Interim Guidance for Treatment of MPV

Summary

- **Infections from monkeypox (MPV),** some severe, continue to be reported. Symptoms may include fever, fatigue, lymphadenopathy, and a pimple- or blister-like rash.
- Supportive care and treatment of symptoms should be initiated for all patients with MPV. This may include medicines or other clinical interventions to control pain, itching, nausea and vomiting. All patients should be evaluated and treated for potential co-infections.
- People with HIV-associated immunocompromise and other immunocompromising conditions are at risk for severe disease. It is important to determine HIV status in people with suspected or confirmed MPV, and to start treatment early in those who have concurrent HIV infection with poor or unknown immune status.
- Antiviral treatment of MPV should be considered for people with severe illness, illness complications or risk factors for severe disease.
- **Tecovirimat** (TPOXX or ST-246) is an antiviral medication available through the Centers for Disease Control and Prevention (CDC) that is being used to treat MPV under the **expanded access investigational new drug protocol (EA-IND).**
- Tecovirimat should be prescribed when indicated for patients who have either a positive test result or are awaiting test results with a clinically compatible illness.
- Any health care facility or provider can prescribe tecovirimat if they can adhere to the EA-IND protocol. Tecovirimat can be prescribed upon obtaining **informed consent** from the patient. Additional forms can be submitted to the CDC after initiating treatment.
- Providers in New York City (NYC) who want to prescribe tecovirimat for their patients and can adhere to the EA-IND protocol can email **MPXtherapeutics@health.nyc.gov** for information on NYC’s pharmacy home delivery service, to request supplies for an on-site pharmacy at their facility, or to discuss other therapeutic options.
- For very severe cases or those at risk for becoming severe, providers should reach out to the NYC Department of Health and Mental Hygiene (NYC Health Department) Provider Access Line (866-692-3641) or CDC’s clinical consultation service (eocevent482@cdc.gov; 770-488-7100), and additional therapies (such as VIGIV) may be considered.

Background and Clinical Presentation Consistent With MPV

MPV is a disease caused by infection with an orthopoxvirus. MPV is part of the same family of viruses as smallpox virus. MPV symptoms are similar to smallpox symptoms but milder and can include a flu-like prodrome followed by a rash. Prodromal symptoms might not develop or can occur concurrently with or after rash onset, and may include fever, headache, muscle aches, swollen lymph nodes and fatigue. Patients may not experience the entire constellation of these symptoms.
The rash often starts in a mucosal area, including the mouth, genital or rectal areas, and may remain in a limited area or become more widespread to the face, torso or extremities (including palms or soles). The initial rash has also been documented in other nonmucosal locations. Lesions may start as a macule and then progress to papule, vesicle, pustule and then scab. Visit cdc.gov/monkeypox and search for Clinical Recognition to see examples of MPV rash photos. Providers may also refer to photos in Thornhill, et al (NEJM, 2022). Pain and pruritus (itching) may be prominent and disproportionate to rash appearance. Oral mucositis is well known with MPV, and in the current outbreak, epiglottitis has been reported. Severe proctitis (inflammation of the lining of the rectum and lower digestive system) has been a presenting symptom and can be associated with rectal tenesmus (cramping) and bleeding. Penile lesions, especially around the foreskin, can cause severe pain and swelling, and lead to complications such as phimosis or paraphimosis. In women, vulvovaginal lesions may cause dyspareunia or dysuria. In both men and women, dysuria or hematuria may also occur due to lesions in and around the urethra. Pain may be severe enough to interfere with basic functions such as eating, urination and defecation, and can cause significant distress.

Co-infections with sexually transmitted infections, including gonorrhea, chlamydia and syphilis are common; group A strep pharyngitis, superimposed bacterial infections of lesions, and other viruses (for example, varicella zoster virus or herpes simplex virus) have been diagnosed concomitantly. All people with suspected MPV should be screened for sexually transmitted infections and especially HIV. There have been reports of severe and life-threatening MPV infections concurrent with new HIV diagnoses and AIDS.

Ocular involvement is a potentially debilitating manifestation for people with MPV and is suggestive of more severe disease. Photophobia may be present. Patients may present with blepharitis, conjunctivitis or keratitis, and more severe infection may lead to ulceration. Corneal scarring and vision loss are potential severe consequences of ocular involvement of MPV infection. Bacterial superinfection of corneal ulcerations has been reported and can cause severe complications.

Myocarditis has been reported, including in this current outbreak.

MPV occurring in people living with HIV or other immunocompromising conditions, who are pregnant or breastfeeding, or who have a history of eczema or certain other certain skin conditions are at increased risk for severe disease. This makes it especially important to monitor symptoms and offer antiviral treatment early in the disease course, especially in the context of concurrent HIV infection with unknown immune status (for example, CD4+ cell count) or CD4 less than 200.

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Supportive Care

Supportive care includes maintenance of adequate fluid balance, pain management, treatment of bacterial superinfections, or co-occurring sexually transmitted or superimposed bacterial skin infections. Providers should give anticipatory guidance and address these symptoms adequately and early to prevent hospitalizations.

Skin Lesions

- Skin lesions should be kept clean and dry when not showering or bathing to prevent bacterial superinfection.
- Pruritus can be managed with oral antihistamines and inert, anti-irritant topical agents (such as calamine lotion or petroleum jelly) and cooling lotions (such as menthol or camphor lotions). Warm oatmeal baths can also reduce itching and pain.
- Instruct patients to seek care if they observe increases in pain, redness, swelling, or milky or cloudy fluid at the site of the sores.
- In severe cases, consider consultation with dermatology.

Prevention and Treatment of Post-infection Scarring

- A primary concern of patients is post-infection scarring, including post-inflammatory discoloration or keloid formation.
- When patients have active lesions, counsel patients to avoid touching or picking at lesions to avoid spread to other areas of the body.
- Once lesions have re-epithelialized, patients should be counseled to regularly use a petroleum-based product (such as Vaseline), silicone-based gel or scar patches, and sunscreen.
- Consider referring patients to a dermatologist, particularly in cases of severe scarring or patients who are at risk for or have keloid formation. For a list of dermatologists who are skilled at treating skin of color, visit skinofcolorsociety.org.

Oral Lesions

- For oral lesions, patients can rinse their mouths with salt water at least four times per day. Alcohol-free oral antiseptics (such as Listerine Zero Alcohol and chlorhexidine mouthwash) can be used to keep lesions clean.
- For pain, patients can suck on ice chips or ice pops, or use compounds such as “magic” or “miracle” mouthwashes (prescription solutions used to treat mucositis). Topical treatments such as patches (for example, Dentemp Canker Covers) and benzocaine or lidocaine gels can be used for temporary relief, especially to facilitate eating and drinking, but should be limited to recommended doses.

Anogenital Lesions

- For painful genital and anorectal lesions, warm sitz baths lasting at least 10 minutes several times per day or irrigation with warm water during urination or defecation may be helpful.
• Topical benzocaine or lidocaine gels or creams at the recommended doses may provide temporary relief.
• For severe localized lesions, topical cidofovir may be considered, ideally in consultation with an infectious disease specialist or the NYC Health Department.
• Instruct patients to seek care if they have blood in their urine, difficulty urinating, are unable to retract their foreskin (phimosis), or their foreskin cannot return to its normal position after being retracted (paraphimosis).

Proctitis
• Proctitis can occur with or without internal or external lesions and, though often manageable with appropriate supportive care, can progress to become severe and debilitating.
• Stool softeners such as docusate should be initiated early.
• Sitz baths, as described above, are also useful for proctitis and may calm inflammation.
• Over-the-counter pain medications (such as acetaminophen and ibuprofen) can be used (including together, alternating, if needed).
• Topical anesthetics such as dibucaine ointment, often used for hemorrhoids, and lidocaine gel have been effective for temporary relief.
• Pain from MPV proctitis may require prescription medications (such as gabapentin or opioids), the use of which should be balanced with the possibility of side effects, like constipation.
• Proctitis may be accompanied by rectal bleeding. Though rectal bleeding has been observed to be self-limited, patients should be evaluated by a health care provider.

Ocular Involvement
• Trifluridine, a topical antiviral, can be used for ocular complications of MPV in addition to tecovirimat.
• Given the risk of autoinoculation, patients with lesions on the eyelid or near the eye should be initiated on tecovirimat and trifluridine drops should be considered for prophylactic treatment.

Gastrointestinal Complications
• For gastrointestinal symptoms, nausea and vomiting may be controlled with anti-emetics as appropriate.
• Diarrhea should be managed with appropriate hydration and electrolyte replacement. The use of antimotility agents is not generally recommended given the potential for ileus (inability of the intestine to contract normally).

Antiviral Treatment: Tecovirimat

Tecovirimat is an antiviral medication that is FDA-approved to treat smallpox. In animal studies, tecovirimat has been shown to decrease the chance of dying from infections with orthopoxviruses when given early in the disease course. In people, efficacy studies have been limited to drug levels in blood and a few case studies. In a case series of people with MPV infection, one patient
received tecovirimat with results suggesting tecovirimat might shorten the duration of illness and viral shedding, though the efficacy is unknown.\textsuperscript{3}

Tecovirimat is not yet approved for treatment of MPV in the U.S., though it has been \textbf{authorized for MPV treatment in Europe}. In the U.S., tecovirimat is only available through the federal strategic national stockpile (SNS) and must be prescribed under a CDC-held, nonresearch, EA-IND protocol for the use of tecovirimat as treatment of adults and children with confirmed or presumed MPV infection.

\textbf{Considerations for Use of Tecovirimat}

Patient selection is at the discretion of the treating clinician under the EA-IND. When considering the use of tecovirimat, clinicians and patients should understand 1) the current lack of published tecovirimat effectiveness data in people with MPV, 2) the lack of data indicating which patients might benefit the most from tecovirimat and 3) the concern for the development of resistance to tecovirimat, which could render the drug ineffective for any treated patients. Patients meeting the criteria in the following table should be prioritized for treatment. Both oral and intravenous formulations are available. Any patient with suspected MPV should be tested; however, empiric treatment can be considered if there is appropriate clinical indication prior to laboratory confirmation, especially in the context of limited or delayed testing.

Situations where tecovirimat should be prioritized for use include:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Patients with severe disease</td>
<td>Patient has conditions such as hemorrhagic disease; large number of lesions such that they are confluent; sepsis; encephalitis; ocular or periorbital infections; other conditions requiring hospitalization</td>
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<tr>
<td>Patients with involvement of anatomic areas which might result in serious sequelae that include scarring or strictures</td>
<td>Patients with lesions directly involving the pharynx causing dysphagia, inability to control secretions, or need for parenteral feeding; penile foreskin, vulva, vagina, urethra or rectum with the potential for causing strictures or requiring catheterization; anal lesions or proctitis interfering with bowel movements (for example, severe pain); severe infections (including secondary bacterial skin infections), especially those that require surgical intervention such as debridement</td>
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Patients at high risk for severe disease

Patients with severe immunocompromising conditions including people living with HIV who are not virally suppressed, have CD4 less than 200 or active opportunistic infection or unknown immune status (for example, no recent CD4+ results or new HIV diagnosis); malignancy; history of solid organ transplantation; hematopoietic stem cell transplant less than 24 months post-transplant or greater than or equal to 24 months but with graft-versus-host disease or malignant disease relapse; any condition actively requiring chemotherapy, radiation, tumor necrosis factor inhibitors or continuous or high-dose systemic corticosteroids; autoimmune disease requiring immunosuppression or with immunodeficiency as a clinical component

Pediatric patients, particularly younger than 8 years old

Pregnant or breastfeeding patients

Patients with a condition affecting skin integrity, such as atopic dermatitis; eczema; impetigo; varicella, zoster or herpes infections; severe acne; severe diaper dermatitis with extensive areas of denuded skin; psoriasis or Darier disease (keratosis follicularis)

How To Prescribe and Access Tecovirimat

Any health care facility, provider or system can prescribe tecovirimat under the CDC’s EA-IND protocol. The EA-IND was recently simplified to make it easier for providers to prescribe tecovirimat to patients, including to allow the use of telemedicine for all patient encounters if the patient can submit the signed consent form electronically. Tecovirimat can be initiated empirically prior to a positive lab result; patients should be evaluated in-person with appropriate testing performed for MPV and other potential co-infections prior to prescribing.

The decision to prescribe tecovirimat is based on clinical judgement and discussions between the clinician and patient. Facilities and providers should take the necessary steps to make sure they are able to prescribe tecovirimat (in compliance with the EA-IND’s requirements) when indicated to ensure timely treatment for patients. Tecovirimat is provided at no cost by the federal government. Providers can prescribe for individual patients from a dedicated NYC supply managed by a partner pharmacy. Providers can also coordinate with the NYC Health Department to request a supply from the SNS to have on-site at a facility or health system pharmacy.

Follow these steps to prescribe tecovirimat for eligible patients:
1. Have the patient sign the Informed Consent Form. The completed informed consent form should be retained by the treating institution or facility. If unable to retain, this form can be submitted to the CDC.
2. Email MPXtherapeutics@health.nyc.gov to receive instructions on how to:
• Record patient identifiers and indication for treatment in a Health Insurance Portability and Accountability Act-compliant, secure, web-based REDCap form

• Arrange to have individual prescriptions delivered to your site or directly to the patient by the NYC pharmacy courier service

3. Submit the following to the CDC:

• **U.S. Food and Drug Administration Enrollment Form 1572**
  - This is a facility and provider enrollment form and is not required for each patient. Only one form is required for each facility or provider. The form, once submitted, will cover all prescriptions for that provider and all listed providers within a facility. Facilities and providers can enroll at any time and submit this form in advance of prescribing tecovirimat to patients.
  - If submitting for the first time to prescribe tecovirimat for a patient, it should be submitted within seven days of starting treatment for the patient.

• One EA-IND form (the **Patient Intake Form**) is required for each individual prescription. This form can be submitted after treatment begins but should be submitted within seven days of starting treatment for each patient.

4. Report life-threatening or serious adverse events associated with tecovirimat by sending a completed **MedWatch Form** to regaffairs@cdc.gov within 72 hours of awareness.

Optional steps:

5. **Patient diary**: Ideally, give the **diary** to the patients during initial assessment. Patient can use this form to record how they feel and any side effects to tecovirimat that can be submitted to the CDC at the end of treatment.

6. **Conduct one follow-up visit**: When possible, a follow-up visit within three to 14 days after completion of treatment is highly recommended. Within seven days, submit the required **Clinical Outcome Form** to the CDC.

Facilities or providers interested in ordering a supply of tecovirimat to maintain at an on-site pharmacy or serving as a referral site that is set up to prescribe tecovirimat for patients who do not have a primary care provider can email MPXtherapeutics@health.nyc.gov.

For more information on the EA-IND protocol and associated forms, visit [cdc.gov/monkeypox](http://cdc.gov/monkeypox) and search for **Obtaining and Using TPOXX (Tecovirimat)**.

**Who Should Not Receive Tecovirimat**

People who are ineligible for tecovirimat treatment under EA-IND include those unwilling to sign informed consent documentation and those with a known allergy to the drug or its components.

**Absorption Considerations and Adverse Effects of Tecovirimat**

**Oral tecovirimat**: Standard adult oral dosing of tecovirimat is 600 milligrams (mg) every 12 hours for 14 days. For most adults, this will require taking three pills every 12 hours. Drug absorption of the oral formulation is dependent on adequate intake of a full, fatty meal about 30 minutes prior to taking the medication. The meal should contain about 600 calories and 25 grams of fat such as a cheeseburger with fries, rice with fried chicken, pasta Alfredo, bagel with cream cheese, two...
avocados, 4 cups of whole milk, 6 tablespoons of peanut butter, ready-to-drink meal and so on. Patients can use a nutrition calculator for meal planning while taking tecovirimat. Reported adverse effects include headache (12%), nausea (5%), abdominal pain (2%) and vomiting (2%). Neutropenia was found in one study participant.

**IV tecovirimat:** IV tecovirimat should not be administered to patients with severe renal impairment (creatinine clearance [CrCl] less than 30 milliliters per minute [mL/min]). Oral formulation remains an option for this population. IV tecovirimat should be used with caution in patients with moderate (CrCl 30 to 49 mL/min) or mild (CrCl 50 to 80 mL/min) renal impairment as well as patients younger than age 2 given immature renal tubular function. Reported adverse effects of the IV formulation include infusion site pain (73%), infusion site swelling (39%), infusion site erythema (23%), infusion site extravasation (19%) and headache (15%).

**Drug-drug interactions:** Significant interactions have been reported in healthy adults with co-administration of repaglinide (hypoglycemia) and midazolam (decreased effectiveness of midazolam). According to recent CDC guidance and the University of Liverpool, clinically relevant drug interactions that may require dose adjustment would be anticipated only between tecovirimat and the non-nucleoside reverse transcriptase inhibitors (NNRTIs) doravirine and rilpivirine as well as the CCR5 antagonist maraviroc. Dose increases for doravirine, rilpivirine and maraviroc should be considered when co-administered with tecovirimat and for two weeks after completion of tecovirimat therapy. When co-administering tecovirimat with long-acting cabotegravir or rilpivirine, consider adding oral rilpivirine 25 milligrams [mg] once daily during treatment with tecovirimat and for approximately two weeks after treatment (as any reduction in rilpivirine exposure may persist for up to 14 days after stopping tecovirimat). Alternatively, if unable to obtain oral rilpivirine, consider adding the oral ART regimen the patient was taking prior to initiation of long-acting cabotegravir or rilpivirine. Continue that oral regimen for two weeks after completing tecovirimat.

**Drug resistance:** Data from the published literature and additional recently released data from the FDA suggest that there may be a low barrier to virus developing resistance to tecovirimat; indiscriminate use could promote resistance and render tecovirimat ineffective for patients. However, available alternative therapeutics (for example, cidofovir) have more concerning safety profiles than tecovirimat. If concern for tecovirimat resistance exists, more information on resistance testing can be obtained by calling the NYC Health Department Provider Access Line (866-692-3641).

**Requesting Tecovirimat**

Tecovirimat is only available through the federal Strategic national stockpile. Any provider who wishes to prescribe must do so in compliance with the EA-IND requirements that also ensures liability coverage for prescribers under the PREP Act and allows for compensation to patients if seriously injured. For facilities interested in ordering tecovirimat to dispense from an on-site or partner pharmacy, medication must be requested through the NYC Health Department. NYC has also partnered with a local pharmacy to provide delivery of the medication to NYC residents at their preferred address. For more information on prescribing or accessing tecovirimat for your
patients, email MPXtherapeutics@health.nyc.gov. Do not send patient identifiers to this email address.

Racism as a Public Health Crisis and Treatment Decisions

The NYC Board of Health has resolved that racism is a public health crisis and committed to shifting resources and power to the communities that bear the greatest burden of marginalization racismd and health inequities. The current MPV outbreak will disproportionately impact people of color and people experiencing housing instability or poverty. Potential delays in testing and treatment for people of color will emerge without concerted efforts to address barriers owing to the compounding effects of racism. Providers should take the impacts of limited access to information, resources and services for these communities into account in operational, institutional and treatment decisions.

Other Therapeutic Agents

Other therapeutic options are under investigation and include the antivirals cidofovir and brincidofovir as well as Vaccinia Immune Globulin Intravenous (VIGIV). The use of cidofovir has been limited by serious renal toxicity. Use of VIGIV has no proven benefit in the treatment of MPV and it is unknown whether a person with severe MPV infection will benefit from treatment with VIGIV. However, health care providers may consider its use in severe cases under a CDC EA-IND. VIGIV can be considered for prophylactic use in an exposed person with severe immunodeficiency in T-cell function for which smallpox vaccination following exposure to MPV is contraindicated. Please contact the NYC Health Department (866-692-3641; MPXtherapeutics@health.nyc.gov) or CDC’s clinical consultation team (eocevent482@cdc.gov; 770-488-7100) for more information on VIGIV EA-IND if this medication is under consideration for severe infections or other therapeutic options. Visit cdc.gov/poxvirus/monkeypox/clinicians/treatment.html for information and updates on the status of these therapeutics in MPV treatment.

Technical Assistance

Facilities or providers should contact the NYC Health Department for technical assistance at MPXtherapeutics@health.nyc.gov if they are:

- Interested in ordering a supply of tecovirimat to maintain at an on-site pharmacy
- Requesting instruction and assistance with the EA-IND paperwork (or other institutional approvals or review board issues)
- Interested in serving as a referral site that is set up to prescribe tecovirimat for patients who do not have a primary care provider can email
- Unable to complete the required EA-IND forms to prescribe tecovirimat and would like help referring patients to another provider
- Evaluating a patient that might need additional therapeutic options other than tecovirimat in the setting of potential tecovirimat resistant infection, or severe or atypical disease

Do not send patient identifiers to this email address.
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The NYC Health Department may change recommendations as the situation evolves. 10.31.22