NORTH Dakota | Health & Human Services
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HEALTH ALERT NETWORK | HEALTH ADVISORY | November 22, 2022

Therapeutics Update for Monkeypox Infections

The North Dakota Department of Health and Human Services (HHS) is providing this information from the Centers for Disease Control and Prevention (CDC) regarding managing patients receiving therapeutics. The CDC is alerting providers of two cases monkeypox with confirmed tecomirivat resistance. Both patients had immunocompromising conditions and progressive, severe manifestations of monkeypox and received prolonged courses (>14 days) of tecomirivat. Providers are encouraged to reach out to HHS for further guidance and consultation when these situations arise.

The Laboratory Services Section at HHS offers PCR testing for monkeypox. More information on laboratory testing, including specimen collection and transport, is available by calling 701-328-6272.

Tecomirivat can be obtained by calling HHS Department Operations Center at 701-328-0707.

This is an official
CDC HEALTH UPDATE

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Update on Managing Monkeypox in Patients Receiving Therapeutics

Summary
Monkeypox cases have declined since mid-August 2022 in the United States; however, new cases—including clinically severe cases—continue to occur. While there are currently no treatments specifically approved for monkeypox, therapeutics developed for patients with smallpox have been deployed during the current outbreak. This Health Alert Network (HAN) Health Update provides clinicians and public health officials with new information about managing monkeypox in patients requiring therapeutics.

Specifically, this Health Update

- Notifies healthcare providers and public health departments about two cases of laboratory-confirmed tecovirimat resistance. The patients in both cases had immunocompromising conditions and progressive, severe manifestations of monkeypox, and both patients received prolonged courses (>14 days) of tecovirimat.
- Highlights that viral resistance to tecovirimat has been rare, and when documented has occurred with prolonged administration and severe clinical outcomes.
- Highlights therapeutics, including cidofovir, brincidofovir, and vaccinia immune globulin intravenous (VIGIV), each of which can be administered concurrently with tecovirimat for certain patients with (or at high risk for) severe monkeypox.
- Encourages testing for tecovirimat resistance and pharmacokinetics for public health surveillance purposes in patients who have persistent or progressive monkeypox after completing 14 days of tecovirimat.
- Encourages diagnostic testing for monkeypox, HIV, and other sexually transmitted infections in every sexually active person for whom monkeypox is suspected.

Background

Tecovirimat

Tecovirimat is a virostatic agent that targets a major envelope protein conserved across orthopoxviruses (VP37 in monkeypox virus). While naturally circulating tecovirimat-resistant monkeypox viruses have not been observed, previous cell culture experiments performed during drug development and independent studies performed prior to the current outbreak have demonstrated induction of resistance following tecovirimat exposure. Furthermore, experimental data have highlighted a relatively low barrier to resistance, with single amino acid substitutions at various locations in the F13L gene coding VP37 conferring substantial reductions in tecovirimat's antiviral activity.[1]

For most patients with intact immune systems, monkeypox is a self-limited illness that does not require anti-viral treatment to clear disease. For those who do require tecovirimat treatment, disease usually resolves during a 14-day course of oral tecovirimat. Most patients with indications for tecovirimat do not require treatment with any additional therapeutics.

Identification of Tecovirimat Resistance

Since the start of the current monkeypox virus outbreak and as part of routine surveillance activities, the Centers for Disease Control and Prevention (CDC) and other laboratories have evaluated clinical monkeypox specimens from patients receiving tecovirimat and those not receiving tecovirimat. The evaluation has included a focus on the presence of F13L mutations that might indicate tecovirimat resistance. Specifically, CDC has been evaluating suspect cases (identified either by F13L sequencing efforts or by suspicion based on clinical course) for phenotypic resistance.

CDC has confirmed the presence of tecovirimat-resistant viruses in two patients. CDC was notified of one patient with persistent monkeypox whose viral isolates demonstrated tecovirimat resistance. Isolates from this patient, sequenced by the state laboratory, demonstrated genotypic changes in F13L associated with tecovirimat resistance. In addition, CDC confirmed phenotypic resistance to tecovirimat in cell culture. CDC also confirmed tecovirimat resistance in another patient who was tested due to poor response to tecovirimat treatment; genotypic and phenotypic testing subsequently confirmed resistance.

Both patients had severe immunocompromising conditions with disseminated and progressive monkeypox infection despite prolonged treatment (>14 days) with tecovirimat. Both patients required inpatient treatment. These are the first known cases of monkeypox with laboratory-confirmed tecovirimat resistance in the United States.

CDC has analyzed sequences from more than 4,000 specimens from across the world, and only 13 changes in the F13L protein were found, including the two cases included in this HAN Update. Isolates from the other 11 cases were sensitive to tecovirimat in cell culture. These 4,000 specimens in which the F13L gene was analyzed are from CDC surveillance efforts and include isolates from individuals receiving and not receiving tecovirimat.

Orthopoxvirus resistance to tecovirimat had been observed previously in a person with progressive vaccinia following vaccination with ACAM2000.[2] This patient was severely immunocompromised from chemotherapy, and tecovirimat resistance developed late in disease after prolonged treatment during which levels of tecovirimat below target concentrations were intermittently observed. The patient recovered after receiving brincidofovir and VIGIV as concurrent therapies with tecovirimat.

Tecovirimat resistance testing is an important part of ongoing public health surveillance during the current outbreak. For patients with suspected resistance, ideally both resistance testing and pharmacokinetic testing should be performed to determine if any cases of confirmed resistance are associated with drug levels below target concentrations. However, neither tecovirimat resistance nor pharmacokinetic test results are available to inform patient treatment because neither are approved as Clinical Laboratory Improvement Amendments (CLIA) regulated procedures, and culture-based resistance testing requires multiple viral propagation steps and takes weeks to perform. Therefore, management of patients for whom resistance is suspected will need to be guided by the patient's clinical status and may warrant consideration of additional therapeutics as outlined below.

Other Therapeutics for Managing Monkeypox
In patients who have severe disease or certain patients who are at high risk for progression to severe disease, such as patients with HIV and CD4 counts <350 cells/mm^3 or other severely immunocompromising conditions, the use of two or more therapeutics should be considered based on the individual clinical situation. In addition to tecovirimat (oral and intravenous), available therapeutics include cidofovir (intravenous), brincidofovir (oral), and VIGIV. Cidofovir is commercially available; intravenous tecovirimat, brincidofovir, and VIGIV are only available via CDC or FDA approval for release from the Strategic National Stockpile (SNS).

For any patients who may benefit from multiple therapeutics, consultation with CDC as well as infectious disease specialists and other experts is encouraged. For CDC consultation, contact the CDC Emergency Operations Center (EOC) at 770-488-7100.

Cidofovir and Brincidofovir
Cidofovir is a commercially available antiviral medication that is approved by the FDA for the treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS). It has been shown to be effective against orthopoxviruses in *in vitro* and animal studies. As of October 31, 2022, brincidofovir, an oral prodrug of cidofovir, is available from the SNS to treat monkeypox infections through an FDA-authorized single-patient emergency use Investigational New Drug protocol (IND) upon clinician-request (submitted to FDA). Serious renal toxicity or other adverse events have not been observed during treatment of cytomegalovirus infections with brincidofovir as compared to treatment using cidofovir. Cidofovir should not be used simultaneously with brincidofovir.

Brincidofovir is available for people with positive test results for orthopoxvirus or monkeypox virus who:

1. Have severe disease OR are at high risk for progression to severe disease
2. AND meet either of the following:
    - Experience clinically significant disease progression while receiving tecovirimat (oral or IV) or develop recrudescence of disease after an initial period of improvement, OR
    - Are otherwise ineligible or have a contraindication for oral or intravenous tecovirimat

In deciding whether to request and administer brincidofovir, clinicians should be aware of its side effect profile. Clinicians who would like to treat their patients with brincidofovir should submit an e-IND request to FDA by email (DDI.EIND@fda.hhs.gov) or call (301-796-3400 or 1-855-543-3784) during normal business hours (8:00 am-4:30 pm ET Mondays-Fridays). After hours, call the FDA Emergency Coordinator at 1-866-300-4374 or 301-796-8240, or email CDER-EIND@fda.hhs.gov, and call the CDER Emergency Coordinator at 301-796-9900.

Recommendations for Healthcare Providers
- Consider tecovirimat as first-line therapy for eligible patients with monkeypox. It is an antiviral medication approved by the FDA for treating smallpox in adults and children. Data are not available on the effectiveness of tecovirimat in treating monkeypox infections in people, but studies

using a variety of animal species have shown that tecovirimat is effective in treating disease caused by orthopoxviruses.

- Consider testing lesion swab specimens for tecovirimat resistance and plasma pharmacokinetic sample collection for any patient who, after completing 14 days of tecovirimat treatment, experiences persistent or newly emergent monkeypox lesions. Ideally, both resistance testing and pharmacokinetic testing should be performed to determine if any cases of confirmed resistance are associated with drug levels below target concentrations. CDC provides detailed instructions for collecting and submitting specimens for resistance testing and pharmacokinetic testing. Pharmacokinetic testing is performed by a designated lab, not at CDC.
- Recognize that patients with severe immunocompromise may require longer courses of tecovirimat, as well as additional therapies, until their immune systems can effectively clear the virus. Tecovirimat can be extended on a day-by-day basis beyond its standard 14-day course based on clinical course.
- Note that no transmission of tecovirimat-resistant monkeypox virus has been documented so far.
- Concurrent with tecovirimat therapy, for immunocompromised patients, make efforts to facilitate competent native immunity (e.g., ensure persons with HIV are receiving effective antiretroviral therapy) and limit the use of immunocompromising therapies (e.g., chemotherapy, TNF inhibitors), if feasible. Restoring immune function is an important strategy to minimize morbidity and mortality associated with monkeypox and may decrease the duration of tecovirimat therapy for these patients.
- Counsel patients about the critical importance of taking oral tecovirimat with fatty meals to ensure adequate gastrointestinal absorption and maximize serum levels of the drug. Inadequate serum levels could promote resistance as described above.
- If you are a provider prescribing tecovirimat, consider first seeking access through enrollment in the AIDS Clinical Trials Group (ACTG) Study of Tecovirimat for Human Monkeypox Virus (STOMP) trial, which is evaluating the efficacy of tecovirimat. In this study, all adults with severe monkeypox, severe immunodeficiency, or other noted criteria will be enrolled in the open-label arm to receive oral tecovirimat.
- For patients not eligible for the STOMP trial or who decline to participate, contact your local health department to receive tecovirimat through the CDC's Expanded Access-IND.
- Consider the use of two or more therapeutics in patients who have severe monkeypox or certain patients who are at high risk for progression to severe disease. These include patients with HIV and CD4 counts <350 cells/mm^3 and patients with other severely immunocompromising conditions. Consultation with CDC, infectious disease specialists, and other experts for any patient who may benefit from receiving multiple therapeutics is encouraged.
- Vaccination with JYNNEOS remains an important tool to prevent monkeypox in at-risk patients.
- Test for monkeypox, HIV, and other sexually transmitted infections in every sexually active adult and adolescent in whom monkeypox is suspected.
- Contact local and state health departments early for guidance and to secure necessary resources for treatment when there is concern for progression to severe manifestations or when severe manifestations are present. To request CDC clinical consultation, contact the CDC Emergency Operations Center (EOC) at 770- 488-7100.

Recommendations for Public Health Jurisdictions

- Encourage healthcare providers to submit specimens for tecovirimat resistance (sequencing and/or culture-based phenotypic testing) and pharmacokinetic testing efforts in patients with persistent or progressive monkeypox virus lesions despite completing a 14-day course of treatment with tecovirimat.
- Contact the CDC Emergency Operations Center (EOC) at 770-488-7100 with concerns related to possible tecovirimat-resistant cases of monkeypox in your jurisdiction based on clinical suspicion or F13L sequencing.
- Encourage all providers prescribing oral tecovirimat to first seek access through enrollment in the ACTG STOMP trial.
- Facilitate easy and quick access to monkeypox therapeutics across jurisdictions.
- Facilitate and encourage diagnostic testing for monkeypox, HIV, and other sexually transmitted infections in every sexually active adult and adolescent in whom monkeypox is suspected.

Recommendations and Information for the Public

- There are no treatments specifically for monkeypox. However, because the viruses that cause monkeypox and smallpox are similar, drugs developed to treat smallpox can be used to treat monkeypox.
- Talk to your healthcare provider about getting vaccinated if you have risk factors for monkeypox or may have been exposed to monkeypox.
- If you are living with HIV and are at risk for monkeypox, taking antiretroviral therapy as prescribed is essential for your overall health and to reduce your risk of developing severe monkeypox if you get infected.
- Oral tecovirimat (also known as TPOXX) is best absorbed into your body when taken at the same time as you eat fatty food. If your doctor has prescribed you oral tecovirimat, take each dose with a fatty meal (at least 25 grams of fat, such as a large cheeseburger and fries) to ensure the medication is as effective as possible.
- If your doctor has prescribed you oral tecovirimat, take your tecovirimat as prescribed by your doctor with fatty meals, and for the full time period your doctor prescribed. If your monkeypox sores do not go away or continue to get worse after you have taken 14 days of oral tecovirimat, please seek medical care.

For More Information

- For access to treatment or guidance on how and when to administer different monkeypox treatment options, contact the CDC Emergency Operations Center (EOC) at 770-488-7100.
- Information on available therapeutics for monkeypox
- Information on the AIDS Clinical Treatment Group (ACTG) STOMP trial

References

1. Food and Drug Administration. Drug Approval Package: TPOXX (tecovirimat). https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/208627Orig1s000TOC.cfm Accessed November 8, 2022.
2. Lederman ER, et al. Progressive vaccinia: case description and laboratory-guided therapy with vaccinia immune globulin, ST-246, and CMX001. J Infect Dis. 2012 Nov;206(9):1372-85. doi: 10.1093/infdis/jis510. Epub 2012 Aug 16. PMID: 22904336; PMCID: PMC3529603. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3529603/pdf/jis510.pdf Accessed November 8, 2022.

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