



November 22, 2022

Update: Managing Mpox in Patients Receiving Therapeutics

On November 17, 2022, the U.S. Centers for Disease Control and Prevention issued [an update](#) on managing mpox in patients receiving therapeutics related to viral resistance to tecovirimat (TPOXX) and the role of concurrent administration of additional therapeutics with tecovirimat for certain patients with (or at high risk for) severe mpox.

Summary of Update:¹

Mpox 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 mpox, therapeutics developed for patients with smallpox have been deployed during the current outbreak. 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 mpox.
- Encourages testing for tecovirimat resistance and pharmacokinetics for public health surveillance purposes in patients who have persistent or progressive mpox after completing 14 days of tecovirimat.
- Encourages diagnostic testing for mpox, HIV, and other sexually transmitted infections in every sexually active person for whom mpox is suspected.

Tecovirimat Resistance:¹

Since the start of the current mpox virus outbreak and as part of routine surveillance activities, the Centers for Disease Control and Prevention (CDC) and other laboratories have evaluated clinical mpox 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. Both patients had severe immunocompromising conditions with disseminated and progressive mpox infection despite prolonged treatment (>14 days) with tecovirimat. Both patients required inpatient treatment. These are the first known cases of mpox with laboratory-confirmed tecovirimat resistance in the United States.

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 Mpox:¹

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/mm³ 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 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 mpox 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 mpox 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. 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:¹

- Consider tecovirimat as first-line therapy for [eligible patients](#) with mpox. 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 mpox 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 mpox 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 mpox 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 mpox 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 mpox Virus \(STOMP\) trial](#), which is evaluating the efficacy of tecovirimat. In this study, all adults with severe mpox, 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 mpox or certain patients who are at high risk for progression to severe disease. These include patients with HIV and CD4 counts <350 cells/mm³ 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 mpox in at-risk patients.
- Test for mpox, HIV, and other sexually transmitted infections in every sexually active adult and adolescent in whom mpox 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.

References:

1. U.S. Centers for Disease Control and Prevention (CDC). Health Alert Network (HAN) 00481. [Update on Managing Mpox in Patients Receiving Therapeutics](#). Published online November 17, 2022.