tecovirimat will address these unmet needs, or provide benefit over potential risks.

Furthermore, the panel discussed the unmet need with regards to overall clinical management, and therefore agreed that provision of adequate supportive care with monitoring, pain control, hydration, and management of secondary infections plays an important role in the management of monkeypox beyond antiviral therapy.

Use of Tecovirimat in a Vaccinated Population

The use of tecovirimat in vaccine breakthrough infections has not been studied. Vaccinated individuals may be expected to have less severe disease; however, in the absence of data on how much risk reduction they may have, if these individuals display progressive infection, the panel suggested they be eligible for treatment with tecovirimat if they meet the criteria outlined in Table 1.

Prescribing Advice

- The panel advised that when tecovirimat is assessed as being indicated, treatment with the drug should be initiated as soon as possible and in accordance with local approval processes, where established.
- The panel advised that when prescribing tecovirimat, care should be taken for people in whom actual or potential drug-drug interactions exist, such as when tecovirimat is taken in combination with drugs that are metabolized by CYP3A4 enzymes (for example: certain HIV antiretroviral drugs) as tecovirimat is a known inducer of this enzyme.
- At the time of its review, the panel members agreed that there is a lack of evidence on the safety of tecovirimat in humans; therefore, individuals being treated with tecovirimat should be monitored for additional side effects or adverse drug reactions that may occur. Monitoring may include QT corrected for heart rate (QTc) prolongation if these individuals already have existing risk factors, as QTc prolongation has been reported in some animal studies.
- The panel advised that a patient-centred care discussion be held to discuss risks and benefits before prescribing tecovirimat to any patients, including the off-label nature of the treatment, and that informed consent should be obtained as part of the discussion. Furthermore, for individuals who are pregnant, a discussion should occur with their health care provider to properly determine whether tecovirimat is appropriate.

- The panel acknowledged the importance of supportive care. Initiating therapy with tecovirimat does not replace usual supportive care (e.g., hydration), as individuals may still be at risk for ongoing symptoms (e.g., poor oral intake, pain).

Other Discussion Points

- As of August 24 ,2022, there has been 41,664 documented cases of monkeypox globally, of which 12 deaths have been reported (5 of which are from nonendemic areas).[1] The mortality rate of 0.02% (0.01% in nonendemic areas) is important to consider when weighing the need for treatment for monkeypox, as it appears that recent cases have mostly been self-limiting in nature.
- Use of tecovirimat as PEP in individuals at high risk of severe disease was considered by the panel at request; however, the absence of evidence on the safety and efficacy of tecovirimat in this circumstance did not support the use of tecovirimat in uninfected individuals outside the context of a clinical trial. In the future, based on evolving evidence, tecovirimat may be considered as PEP for higher-risk individuals. Vaccination was acknowledged to be the main pre- and post-exposure measure currently supported.
- The panel members acknowledged that individuals who have contraindications to the vaccine would be considered a potential unmet need if at high risk of exposure or exposed to monkeypox infection. However, as previously noted, given the lack of evidence for the use of tecovirimat in PEP, based on expert opinion, the panel members agreed that tecovirimat should not be viewed as a replacement to vaccines.
- The panel discussed that people who have a documented laboratory-confirmed diagnosis of monkeypox should have a risk-benefit discussion with their providers about breastfeeding, to minimize the risk of transmission of the disease to infants, who have been highlighted as a group at higher risk of poor outcomes. This should be discussed with the individual to ensure that this is consistent with their values and preferences.
- While, based on the product monograph, tecovirimat is not recommended for individuals weighing less than 13 kg, its use should be assessed on a case-by-case basis. There is experience with use in the pediatric population, including a case report of a 28-month-old individual treated with tecovirimat. Currently, the sponsor is evaluating weight-based dosing of the liquid formulation for people weighing less than 13 kg.
- The panel discussed that vaccination status is only a consideration when evaluating the risk of progressing to severe disease. Being unvaccinated is a risk factor that should be considered in combination with other factors (e.g., severity of disease, comorbidities, immunocompromised host) when assessing the need for treatment with tecovirimat. While vaccination with previous generations of the smallpox vaccine may offer protection from monkeypox, individuals may still not be fully protected given the timing of the vaccination (i.e., before the 1980s).
- The panel discussed at length the potential role of tecovirimat in reducing viral shedding or duration of active lesions. Given the lack of available evidence at this time, the use of tecovirimat in this context should be restricted to controlled clinical studies. Public health measures to reduce transmission should continue to be followed.

- Available epidemiology data indicate that individuals living with HIV are represented in confirmed cases of monkeypox, but those who are HIV positive have varying degrees of immunosuppression. The panel noted that treatment of monkeypox for this population should be focused on those with significant immunosuppression: CD4 < 200 cells/uL or CD4% < 15%, or without HIV viral suppression if they meet the criteria in Table 1.
- The panel suggested the importance of public health measures being implemented within the different jurisdictions. These could include, but are not limited to, promotion of vaccination to eligible populations, communications to sexual health clinics, and preventive response (e.g., isolation, identification of new lesions, and avoidance of sexual contacts when feeling unwell) to those at high risk of exposure and transmission.

Background

An overview of the details for the drug under review is provided in Table 2.

Table 2: Review Details

Item	Description
Drug product	Tecovirimat (as tecovirimat monohydrate) 200 mg capsule for oral administration
Indication	For the treatment of human monkeypox
Health Canada approval status	Approved for human smallpox
NOC date	November 29, 2021
Sponsor	SIGA Technologies, Inc.

NOC = Notice of Compliance.

Human Monkeypox

Monkeypox is a virus that was first discovered in monkeys in 1958 and found in humans in the 1970s. Monkeypox is a viral zoonotic disease that occurs mainly in tropical rainforest areas of central and west Africa. While this virus was previously predominantly found in Africa, recent new cases have been identified in Europe and North America.[7]

The monkeypox virus is a member of the Orthopoxvirus genus in the Poxviridae family, to which other viruses, such as smallpox and cowpox, also belong. As such, vaccines and therapeutics that have been developed for smallpox are thought to be effective for monkeypox, as well.[8]

Epidemiology

In Canada, the Public Health Agency of Canada (PHAC) first announced the confirmation of 2 monkeypox cases in Quebec on May 19, 2022. The number of human monkeypox cases continues to rise globally. According to WHO's *Multi-country outbreak of monkeypox, External situation report #3* on August 10, 2022,[9] the total global cases have risen to 27,814, affecting 6 WHO regions, involving a total of 11 deaths, with 7 from the

endemic region (African Region) and 4 from nonendemic regions. Of these 4 deaths, 2 occurred in Spain, 1 occurred in Brazil, and 1 occurred in India.

Table 3: Global Monkeypox Cases

WHO region	Confirmed cases	Death
African region	375	7
Region of the Americas	10,815	1
Eastern Mediterranean region	31	0
European region	16,495	2
South-East Asia region	13	1
Western Pacific region	85	0
Cumulative	**27,814**	**11**

In Canada, the total number confirmed monkeypox cases has increased to 1,168 as of August 19, 2022.[10] Outbreaks are occurring in 7 provinces or territories, including 571 cases in Ontario, 453 cases in Quebec, 119 cases in British Columbia, 19 cases in Alberta, 3 cases in Saskatchewan, 2 cases in Yukon, and 1 case in New Brunswick. So far in Canada, 30 individuals with monkeypox have been hospitalized with no reports of death.

Monkeypox infections continues to be a condition with a wide spectrum of symptoms, with some individuals presenting with mild self-limiting lesions and others presenting with very severe complications requiring hospitalization. Some of these complications include bacterial superinfection, corneal infection or permanent scarring, bronchopneumonia, sepsis or septic shock, cellulitis, respiratory distress, encephalitis, and dehydration.[11]

According to WHO, the case fatality ratio from monkeypox infection and its complications (e.g., sepsis) in the endemic areas is about 3% to 6%.[12] The causes of death were also documented in high-risk groups, including infants, children younger than 10, pregnant individuals, and those who are immunocompromised.[13]

So far, the current global monkeypox outbreak, which is predominantly due to a different clade of the infection, appears to have a much lower mortality rate (e.g., 4 deaths among approximately 27,814 cases).

In Canada, the PHAC National Emergency Strategic Stockpile (NESS) has a supply of vaccines and drugs in the event of a future smallpox emergency. The NESS stockpile includes Imvamune and Tpoxx capsules,[10] which would be available to address the monkeypox outbreaks in Canada.

Four Deaths in Nonendemic Area

According to a report from Spain,[14] the 2 deaths occurred in 2 males, 1 aged 31 and the other 44. Both developed encephalitis and had no epidemiological link to one another. They were not known to be immunocompromised or have any chronic diseases. The

death that occurred in Brazil is a 41 year old male reported to have lymphoma and a weakened immune system[15] who developed septic shock in the intensive care unit. The 1 death that has been reported in India occurred in a 22-year-old male who had recently travelled to United Arab Emirates.[16]

Clinical Presentation

Historically, the transmission of monkeypox had been known to occur primarily through prolonged face-to-face contact; however, it can also be transmitted via bodily fluids.

The traditional presentation of monkeypox includes fever, headache, muscle aches, backaches, swollen lymph nodes, chills, and exhaustion.[17] A rash will often develop on the face but can spread to other areas (e.g., genitals). The rash will evolve through different stages before forming into scabs that will eventually fall off.[17]

Observational Studies

Since the last panel on June 23, 2022, more information is available about monkeypox's nature, mode of transmission, risk factors, clinical presentation, and outcomes of infections.

An International Case Series From 16 Countries

According to an international case series from 16 countries published by Thornhill et al.,[18] 98% of the persons with infection were men who identified as gay or bisexual, 75% were in individuals who were White, and 41% had HIV. The median age of those in the case series was 38 years. It was suspected that transmission occurred through sexual activities in 95% of the persons with infection. According to Thornhill et al.,[18] 95% of the persons with infection presented with a rash, 73% had anogenital lesions, and 41% had mucosal lesions. Common systemic prodromal symptoms included fever (62%), lethargy (41%), myalgia (31%), and headache (27%); and lymphadenopathy was reported in 56% of persons. Antiviral treatment was given to 5% of the persons, and 13% were hospitalized. The reasons for hospitalization were pain management, with the most common reasons related to severe anorectal pain, soft tissue superinfection, pharyngitis limiting oral intake, eye lesions, acute kidney injury, myocarditis, and infection-control purposes. In this case series, no deaths were reported.

An Observational Analysis From London, England

In an observational analysis conducted by Girometti et al.,[19] a similar descriptive analysis of demographic and clinical characteristics of confirmed human monkeypox virus cases were reported in individuals attending a sexual health centre in London, England.[19] Among the 54 confirmed individuals with monkeypox, all identified as men having sex with men. The median age was 41 years, 70% were White, 48% were born in the UK, 24% were living with HIV, 67% reported fatigue or lethargy, 57% reported fever, and 18% had no prodromal symptoms. All individuals presented with skin lesions, with 94% having anogenital lesions. Eight-nine percent of individuals had skin lesions affecting more than 1 anatomical site and 4 individuals had oropharyngeal lesions. Fifty-five percent of

individuals developed lymphadenopathy. One in 4 patients had a concurrent sexually transmitted infection. Nine percent of individuals required admission to hospital due to pain or localized bacterial cellulitis requiring antibiotics or analgesia. No fetal outcomes were reported in this analysis.

A Prospective Observational Cohort in Spain

In another prospective observation cohort study conducted in Spain by Tarín-Vicente et al.,[20] similar demographics and clinical presentations were also reported. In this study, 181 patients with confirmed monkeypox diagnosis were included. In total, 166 (92%) patients identified as gay men, bisexual men, or men having sex with men. The median age was 37, 18% of patients reported previous smallpox vaccination, and 40% were reported to be HIV positive, with 11% having a CD4 cell count of less than 500 cells/uL. In total, 17% were diagnosed with current sexually transmitted infections, all patients presented with skin lesions, 78% had lesions in the anogenital region, 43% developed lesions in the oral and perioral region, 39% had complications requiring treatment, 25% had proctitis, 10% developed tonsillitis, 8% developed penile edema, 2% developed abscess, 4% had an exanthem, and 2% required hospital admission. It was also reported that the median incubation period was about 7 days.

Based on these 3 studies, it appears that the majority of monkeypox cases occur in men, with the most probable source of transmission via sexual activity. Individuals with HIV are among those who were infected, although the prevalence varies by region. Hospitalization of those with monkeypox ranges from 2% to 13%. Only the international case series reported that antiviral treatment was used in 5% of total patients.[18] Tarín-Vincente reports that at least 39% of the study's patients required treatment related to complications;[20] however, it is unclear whether they were supportive treatments (e.g., antipyretics, hydration) or specific antiviral therapies for monkeypox infection.[20]

Human-to-Pet Transmission

Recently, there is also evidence that monkeypox can be transmitted from humans to pets.,[21] prompting the discussion that pets that have been exposed to infected humans should be isolated from other contacts.

Given the rapid transmission of monkeypox across Canada, a strategy is needed to prevent transmission, to contain outbreak, and to treat confirmed cases. For those who have been previously vaccinated for smallpox (i.e., eligible for vaccine in 1980 or earlier), the degree of protection conferred from the smallpox vaccine against monkeypox infection may be up to 85%.[2]

NACI Interim Recommendations on Vaccines

In Canada, previous smallpox vaccines, including the freeze dried or frozen liquid formulations, were prepared from live vaccinia virus.[22] They had a relatively high rate of side effects and were contraindicated for those who are immunocompromised, as well as for individuals with eczema or atopic dermatitis.[22]

More recently, a new live-attenuated but non-replicating vaccinia vaccine (Imvamune) has been developed. It is also called Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN), and is marketed under the brand name Jynneos in the US and Imvaxnex in Europe.

On June 10, 2022, NACI issued interim guidance on the use of Imvamune for PEP in adults with high-risk exposures to a probable or confirmed case of monkeypox, or within a setting where transmission is occurring. The guidance outlined that Imvamune for PEP of monkeypox should be offered as soon as possible and within 4 days of last exposure, though can be considered for up to 14 days since last exposure.[2]

NACI also recommends PrEP for adults at high risk for occupational exposure in a laboratory research setting.

For special populations, NACI has recommended that the Imvamune vaccine be offered for:

- individuals who are immunocompromised due to disease or treatment
- individuals who are pregnant
- individuals who are lactating
- children and youth younger than 18 years
- individuals with atopic dermatitis.

NACI also recommends that Imvamune (given as PEP or PrEP) not be delayed due to recent receipt of a messenger ribonucleic acid (mRNA) COVID-19 vaccine. If vaccine timing can be planned (i.e., before employment within a research laboratory), NACI recommends that Imvamune be given at least 4 weeks after or before an mRNA vaccine for COVID-19.

According to an update by PHAC on July 23, 2022, more than 70,000 doses of the monkeypox vaccine have been deployed to provinces and territories in Canada.[23]

In Quebec and Ontario, the provinces with the highest number of monkeypox cases to date, the immunization strategy has evolved over time. Both provinces began offering the vaccines as PEP for individuals with high-risk exposures; however, this strategy has developed to also incorporate PrEP in populations or areas identified to be high risk for monkeypox transmission.

Table 4: Vaccine Strategy for Monkeypox Infection — Examples (Quebec and Ontario)

Quebec's vaccine strategy	Ontario's vaccine strategy

In Quebec, where monkeypox transmission was the highest in May and June, the immunization strategy[24] has quickly evolved over time.
 	
Pre-Exposure Prophylaxis
By the end of May, the vaccine strategy began as a PEP of traceable contacts by end of May. PEP was defined as having exposure in the last 14 days. High-risk exposure includes direct contact of the skin or mucous membranes with the lesions, bodily fluids, or surfaces and objects contaminated by a probable or confirmed symptomatic case of monkeypox. Intermediate-risk exposure includes close contact within 1 metre for at least 3 hours (cumulative over 24 hours) face to face without wearing a mask.
 	
Extended Pre-Exposure Prophylaxis
In Montreal, where the majority of monkeypox cases were occurring the most frequently, extended PEP was indicated and implemented between June 3 and 13, 2022. These include the following groups:
• men (cis or trans) who had sex with men (cis or trans) in a social and sexual venue or space in Montreal in the last 14 days
• men (cis or trans) who gave or received money or other goods or services in exchange for sex with another man (cis or trans) in Montreal in the last 14 days
• workers or volunteers who came in contact with potentially contaminated objects or bedding in a social or sexual venue or space in Montreal in the last 14 days
• men (cis or trans) who had sex with 2 male (cis or trans) partners or more in Montreal in the last 14 days.
 	
Pre-Exposure Prophylaxis
By June 14, 2022, the vaccine strategy has evolved quickly into including PrEP for the following groups:
• any man (or person trans or queer) who has or plans to have sexual encounters in Montreal with another man (or person trans or queer):
  ○ who isn't a unique stable sexual partner (e.g., with an agreement of sexual exclusivity)
  ○ at a social venue or space with sexuality-on-premises between men
  ○ in exchange for money or other goods or services (received or given)
  ○ any worker or volunteer at social venue or space with sexuality-on-premises between men.
	As of June 14, 2022, Ontario is using a ring vaccination approach with a single dose of Imvamune in locations with confirmed cases.[25]
	
	Pre-Exposure Prophylaxis
	a. Two-spirited, non-binary, trans-, or cis-gender individuals or have sexual partners who self-identify as belonging to the gay, bisexual, and other men who have sex with men (gbMSM) community AND at least 1 of the following:
	  ○ have received a diagnosis of bacterial STI (e.g., chlamydia, gonorrhea, syphilis) in the past 2 months
	  ○ have had 2 or more sexual partners recently or maybe planning to
	  ○ have attended venues for sexual contact recently (e.g., bath houses, sex clubs) or may be planning to, or who work or volunteer in these settings
	  ○ have had anonymous sex recently (e.g., using hookup apps) or may be planning to
	  ○ are a sexual contact of an individual who engages in sex work.
	b. Any individual who engages in sex work or may be planning to.
	
	Household and/or sexual contacts of those identified for PrEP eligibility in parts (a) or (b) AND are moderately to severely immunocompromised or pregnant may be a higher risk for severe illness from a monkeypox infection may be considered for PrEP and should contact their health care provider (or their local public health unit) for more information.
	
	Post-Exposure Prophylaxis
	The provision of Imvamune for PEP requires an assessment of the risk of exposure by the public health unit. A single dose of the vaccine should be offered ideally within 4 days (up to 14 days) from the date of the last exposure to individuals who are a high risk contact of a confirmed or probable case of monkeypox.
	
	Intermediate-risk contacts may be offered PEP, following the public health unit's assessment of individual risks and benefits.
	
	PEP is not recommended for low-risk contacts.

PEP = post-exposure prophylaxis; PrEP = pre-exposure prophylaxis.

While vaccination remains the first line of defence in reducing monkeypox transmission, there may be logistical challenges, including vaccination within 4 days of exposure to reduce the risk of breakthrough infection, which require rapid identification and contact tracing of cases. In Paris, it has been reported that among 276 individuals who have received a dose of monkeypox vaccine, 12 individuals eventually developed monkeypox infection.[26] These breakthrough infections may be related to the delayed administration of the vaccines, as when the vaccine is given between 5 and 14 days after exposure, it may not prevent monkeypox infection but may decrease the severity of the disease.[27]

Recently, there have been reports of monkeypox vaccine shortages in some jurisdictions, prompting the US to review its vaccine strategy, such as considering a dose-sparing strategy where one-fifth of the current dose is to be administered intradermally.[28] The preliminary evidence suggests this change of dosing strategy does not impact immunogenicity.[29] At this time, this strategy is not being considered or required in Canada.[30]

Tecovirimat (Tpoxx)

Mechanism of Action and Indication

Tecovirimat (Tpoxx) is an antiviral therapy that is specific for orthopoxvirus. Tecovirimat works by inhibiting orthopoxvirus VP37 envelope-wrapping protein activity and preventing the formation of egress-competent enveloped virions.[31]

Currently in Canada, tecovirimat is approved for the treatment of smallpox in adult and pediatric patients weighing at least 13 kg.

While tecovirimat is only approved for the treatment of smallpox, there is evidence from animal data to suggest it is likely to be an effective treatment for monkeypox, given that smallpox and monkeypox belong to the same family of orthopoxvirus.

Dosage and Administration

The usual treatment dose for individuals weighing more than 40 kg is 600 mg (three 200 mg capsules) taken twice daily orally for 14 days. Some jurisdictions are altering the dose or treatment duration (e.g., shortening duration to 7 days with the potential to complete 14 days depending on clinical response). Weight-based dose adjustment is necessary for those weighing less than 40 kg but more than 13 kg:

- 40 kg or more takes a dosage of 600 mg twice daily for 14 days
- 25 kg to less than 40 kg takes a dosage of 400 mg twice daily for 14 days
- 13 kg to less than 25 kg takes a dosage of 200 mg twice daily for 14 days.

Tecovirimat is not recommended for those weighing less than 13 kg; however, the sponsor has provided a proposed weight-based liquid formulation dosing and treatment with tecovirimat may be considered on a case-by-case basis.[32] It is also recommended that tecovirimat be taken within 30 minutes after a moderate- or high-fat meal.[3]

Safety (Side Effects and Drug Interactions)

The most reported treatment-emergent adverse events related to tecovirimat have been headache, nausea, abdominal pain, and vomiting. Most treatment-emergent adverse events were mild or moderate. Data for side effects was generated with healthy volunteers; therefore, information on adverse events in infected patients is lacking, and merits close monitoring of patients who are treated with tecovirimat.

Table 5: Adverse Reactions Reported in 1% or More of Healthy Adults Receiving at Least 1 Dose of Tpoxx 600 mg

Adverse reaction	Tpoxx 600 mg N = 359 (%)	Placebo N = 90 (%)
Very common headache (≥ 10%)	12	8
Common nausea (≥ 1%)	5	4
Abdominal pain[a]	2	1
Vomiting	2	0

[a] Includes abdominal pain, abdominal pain upper, abdominal distension, abdominal discomfort, abdominal pain lower, and epigastric pain.[3]

Tecovirimat is a weak inducer of CYP3A4 and a weak inhibitor of CYP2C8 and CYP2C19 enzymes. These effects are not expected to cause any clinically significant drug interactions. According to the product monograph,[3] the 2 identified potential drug-drug interactions of note are with repaglinide, where the serum concentration may be elevated with increased risk for hypoglycemia, and with midazolam, where the serum concentration may be reduced, and for which the effectiveness of midazolam should be closely monitored.

It has also been reported that no clinically relevant drug interactions were observed when tecovirimat was administered with bupropion, flurbiprofen, or omeprazole.[33]

Recently, the US Centers for Disease Control and Prevention (CDC) interim guidance for persons with HIV infection[27] provided management strategies for drug interactions.

Specifically for monkeypox treatment with tecovirimat, the guidance document has highlighted antiretroviral therapies with potential drug interactions with tecovirimat due to induction of CYP3A4, which is outlined in Table 6.

Table 6: Potential Drug Interactions With Tecovirimat[27]

Antiretroviral therapy	Mechanism	Clinical comments
Doravirine **Rilpivirine** **Maraviroc**	Induction of CYP3A4	Per the Liverpool HIV interactions database, dose increases could be considered for these antiretroviral medications during therapy and for 2 weeks after completion of tecovirimat therapy. However, based on evidence graded as very low quality and the short treatment course of tecovirimat, some experts believe neither dose adjustments nor additional ART are needed.
Long-acting cabotegravir-rilpivirine	Induction of CYP3A4	Per the Liverpool HIV interactions database, additional oral rilpivirine 25 mg once daily (or the patient's prior ART regimen) during treatment with tecovirimat and for approximately 2 weeks after the end of treatment could be considered. However, some experts believe no additional therapy is necessary during tecovirimat treatment. Initiation of long-acting cabotegravir-rilpivirine should be avoided during tecovirimat therapy and for 2 weeks after conclusion of tecovirimat therapy.

ART = antiretroviral therapy.

QT prolongation has been reported with the use of tecovirimat. At this time, tecovirimat has not been added to CredibleMed's QT drug list, a website with a database of medications known to cause QT prolongation. Based on internal documents provided by the sponsor, QT prolongation has not been seen with any of their clinical studies, including a specific one that studied electrocardiogram effects with a supratherapeutic dose of tecovirimat. Prolonged QT was noted in only 1 animal study (e.g., beagle) where it was observed in 1 incident.[32]

Other Treatment Options for Human Monkeypox

In addition to tecovirimat, other treatment options are available, including the antiviral drug cidofovir and vaccinia immunoglobulins, both of which require IV administration. There are also documented cases of resistance to cidofovir,[34] as well as hydration requirements to reduce toxicity risk. In the US, brincidofovir—a prodrug of cidofovir available as an oral formulation—may be available; however, brincidofovir is not approved for use in Canada.[35] An elevated risk of transaminitis has been observed with brincidofovir.[36]

Recommendations From International Health Technology Assessment or Other Jurisdictions

While tecovirimat is officially approved for the treatment of smallpox, its use in monkeypox has been recommended or endorsed by various regulatory bodies and/or health technology agencies.

In the US, the CDC has released an interim guidance for which tecovirimat is 1 of several options that can be considered for human monkeypox treatment.[37]

The CDC guidance for tecovirimat use was outlined under the expanded access investigational new drug protocol in 2022. According to this guidance, tecovirimat may be considered in the following situations:

- for those with severe disease (e.g., hemorrhagic disease, confluent lesions, sepsis, encephalitis, or other conditions requiring hospitalization)
- for those who are at high risk of severe disease:
    - people with immunocompromised conditions (e.g., HIV and AIDS, leukemia, lymphoma, generalized malignancy, solid-organ transplant, therapy with alkylating agents, antimetabolites, radiation, tumour necrosis factor inhibitors, high-dose corticosteroids, being a recipient with hematopoietic stem cell transplant < 24 months post-transplant or ≥ 24 months but with graft-versus-host disease or disease relapse, or having autoimmune disease with immunodeficiency as a clinical component)
    - pediatric populations, particularly patients younger than 8 years
    - pregnant or breastfeeding individuals
    - people with a history or presence of atopic dermatitis, people with other active exfoliative skin conditions (e.g., eczema, burns, impetigo, varicella zoster virus infection, herpes simplex virus infection, severe acne, severe diaper dermatitis with extensive areas of denuded skin, psoriasis, or Darier disease [keratosis follicularis])
    - people with 1 or more complications (e.g., secondary bacterial skin infection; gastroenteritis with severe nausea, vomiting, diarrhea, or dehydration; bronchopneumonia; concurrent disease or other comorbidities)
- those with aberrant infections involving accidental implantation in eyes, mouth, or other anatomic areas where monkeypox virus infection might constitute a special hazard (e.g., the genitals or anus).

Furthermore, the CDC has recently released an interim guidance for the prevention and treatment of monkeypox in persons with HIV infection.[27] The main focus is that the treatment of monkeypox in this population should take into consideration disease severity, degree of immunosuppression (e.g., CD4 count, viral suppression), or vulnerable sites of infection (e.g., the genital or anus). The guidance also provides targeted advice on whether to continue with existing antiretroviral therapy, how to approach the use of potential antiviral options for monkeypox infection, and potential drug interactions to consider.

The European Medicine Agency has also approved the use of tecovirimat for smallpox, monkeypox, and cowpox. The European Medicine Agency has reviewed the results in animal studies, where tecovirimat was able to reduce mortality caused by orthopoxviruses such as smallpox, monkeypox, and cowpox.[38]

Experience With Tecovirimat (Tpoxx)

Table 7 is a summary of how tecovirimat may be accessed in Quebec, Ontario, and British Columbia. For more information from other jurisdictions, please contact regional public health officers.

Table 7: Access to Tecovirimat in Quebec, Ontario, and British Columbia

Accessing tecovirimat in Quebec[39]	Accessing tecovirimat in Ontario[40]	Accessing tecovirimat in British Columbia[41]
"To obtain tecovirimat, the patient must be referred to a microbiologist-infectious disease specialist who will assess the treatment indication and take the prescribed steps according to the process of special medical need (concerted decision of the care team), considering that the product is not listed on the establishments' list of medications. The CHUM's pharmacy department is the custodian of a pre-positioned stock of tecovirimat as this is the only access channel to the product. It is up to the head of the pharmacy department of the health care establishment who wishes to prescribe tecovirimat to formulate a request to the pharmacy department of CHUM in order to obtain the product, indicating that the process of special medical necessity has been respected. Note that close monitoring of the use of tecovirimat must be carried out by clinicians in order to properly document its use (e.g.: adverse effects, efficacy, compliance)."	To treat individuals who are severely ill/disabled due to monkeypox infection or at high risk for severe disease. "Tecovirimat should be considered for the following: • Hospitalized patients with severe disease (e.g., hemorrhagic disease, sepsis, encephalitis, myocarditis, esophagitis, or other conditions requiring hospitalization) • Persons who may be at high risk of severe disease: o Persons who are severely immunocompromised (e.g., individuals with HIV with current CD4 counts < 200/mm^3 or with uncontrolled viral loads; receiving active treatment for solid tumour or hematologic malignancies such as chemotherapy, targeted therapies, or immunotherapy; recipients of solid-organ transplant and taking immunosuppressive therapy; recipients of hematopoietic stem cell transplant within 2 years of transplantation or taking immunosuppression therapy; autoimmune with immunodeficiency as a clinical component; on treatment with agents such as tumor necrosis factor or high-dose corticosteroids); o Pediatric populations, particularly patients younger than 10 years of age; o Pregnant or breastfeeding women; o Persons with one or more complications (e.g., severe secondary bacterial skin infection; gastroenteritis with severe nausea/vomiting, diarrhea, or dehydration; bronchopneumonia; concurrent disease or other comorbidities).Persons with monkeypox virus infections with lesions that are leading to	"Treatment with oral tecovirimat can be considered in consultation with a physician from the Monkeypox Advisory and Guidance in the following patients with confirmed monkeypox infection: • Individuals (adults and children irrespective of age or smallpox vaccine status) with severe disease defined as either: o Requiring hospitalization or hospital-level care for monkeypox (e.g., due to severe, extensive and widespread lesions*) OR o Requiring hospitalization or hospital-level care for complications directly related to monkeypox (e.g., encephalitis, sepsis, pneumonia), OR o Significantly interfering with normal physiological body function (e.g., oral food intake, hydration, pain that is difficult to control or severe pain with bowel movements or urination) *Note: Many patients will present with genital, anal and/or oral lesions, as well as conjunctivitis. The location of lesions itself is not an indication for treatment. Treatment decisions should be based on the severity of the presentation. OR • Individuals who may be at high-risk# of developing severe disease due to severe immunocompromise such as: o human immunodeficiency virus with a CD4 count < 200 cells/mm^3, or a diagnosis of acquired immune deficiency syndrome for adults or a diagnosis of HIV for children o current treatment for a hematological malignancy such as leukemia or lymphoma o bone marrow/HSCT transplantation in the past 2 years o generalized malignancy (e.g., solid tumor or metastatic cancer) o solid organ transplantation o therapy with severely immunosuppressing agents (e.g., alkylating agents, antimetabolites,

Accessing tecovirimat in Quebec[39]	Accessing tecovirimat in Ontario[40]	Accessing tecovirimat in British Columbia[41]
	significant disability (e.g., proctitis, keratitis or other ocular involvement, pharyngitis/epiglottitis or other breathing/swallowing compromise)"	radiation, tumor necrosis factor inhibitors, high-dose corticosteroids, treatment for graft-versus-host disease or receiving immunosuppressive therapy for an autoimmune disease with immunodeficiency as a clinical component) • Neonates and infants < 1-year-old • Children aged 1-17 years with immunocompromising conditions (e.g., HIV, cancer, currently taking immunosuppressive therapy) • Pregnant persons"

CHUM = Centre hospitalier de l'Université de Montréal; HSCT = hematopoietic stem cell transplant.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including Medline, Embase, the Cochrane Database of Systematic Reviews, the international HTA database, the websites of Canadian and major international health technology agencies, as well as a focused internet search excluding preprints. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was tecovirimat. No filters were applied to limit the retrieval by study type. The search was completed on June 10, 2022, and limited to English-language documents. Retrieval was not limited by publication date.

Prior to the panel on August 30, 2022, an updated search was conducted between June and August 2022 to identify relevant new publications from the Medline database. Keywords used were tecovirimat and monkeypox.

Summary of Evidence

Health Canada Extraordinary Use New Drugs Regulatory Pathway

In 2011, Canada's Food and Drug Regulations were amended to include a pathway for EUNDs, where due to logistical or ethical reasons, it is not possible for the sponsor to conduct human clinical trials.[42] The EUND regulatory pathway was developed for cases where there is limited clinical information and standard regulatory pathways for authorization cannot be used. This regulatory pathway allows sponsors to use results of animal studies, as well as results from human safety and efficacy data that are available. Drugs approved through the EUND pathways are monitored more extensively for clinical safety and effectiveness in the post-market phase.[42]

A manufacturer of a new drug may file an EUND submission for the new drug if the following criteria are met.[42]

- the new drug is intended for:
    - emergency use in situations where persons have been exposed to a chemical, biological, radiological, or nuclear substance and action is required to treat, mitigate, or prevent a life-threatening or other serious disease, disorder, or abnormal physical state, or its symptoms, that results, or is likely to result, from that exposure, or
    - preventive use in persons who are at risk of exposure to a chemical, biological, radiological, or nuclear substance that is potentially lethal or permanently disabling; and
- the requirements set out in paragraphs C.08.002(2) (g) and (h) of the Food and Drug Regulations cannot be met because:
    - exposing human volunteers to the substance referred to in paragraph (a) would be potentially lethal or permanently disabling, and
    - the circumstances in which exposure to the substance occurs are sporadic and infrequent.

In Canada, tecovirimat is authorized under the EUND pathway.

FDA Animal Efficacy Rule and Its Relevance for Tecovirimat

In 2002, the FDA established the Animal Rule (Code of Federal Regulations title 21, part 314, subpart I), which supports a regulatory approval pathway in which studies using suitable animal models contribute directly to drug approval.[43]

The Animal Rule is intended to support drug development of therapies where clinical efficacy trials are not feasible due to ethical concerns. However, there are strict

guidelines to follow; therefore, the US FDA will recognize evidence from animal studies only when all of the following criteria are met:[44]

- there is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention and substantial reduction by the product
- the effect is demonstrated in more than 1 animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans
- the animal study end point is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity
- the data or information on the kinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allow selection of an effective dose in humans.

Because smallpox is potentially fatal and studies with variola virus in humans would not be permitted, tecovirimat was approved via the Animal Rule.

Nonclinical Animal Efficacy Studies

Four pivotal studies in nonhuman primates and 2 pivotal studies in rabbits were conducted in which the primary end point was survival. In the nonhuman primate studies, cynomolgus macaques were lethally challenged by IV with 5 x 10^7 plaque-forming units of the monkeypox virus. Tecovirimat was administered orally at a 10 mg/kg dose for 14 days, starting at day 4, 5, or 6 postchallenge.[45]

In the studies with rabbits, the animals were lethally challenged intradermally with 1,000 plaque-forming units of the rabbitpox virus. Tecovirimat was administered orally at 40 mg/kg, starting at day 4 of postchallenge.[45]

All animals were noted for clinical signs of disease (e.g., onset of lesions) by day 4 postchallenge. Survival was monitored for 3 to 6 times the mean time to death for untreated animals in each model. As noted in Table 8, all but 1 subject from the placebo group did not survive. However, the animal subjects from the tecovirimat group had a survival that ranged between 50% and 100%. The lower survival rate appears to be related to later treatment initiation.

Table 8: Survival Rates in Tecovirimat Treatment Studies in Cynomolgus Macaques and NZW Rabbits Exhibiting Clinical Signs of Orthopoxvirus Disease

Study	Treatment initiation	Survival percentage		P value[b]	Survival rate difference (95% CI)[a]
		Placebo	Tecovirimat		
Cynomolgus macaques					
AP-09-026G	Day 4	0% (0/7)	80% (4/5)	0.0038	80% (20.8% to 99.5%)
FY10-087	Day 4	0% (0/6)	100% (6/6)	0.0002	100% (47.1% to 100%)
SR10-037F	Day 4	0% (0/3)	83% (5/6)	0.0151	83% (7.5% to 99.6%)
	Day 5		83% (5/6)	0.0151	83% (7.5% to 99.6%)

Study	Treatment initiation	Survival percentage		P value[b]	Survival rate difference (95% CI)[a]
		Placebo	Tecovirimat		
	Day 6		50% (3/6)	0.1231	50% (−28.3% to 90.2%)
SR10-038F	Day 4 (3 doses)	25% (1/4)	50% (2/4)	0.3643	25% (−51.0% to 83.0%)
	Day 4 (5 doses)		100% (6/6)	0.0141	75% (8.1% to 99.4%)
	Day 4 (7 doses)		100% (6/6)	0.0141	75% (8.1% to 99.4%)
	Day 4 (10 doses)		80% (4/5)	0.0972	55% (−20.9% to 93.7%)
NZW rabbits					
SR14-008F	Day 4	0% (0/10)	90% (9/10)	< 0.0001	90% (50.3% to 99.8%)
SR13-025F	Day 4	NA	88% (7/8)	NA	NA

CI = confidence interval; NA = not applicable; NZW = New Zealand White.

[a] Exact 95% CI is based on the score statistic of difference in survival.

[b] P value is from a 1-sided Boschloo test (with Berger-Boos modification of gamma = 0.000001) compared to placebo.

Source: Product monograph.[3]

Other Animal Studies

In addition to the animal studies used to establish efficacy of tecovirimat, other animal studies have been published that evaluated the use of tecovirimat for smallpox or monkeypox. Some of these studies are summarized in Appendix 1.

Studies for Safety, Tolerability, and Pharmacokinetics

Once the efficacy of tecovirimat had been established in animal studies, a placebo-controlled pharmacokinetic and safety trial was conducted in adult volunteers.[45] This expanded trial was a multicenter, randomized, double-blind, safety trial involving adult volunteers 18 to 79 years of age. The baseline characteristics between the treatment and placebo groups were similar in terms of distribution in sex, race, ethnic group, age, weight, height, and body mass index.[45] For a detailed comparison, please refer to the original publication.[45] A lead-in cohort of 40 participants was randomly assigned in a 4:1 ratio, in either a fed or a fasting state, to receive 600 mg of tecovirimat administered orally twice daily or matching-administration placebo. Once safety and pharmacokinetic data confirmed sufficient levels of tecovirimat in blood, the trial was expanded to evaluate safety by randomly assigning an additional 412 participants at 11 sites to receive tecovirimat or placebo in the fed state only.

From this study, the authors concluded that the exposures achieved with a dose of 600 mg twice daily exceeded the efficacious exposures in nonhuman primates. Most reported adverse events were mild, and all events, with the exception of death, resolved without sequelae. The most common adverse event was headache. Patient discontinuation from the trial was rare. Breakdowns of the adverse events are reported in Table 5 and Table 9.

Table 9: Adverse Events That Occurred or Worsened During Receipt of Tecovirimat or Placebo in the Overall Summary Safety Population

Type of event[a]	Tecovirimat (n = 359)		Placebo (n = 90)		Total (n = 449)	
	Number of participants (%)	Number of events	Number of participants (%)	Number of events	Number of participants (%)	Number of events
Any event	134 (37.3)	318	30 (33.3)	68	164 (36.5)	386
Event related to the trial drug	71 (19.8)	176	15 (16.7)	32	86 (19.2)	208
Event leading to discontinuation of trial drug	6 (1.7)	16	2 (2.2)	3	8 (1.8)	19
Serious events and events leading to death	1 (0.3)[b]	1	0	0	1 (0.2)	1

[a] The adverse events considered here included any newly occurring event or previous condition that increased in severity or frequency following administration of the first dose of tecovirimat or placebo.

[b] The death was due to a pulmonary embolus that was judged by the investigators not to be related to tecovirimat.

Source: Grosenbach et al. 2018[45] From N Engl J Med, Grosenbach DW, Honeychurch K, Rose EA, et al., Oral Tecovirimat for the Treatment of Smallpox, Volume 379, Page 44-53. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Evidence for Use in Human Monkeypox

Evidence Prior to the Global Monkeypox Outbreak

Before the global monkeypox outbreak, there was limited experience with monkeypox in the nonendemic areas, as well as with the treatment of tecovirimat for this viral infection. Table 10 provides a summary of case reports where tecovirimat had been used between 2009 and 2022. Among these case reports, individuals who had been treated with tecovirimat also received additional interventions including vaccinia immunoglobulins, cidofovir, and/or corticosteroids, rendering it difficult to draw conclusions on the effectiveness of tecovirimat alone for the management of monkeypox infection.

Table 10: A Summary of Cases in Orthopoxvirus Infections Treated With Tecovirimat

Study	Case	Patient history	Route of infection	Tecovirimat and other antiviral treatment details	Outcome
Lederman et al. (2012)	Progressive vaccinia	US Marine Corps member with unknown myelogenous leukemia	Primary transmission via smallpox vaccination	VIG IV: 6,000 IU/kg, 18,000 IU/kg, 24,000 IU/kg **Tecovirimat** topical **Tecovirimat** oral, escalating dose: 400 mg to 800 mg to 1,200 mg	Discharged 5 months after vaccination with ACAM2000

Study	Case	Patient history	Route of infection	Tecovirimat and other antiviral treatment details	Outcome
CDC (2009)	Vaccinia infection of the hand	35-year-old female taking immunosuppressive medications for IBD	Primary transmission via contact with raccoon rabies vaccine bait	VIG IV: 2 doses given at 6,000 IU/kg **Tecovirimat:** Unknown dose for 14 days	Discharged after 19 days; lesions healed 22 days after first dose of VIG IV and 16 days after tecovirimat
Vora et al. (2008)	Eczema vaccinatum	28-month baby with history of refractory atopic dermatitis and failure to thrive	Secondary transmission via contact military smallpox vaccinee (father)	VIG IV: 3.96 g/kg in 11 doses CDV: 1 dose 5 mg/kg **Tecovirimat:** 5 mg/kg for 14 days Trifluridine: unknown	Discharged 48 days after hospitalization
CDC (2022)	Monkeypox in a traveller from Nigeria	A middle-aged man who returned from Nigeria	Transmission from unknown source	**Tecovirimat** with unknown dose for 2 weeks	Full recovery with discharge after 32 days
Sacks et al. (2021)	Orbital cowpox	A 28-year-old female presented with ocular symptoms, including worsening redness, irritation, and discharge in the right eye	Secondary transmission via contact of pet cat that developed lesions on the paws and head, with PCR test confirmation for orthopoxvirus	Prolonged course of **tecovirimat** Oral prednisolone Topical dexamethasone Topical moxifloxacin	6 months later, visual acuity was 20/20 with mild residual ptosis and restriction of extraocular movement

CDC = Centers for Disease Control and Prevention; CDV = cidofovir; IBD = inflammatory bowel disease; VIG IV = vaccinia immunoglobulins IV; PCR = polymerase chain reaction.

First Retrospective Study on Monkeypox in 2022

At the beginning of the global monkeypox outbreak, Adler et al. conducted a retrospective study reviewing cases of monkeypox infections between 2018 and 2021 in the UK.[36] In this study, 7 patients were identified as having confirmed human monkeypox, 5 patients were in isolation for 3 weeks, 3 patients were treated with brincidofovir (200 mg once a week), and 1 patient was treated with tecovirimat (600 mg twice daily for 2 weeks). The patient treated with tecovirimat was reported to have a shorter duration of viral shedding and illness (10 days of hospitalization) compared with the other 6 patients. The 3 patients who were treated with brincidofovir developed transaminitis that resolved with treatment discontinuation. The 1 patient treated with tecovirimat did not report any adverse effects.

Recent Case Reports and Case Series (July to August 2022)

Between July and August 2022, additional case reports and case series have been published describing further experience with tecovirimat.

Monkeypox May Be Treated as Other Infections Initially

Ajmera et al. published a case report describing a 26-year-old man who was polygamous and homosexual and who have been treated with tecovirimat for monkeypox infection.[51] This individual has a past medical history of syphilis and on HIV PrEP with tenofovir-emtricitabine. He first presented to the emergency department with worsening rash on his tongue and around his mouth that had started 5 days prior. He had unprotected sexual intercourse with a man 1 day before the onset of his symptoms. He was prescribed nystatin for oral thrush and Valtrex for suspected herpes simplex virus infection. His oral lesions continued to increase in number, and he developed a sore throat, tongue swelling, burning sensation in his mouth, and difficulty and pain with swallowing solid food. He had a fever and lymphadenopathy. On day 3 of hospitalization, he was started on tecovirimat due to significant swelling of the tongue and increasing number of lesions. The symptoms started to improve on day 5 of hospitalization. The patient tolerated the diet without difficulty and the lesions began to crust. He was discharged home with a 2-week course of tecovirimat along with fluconazole.

Exploring Use of Tecovirimat in Severe Proctitis

Lucas et al. have also released a publication describing 2 patients with monkeypox infection with severe proctitis who were treated with oral tecovirimat in the District of Columbia.[52] Both patients developed symptoms (e.g., fever, lymphadenopathy) and severe rectal pain that required opioids for management. Following the initiation of tecovirimat at 600 mg oral twice daily, the rectal pain improved within 36 to 48 hours.

The authors concluded that the early use of tecovirimat should be considered for patients with monkeypox and severe proctitis until randomized controlled trials of tecovirimat can be done to inform future use.

Tecovirimat Initiation: At Least a Week From Symptom Onset

Matias et al. published an initial series from Massachusetts describing 3 monkeypox cases treated with tecovirimat.[53] Three men, 2 in their 20s, and one in their 40s, all had confirmed monkeypox infection with polymerase chain reaction (PCR) results. Patient 2 in Table 13 is a man in his 20s with HIV and on antiretroviral therapy with a suppressed viral load and a CD4 count above 500 cells/uL. Patient 3 is in his 40s and is on pre-exposure prophylaxis for HIV. Additional details related to their monkeypox virus and tecovirimat treatment are summarized in Table 11. The preliminary data from this series suggest that tecovirimat is not initiated immediately upon monkeypox confirmation with PCR results. Rather patients were monitored and treatment was initiated if there were clinical signs of worsening (e.g., extensive involvement of lesions) or additional risk factors (e.g., the patient was HIV positive).

Table 11: Three Monkeypox Cases From Massachusetts

Patient	Small vaccination history	HIV, hep B or C status	Systemic symptoms	Lymphadenopathy	Number of lesions	Genital lesions	Distribution of other lesions	Symptom onset to tecovirimat initiation	Days of tecovirimat therapy	7-day self-reported outcomes	21-day self-reported outcomes	Adverse effects at day 7
1	Not reported	None	Urethritis, fever, chills, malaise	Left inguinal	Not reported	Genital	Face, oropharynx, hands, and feet	12	14	No new lesions	Recovered	Headache, ALT elevation
2	Jynneos	HIV	Fever, chills, myalgia, left tonsillar pain, and odynophagia	Cervical	Not reported (but extensive)	Not reported	Forearms and hands, gingival area, upper and lower extremity	8	14	No new lesion	Recovered	Loose bowel movement
3	Not reported	None	Malaise, subjective fevers	Not reported	Not reported	Anal and genital	Chest, arm, eyelid (no corneal involvement)	11	14	Recovered	Not reported	None

ALT = alanine transaminase.

A Case Series of 25 Patients Treated With Tecovirimat

More recently, Desai et al. have also published a case series of 25 patients with confirmed monkeypox infection who were treated with tecovirimat at the UC Davis Medical Center in Sacramento between June 3, 2022, and August 13, 2022.[54] In this review, all patients were self-reported male, the median age was 40.7 years, 9 patients had HIV, 1 patient received the smallpox vaccine more than 25 years ago, and 4 patients received 1 dose of Jynneos after symptom onset, although the timing of exposure relative to the vaccine was not reported. Systemic symptoms, lesions, or both were present for a mean of 12 days at the time of tecovirimat treatment. In total, 92% of patients had genital and/or perianal lesions, and 52% had fewer than 10 lesions over their entire body. All patients had pain associated with lesions. Patient 9 received 21 days of therapy. For this patient, new lesions were still being reported on day 7 and day 14 of therapy. For patient 13, the dose was increased on day 7 due to delayed clinical response and borderline weight-based dosing. Complete resolution of lesions was reported in 10 patients (40%) on day 7 of therapy, while 92% had resolution of lesions and pain by day 21. The most commonly reported adverse events on day 7 of therapy were fatigue, headache, nausea, itching, and diarrhea. The patients' details are summarized in Table 12.

Table 12: Patients With Monkeypox Infection Treated With Tecovirimat

Patient	Small vaccination history	HIV, hep B or C status	Systemic symptoms	Lymphadenopathy	Number of lesions	Genital lesions	Distribution of other lesions	Symptom onset to tecovirimat initiation (days)	Days of tecovirimat therapy	7-day self-reported outcomes	21-day self-reported outcomes	Adverse effects at day 7
1	Unknown	HIV	None	None	10 to 100	Perianal	Chest, eyelid, right hand, right knee, shoulder	24	14	Recovered	Recovered	Backache, fatigue
2	Unknown	None	Fever, backache, fatigue	None	< 10	Perianal	Face, neck, arms	17	14	Recovered	Recovered	None
3	No	None	Nausea, chills, myalgias	None	< 10	Genital		6	14	Recovered	Recovered	None
4	No	None	Fever	None	10 to 100	Genital	Scalp, face, forearm, hands, chest, back, legs, buttock	8	14	No new lesions	Recovered	None
5	No	None	Fatigue	Inguinal	< 10	Genital		15	14	No new lesions	Recovered	Headache, nausea
6	No	HIV	Fever, fatigue	Inguinal and neck	10 to 100	Perianal	Face, abdomen, groin, back, legs	6	14	No new lesions	Recovered	None
7	No	HIV	Fever, backache, headache, diarrhea, chills	None	10 to 100	Perianal	Neck, arms, head, legs, abdomen back	9	14	Recovered	Recovered	Hand burning weak nails

Patient	Small vaccination history	HIV, hep B or C status	Systemic symptoms	Lymphadenopathy	Number of lesions	Genital lesions	Distribution of other lesions	Symptom onset to tecovirimat initiation (days)	Days of tecovirimat therapy	7-day self-reported outcomes	21-day self-reported outcomes	Adverse effects at day 7
8	Unknown	HIV	None	None	<10	Genital		16	14	No new lesions	Recovered	None
9	Unknown	None	Malaise, fever	Neck and inguinal	10 to 100	Genital	Face, back, arms, hands	10	21	New lesions	New lesions	Fatigue, nausea, itching, headache
10	Unknown	HIV	Fever	Cervical	10 to 100	No	Entire body	12	14	No new lesions	Recovered	Fatigue
11	Unknown	HIV	Fever, sore throat, itching, fatigue	Neck and inguinal	10 to 100	Genital	Throat, chest, arm, abdomen, hand, buttocks	9	14	No new lesions	Recovered	Fatigue
12	No	None	Fever, headache	Right inguinal	10 to 100	No	Scalp, face, neck, abdomen, arms, back	14	14	No new lesions	Recovered	None
13	No	HIV	Fever, headache	None	>100	Perianal and genital	Entire body	10	14	No new lesions	Recovered	None
14	No	None	Headache, shoulder and neck pain	None	10 to 100	Genital	Arms, scalp	16	14	No new lesions	Recovered	Nausea, headache
15	Unknown	None	Headache, hoarseness	Inguinal	<10	Genital		7	14	Recovered	Recovered	None
16	No	HIV	Fever, fatigue, headache, constipation, sore throat	Inguinal	<10	Perianal	Arm, chest, face	7	14	No new lesions	Recovered	Fatigue

Patient	Small vaccination history	HIV, hep B or C status	Systemic symptoms	Lymphadenopathy	Number of lesions	Genital lesions	Distribution of other lesions	Symptom onset to tecovirimat initiation (days)	Days of tecovirimat therapy	7-day self-reported outcomes	21-day self-reported outcomes	Adverse effects at day 7
17	Unknown	None	Fever, headache, nausea, fatigue	None	10 to 100	Genital	Chest, back	6	14	Recovered	Recovered	None
18	Jynneos	None	Fever, myalgia, headache, sore throat	Inguinal	< 10	Genital	Face, arm, chest	12	14	No new lesions	Recovered	Headache, diarrhea
19	Jynneos	None	Fever, chills, urethritis	None	< 10	Perianal	Arm, thigh	12	14	Recovered	Recovered	None
20	No	None	Fever	Inguinal	<10	Genital	Chest	7	14	No new lesions	No new lesions	None
21	Jynneos	None	Fever, sore throat, back pain	Cervical, inguinal	<10	Perianal and genital	Wrist, chest	19	14	No new lesions	Recovered	Fatigue
22	Remote	None	Fever, sore throat	Cervical	<10	Genital	Arms, legs	14	14	Recovered	Recovered	Headache
23	No	None	Fever, chills, night sweats	None	<10	Genital	Chest, back, arm, shin	13	14	No new lesions	Recovered	Fatigue, nausea
24	Jynneos	None	Fever, chills, fatigue, painful bowel movement	Inguinal	10 to 100	Genital	Head, arm, legs, foot	10	14	Recovered	Recovered	Dry skin
25	Unknown	HIV	Fever	None	<10	Perianal	Chest, back, arms, legs	22	14	Recovered	Recovered	Diarrhea

Notes: Patients with HIV were receiving antiretroviral therapy and confirmed or reported to be virologically suppressed.

Recovered indicates that all lesions were self-reported as crusted or fallen off.

New lesions refers to development of new lesions.

No new lesions; indicates that no new lesions were reported but not yet recovered.

Tecovirimat Experience From Quebec, Canada

In Canada, there are no publications related to recent cases of monkeypox. However, some preliminary cases from Quebec were shared in a webcast by Dr. Jean Longtin of the National Collaborating Centre for Infectious Diseases.[55] According to this webcast, there were 184 confirmed cases or monkeypox in Quebec as of June 22, 2022, of which 11 patients (6%) were treated with tecovirimat. Five of these individuals have HIV and the average age is 41 years (range, 29 to 63). None of the individuals had received the smallpox vaccine, and 50% of the cases developed bacterial infection. In terms of clinical rationale for tecovirimat, the following are the documented justifications: 5 severe head and neck involvement (5 with odynophagia, 1 with conjunctivitis, 1 with trismus, 1 with peritonsillar abscess), 4 individuals had highly symptomatic genital and/or anorectal lesion, and 2 individuals received tecovirimat with the aim to reduce shedding within family. In this series, therapy was initiated on average at day 12 of symptoms (range, 7 to 23 days). Among the individuals treated with tecovirimat, there were no reported intensive care unit admissions, no surgery, and all noted improvements occurred within a few days, although there is no way to compare this with the untreated natural history. The limitation of this preliminary review is that it does not include any vulnerable population, including a highly immunocompromised group (e.g., CD4 < 200 cells/uL), pediatrics patients, or those who are pregnant. It was suggested by the presenter that tecovirimat should be considered in the following scenarios:

- severe and disseminated disease
- severe head and neck involvement
- severe genital or rectal involvement.

A referral to the infectious diseases' expert was recommended if there is high risk for complications, which includes those with significant immunodeficiency, those who are pediatric patients, and those who are pregnant.

Potential Concerns With Drug Resistance

Drug resistance has been reported for cidofovir.[34] To date, there are no known naturally occurring orthopoxviruses resistant to tecovirimat.[3,44] However, this can theoretically occur under drug selection. Amino acid substitutions and insertions in the VP37 proteins have been noted in cowpox virus, vaccinia virus, and camelpox virus isolated under drug selection pressure with tecorivimat.[44]

The possibility of resistance to tecovirimat should be considered in patients whose virus either fails to respond to therapy or who develop recrudescence of disease after an initial period of responsiveness. At least 1 case report has been published that describes the development of resistance to tecovirimat following extended systemic treatment at subtherapeutic plasma levels, along with concurrent topical tecovirimat application.[46]

There have been reports of using tecovirimat with brincidofovir as the combination, which may allow for synergistic effects while minimizing resistance development.[34] Two animal studies were identified to examine the coadministration of brincidofovir and

tecovirimat, in a lethal-dose model. In various dose combinations, brincidofovir and tecovirimat were able to achieve high levels of protection, whereas monotherapy did not.[34] As the evidence was derived from animal studies, future research is needed to delineate how to best minimize tecovirimat resistance, in the context of treating orthopoxvirus infections, and tolerability in human patients for whom brincidofovir has caused significant side effects.

Tecovirimat Use in PEP

While the focus of this review was tecovirimat for the treatment of monkeypox infection, it is important to be aware of ongoing clinical studies that may provide evidence for an expanded role of tecovirimat in PEP. PEP generally relies on adequate case identification and contact tracing, and the risk versus benefit of tecovirimat in this setting is presently unknown.

Preliminary animal studies support the potential combination use of vaccine and antivirals that may improve and/or extend the efficacy of post-exposure vaccination.[56]

There is currently an active study looking at the use of the MVA-BN vaccine with or without tecovirimat to evaluate the safety and pharmacokinetics of tecovirimat, as well as the impact of tecovirimat on the MVA-BN vaccine's immunogenicity. The studied dose of tecovirimat is 600 mg twice daily for 28 days and the primary outcome is geometric mean titer of vaccinia virus–neutralizing antibodies on day 29 and day 43.[57]

Critical Appraisal and Discussion

Given the ethical concerns with evaluating tecovirimat in human patients for potentially lethal smallpox infections, there have only been animal studies that demonstrated the efficacy of tecovirimat. This is in accordance with the requirements of the FDA Animal Rule and Canada's EUND for drug development and approval processes. Given that the model for approval was for a more highly lethal pathogen, external validity with monkeypox is not guaranteed. While there is some evidence to support an antiviral effect, the clinical benefits in terms of patient-important outcomes require more study before definitive statements about efficacy in monkeypox can be made.

Based on the available case reports and evolving data from case series, individuals infected with monkeypox may present late during the progression of disease for medical attention, beyond the optimal window for preventive post-exposure monkeypox vaccine administration. Monkeypox infection can vary greatly in its severity, ranging from self-limiting to (rarely) life-threatening, with a mortality of less than 0.02% in identified cases (4 nonendemic deaths in 27,814 cases) so far in this global outbreak.

In these cases, tecovirimat has usually been initiated in severe disease when individuals become symptomatic with severe pain, presence of mucosal involvement affecting activities of daily living (e.g., eating or feeding), or when lesions begin to spread to multiple areas beyond the initial site of transmission. Preliminary findings suggest tecovirimat is well tolerated.

There is no high-level evidence supporting the use of tecovirimat in the setting of monkeypox infection, and its approval without such data was predicated on the risks of the much more lethal variola virus (i.e., smallpox.). However, randomized controlled trials are in development to validate the efficacy and safety of tecovirimat in the management of monkeypox infection.[58] Use of this drug for monkeypox should therefore preferentially occur in the setting of supported randomized trials unless the risk to the patient is judged to outweigh the lack of usual standard of evidence, such as human clinical trials, for efficacy and safety.

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Appendix 1: Animal Studies With Tecovirimat

Table 13: Key Animal Studies With Tecovirimat

Author, reference	Study key points and/or abstract	Population	Intervention and comparator	Outcome
Berhanu A et al.[59] Berhanu A, Prigge JT, Silvera PM, Honeychurch KM, Hruby DE, Grosenbach DW. Treatment with the smallpox antiviral tecovirimat (ST-246) alone or in combination with ACAM2000 vaccination is effective as a postsymptomatic therapy for monkeypox virus infection. *Antimicrob Agents Chemother.* 2015;59(7):4296-4300.	The therapeutic efficacies of smallpox vaccine (ACAM2000) and antiviral tecovirimat given alone or in combination starting on day 3 postinfection were compared in a cynomolgus macaque model of lethal monkeypox virus infection. Postexposure administration of ACAM2000 alone did not provide any protection against severe monkeypox disease or mortality. In contrast, postexposure treatment with tecovirimat alone or in combination with ACAM2000 provided full protection. Additionally, tecoviroimat treatment delayed until day 4, 5 or 6 post infection was 83% (days 4 and 5) or 50% (day 6) effective.	Cynomolgus macaque model	With or without ACAM2000	Postexposure treatment at day 3 provide full protection
Smith, Scott K et al. Poxvirus Team[60] Smith SK, Olson VA, Karem KL, Jordan R, Hruby DE, Damon IK. In vitro efficacy of ST246 against smallpox and monkeypox. *Antimicrob Agents Chemother.* 2009;53(3):1007-1012.	In Vitro Efficacy of ST 246 against Smallpox and Monkeypox	N/A	In vitro efficacy study	Support ST-246 as an alternative for treating orthopoxvirus infections
Stabenow J et al.[61] Stabenow J, Buller RM, Schriewer J, West C, Sagartz JE, Parker S. A mouse model of lethal infection for evaluating prophylactics and therapeutics against Monkeypox virus. *J Virol.* 2010;84(8):3909-3920.	Here we report that a relatively low-dose intranasal (IN) infection induces 100% mortality in the stat1 model by day 10 postinfection with high infectious titers in the livers, spleens and lungs of moribund animals. Vaccination with modified vaccinia virus Ankara (MVA) followed by a booster vaccination is sufficient to protect against an intranasal MPXV challenge and induces an immune response more robust than that of a single vaccination. Furthermore, antiviral treatment	Moribund animal	Vaccine + Cidofovir / ST-246	Cidofovir and ST-246 protects when administered on day of infection

Author, reference	Study key points and/or abstract	Population	Intervention and comparator	Outcome
	with CMX001 (HDP-cidofovir) and ST-246 protects when administered as a regimen initiated on the day of infection. Thus, the Stat1 model provides a lethal murine platform for evaluating thearpeutics and for investigating the immunological and pathological response to MPXV infection.			
Sbrana E et al.[62] Sbrana E, Jordan R, Hruby DE, et al. Efficacy of the antipoxvirus compound ST-246 for treatment of severe orthopoxvirus infection. *Am J Trop Med Hyg.* 2007;76(4):768-773.	Efficacy of the new antipoxvirus compound ST-246 was evaluated as treatment of monkeypox (MPX) virus infection in a ground squirrel model of the disease. Ground squirrels were given a lethal dose of MPX virus and were then treated orally at various times post-inoculation (pi) with 100mg/kg/day of ST-246. Morbidity and mortality, clinical laboratory results, viral load, and pathology of placebo and treatment groups were compared. All animals that started treatment with ST-246 on days 0, 1, 2 and 3 pi survived lethal challenge with MPX virus; 67% of animals treated on day 4 pi also survived. In contrast, 100% of the placebo group died. Most of the ST-246 treated animals showed no evidence of clinical disease or alteration of baseline clinical laboratory values and had minimal histopathologic changes. These results suggest that ST-246 is a promising candidate for early treatment of severe orthopoxvirus infection.	Ground squirrel model	Placebo controlled	ST-246 treated animals showed no evidence of clinical disease.

Note: ST-246 is tecovirimat.

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Appendix 2: Summary of Retrospective Study of Monkeypox Cases

Table 14: Clinical Course and Response to Treatment in 7 Patients With Monkeypox[36]

	2018			2019	2021		
Course or response	**Patient 1**	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**	**Patient 6**	**Patient 7**
Site of HCID unit	London	Liverpool	Newcastle	London	Liverpool	Liverpool	Liverpool
Age range, years	30 to 40	30 to 40	30 to 40	40 to 50	30 to 40	0 to 2	30 to 40
Sex	Male	Male	Female	Male	Male	Female	Female
Transmission rank	Isolated	Index	Secondary	Isolated	Index	Secondary	Tertiary
Country of acquisition	Nigeria	Nigeria	UK	Nigeria	Nigeria	UK	UK
Smallpox vaccination history	None	None	MVA-BN 6 days post-exposure or 12 days pre-illness	None	None	None	None
HIV, hepatitis B, and hepatitis C status	Negative	Negative	Negative	Negative	Negative	Not tested (parents negative)	Negative
Prodrome	Fever and night sweats (2 days)	Fever and groin swelling (4 days)	Coryzal illness (1 day)	Fever and headache (2 days)	None	None	None
Lymphadenopathy	Yes	Yes	No	Yes	Yes	Yes	No
Approximate maximum number of concurrent lesions	150	100	32	100	40	30	10
Distribution of lesions	Face, scalp, trunk, limbs, palms, glans penis, and scrotum	Face, trunk, limbs, palms, soles, and scrotum	Face, trunk, hands (including nail bed), and labia majora	Face, scalp, trunk, limbs, penile shaft, palms, and soles	Face, trunk, limbs, palms, and penile shaft	Face, trunk, arms, and legs	Face, trunk, arms, and hands

Course or response	2018			2019	2021		
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Complications of illness	Low mood and emotional lability; ulcerated inguinal lesion with delayed healing	Deep tissue abscesses, severe pain, and low mood	Conjunctivitis, painful disruption of thumbnail from subungual lesion	Ulcerated inguinal lesion with delayed healing	None	Pruritus and contact dermatitis from cleaning products	Low mood
Specific management of complications	Clinical psychology input	Empiric broad-spectrum antibiotics, abscess drainage, and analgesia (including opiate and neuropathic drugs)	Antibacterial eye drops	Empiric azithromycin	Nothing specific	Calamine lotion and short course of antibiotics at the onset of dermatitis	Nothing specific
Monkeypox viral DNA detected							
Blood	Yes	Yes	Yes	Yes	No	Yes	Yes
Nose or throat swab	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Urine	Yes	Yes	Yes	Yes	No	No	No
Antivirals received	Brincidofovir 200 mg (1 dose) orally	Brincidofovir 200 mg (2 doses) orally	Brincidofovir 200 mg (2 doses) orally	None	None	None	Tecovirimat 600 mg twice daily for 2 weeks orally
Days of illness before treatment commenced	7	6	7	—	—	—	5
Complications of treatment	Transaminitis (peak ALT 331 U/L)	Transaminitis (peak ALT 550 U/L)	Transaminitis (peak ALT 127 U/L), nausea, and	—	—	—	None

Course or response	2018			2019	2021		
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
			abdominal discomfort				
Duration of hospitalization with monkeypox, days	26	27	35	39	13	22	10
Outcome of monkeypox infection	Full recovery	Full recovery	Full recovery	Full recovery	Full recovery	Full recovery	Full recovery

ALT = alanine transaminase; HCID = high consequence infectious disease; MVA-BN = modified vaccinia Ankara.

Note: This table has not been copy-edited.