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An opportunity for evidence-based care of individuals with monkeypox

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What is monkeypox and why is it important now?

Monkeypox virus is an orthopoxvirus, in the family poxviridae, which belongs to the same genus as smallpox (the causative agent of smallpox) and vaccinia viruses (the virus used in the smallpox vaccine).[1] Monkeypox is a viral zoonotic infection that is endemic in the tropical forest of central and western Africa and is sporadically exported to other regions. Animal-to-human transmission occurs through contact with infected animal tissue, for example through a bite or the ingestion of infected meat. Human-to-human transmission occurs through direct contact with mucocutaneous lesions and respiratory droplets, fomite or perinatal transmission.[2] Current estimated incubation period ranges between 3 and 20 days.

Monkeypox was first detected in 1958 in an outbreak of monkeys transported to Copenhagen, Denmark from Africa for research purposes, and for the first time in humans at the Democratic Republic of the Congo in 1970.[3] Since then, the number of detected cases increased with reports in Central and West Africa by 1970, 2004 and 2017, in USA by 2003, and UK and Israel by 2018. On 13 May 2022, the WHO reported new cases of monkeypox in 12 Member States where the disease is not endemic, not linked to travel to endemic areas, and on 23 July, the Director of the WHO declared this disease as a public health emergency of international importance.[4 5] As of 29 August 2022, a total of 47 652 cases with 13 total deaths have been reported worldwide, 6 of which were observed in countries where the disease is not usually endemic.[6]

In infected individuals, monkeypox usually presents as a self-limiting illness with most patients recovering within two to four and its most characteristic clinical feature is a smallpox-like rash. Typical symptoms of monkeypox are rash, fever, chills, lymphadenopathy, headache, backache, myalgia, pharyngitis, cough, asthenia, malaise, nausea and vomiting. Is important to differentiate this rash from other vesicular eruptions like herpes simples, varicella and smallpox.[2]

During this emergency outbreak, some patients have presented with severe/intense anorectal pain, tenesmus, rectal bleeding or purulent or bloody stools, associated with perianal/rectal lesions and proctitis.[2] A large retrospective observational study at a health centre in London identified 177 people with the disease between 13 May and 1 July. Hundred per cent had mucocutaneous manifestations, and genital or perianal lesions, or both, in 174 participants (88.3%, 95 CI: 83.0% to 92.4%).[7]

How was monkeypox treated before this outbreak?

Traditional management strategies are focused on the prevention of infection and transmission, and supportive treatment based on symptom control with no disease-specific treatment. Implemented measures included skin and eye cleansing, topical application of liquid trifluridine, analgesic and antipyretic medications, corticosteroids, adequate hydration, and nutrition, vitamin supplementation and of concomitant treatment of secondary bacterial infections.[8]

What is the current evidence on pharmacological interventions?

There are currently four antiviral drugs (tecovirimat, brincidofovir, cidofovir and NIOCH-14) and Vaccinia Intravenous Immunoglobulin in development with potential for the treatment of monkeypox. These treatments are intended to ameliorate the spread of the virus in the body, prevent progression to and treat severe forms of the disease. Currently, terovirimat (SIGA) is the only intervention approved for monkeypox treatment under expanded access (which entails a protocol for data collection), by the United States Food and Drug Administration and the European Medicines Agency.[9 10] Tecovirimat targets and inhibits the activity of the orthopoxvirus VP37 protein (encoded and highly conserved in all members of the orthopoxvirus genus) and blocks its interaction with cellular Rab9 GTPase and TIP47, preventing the formation of enveloped virions capable of spreading to other cells. Terovirimat can be administered orally (600 mg (three capsules) every 8–12 hours for 14 days) or intravenously (200–300 mg every 12 hours for 14 days).[9]

We are currently surveying the emerging evidence with periodic searches in Epistemonikos and study registries (ICTRP platform). Up to 20 August 2022, we have not identified studies informing on antiviral drugs efficacy for the treatment of patients with monkeypox beyond this emergency. Nevertheless, we identified 10 ongoing studies for tecovirimat and one for brincidofovir (table 1).

Table 1 Registered clinical trials for monkeypox antiviral treatments

Trial identification	Design	Intervention and comparison	Population characteristics	Status
NCT02474589	RCT phase III	Tecovirimat vs placebo	Healthy volunteers, 19–80 years.	Completed Has results
NCT00907803	RCT phase II	Tecovirimat vs placebo	Healthy volunteers, 18–75 years.	Completed Has results
NCT00728689	RT phase I	Tecovirimat	Healthy volunteers, 18–50 years	Completed Has results
NCT04971109	RCT phase III	Tecovirimat vs placebo	Healthy volunteers, 18–80 years	Recruiting
NCT04392739	RT phase IV	Tecovirimat vs placebo	Healthy volunteers, 18–50 years., body weight more than 120 kg	Completed
ISRCTN13846827	RT phase I	Tecovirimat	Healthy volunteers, 18–50 years.	Active, not recruiting
NCT02080767	Expanded access	Tecovirimat	Virus exposure, Paediatric and adult	Recruiting
ISRCTN43307947	Expanded access	Tecovirimat	Monkeypox, Paediatric and adult	Recruiting
NCT03972111	RT phase IV	Tecovirimat	Virus exposure and monkeypox, Paediatric and adult	Recruiting
NCT02080767	Expanded access	Tecovirimat	Virus exposure, Paediatric and adult	Recruiting
ACTRN12616001657415	RCT phase I	Brincidofovir vs placebo	Healthy volunteers, 18–55 years	Unknow

RCT, Randomized Controlled Trial; RT, Randomized Trial.

Tecovirimat

We found four registered randomized controlled trials (RCTs), four non RCTs and three Expanded Access studies. Based on the studies that publish results, which included 575 healthy individuals, tecovirimat may increase adverse events based on low certainty evidence due to low number of events, while impact in serious adverse events is uncertain due to very low number of events (very low certainty). Further research is needed.

Brincidofovir

A RCT was identified that compares the effect of increasing doses of intravenous brincidofovir in healthy adult subjects to assess drug pharmacokinetics and safety. Currently no results are available for this study.

In addition, a multiregional international global randomised, placebo-controlled trial to evaluate the safety and efficacy of the new drugs for the treatment of human monkeypox (CORE) has been initiated. This phase III RCT will assess different interventions for the management of adults and children with monkeypox in multinational collaborative platform.[11] The results of this study will help to reduce the uncertainty surrounding these treatments as the studies against COVID-19 did.

What are the current recommendations for the treatment of this condition?

The current WHO recommendations suggest considering antivirals only in the context of clinical trials or under the Monitored Emergency Use of Unregistered and Investigational Interventions framework, which is the ethical framework for the exceptional use of unproven interventions outside of research that corresponds to the "expanded access" regulatory category (table 2).[12]

Considering that antivirals' efficacy and safety for the treatment of patients with monkeypox are currently uncertain, these interventions should not be used outside well-designed randomised controlled trials as suggested by WHO and CDC. Exceptionally, if it is not possible to initiate studies immediately during the emergency, unproven interventions like antivirals for monkeypox may

Table 2 Guideline recommendations on monkeypox antiviral treatments

Institutions	Recommendation
WHO[14]	Recommends considering the use of antivirals in persons with risk for severe disease, or those that present or develop severe monkeypox. The use of antivirals only in the context of clinical trials and, if not possible, they may be used under the MEURI ethical framework that corresponds to the 'expanded access' regulatory category.
CDC[15]	Recommends considering the use of antivirals (any of those approved in the US) in people with severe disease (haemorrhagic disease, confluent lesions, sepsis, encephalitis and other conditions that require hospitalisation), at risk of progressing to severe disease (people with immunocompromise, paediatrics, with a history or history of exfoliative skin, pregnant and lactating women, and in people with complications) and with aberrant infections.
Government of Canada[16]	Does not mention any treatment for monkeypox.
British HIV Association[17]	Recommends the use of antivirals (any of those approved in the UK) only in the context of clinical trials.
Government of India[18]	Does not mention any treatment for monkeypox.

*

CDC, Centers for Disease Control and Prevention ; MEURI, Monitored Emergency Use of Unregistered and Investigational Interventions.

be offered outside research contexts if the following four ethics criteria are met: (1) the use of the unproven intervention must be justified based on its *potential* to benefit patients, which has to be carefully assessed on the basis of the available evidence (2) ethical and regulatory oversight must be ensured; (3) informed consent must be provided by those receiving the intervention; and (4) there must be a contribution to the generation of knowledge, which entail collection of key data that can shed light on the intervention's safety and efficacy.[12]

Until results of appropriately designed studies assessing antiviral effects became available, public health and hygiene measures and symptom control aimed to avoid disease spread continue to be key interventions for the management of monkeypox.[13]

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