Mpox

Updated: July 24, 2023
Reviewed: January 10, 2024

Epidemiology

Mpox is a zoonotic viral disease caused by mpox virus, an enveloped double-stranded DNA virus that belongs to the same *Orthopoxvirus* genus of the *Poxviridae* family as the causative agent of smallpox. Mpox virus circulates among certain small mammals found in the forested regions of some parts of Africa, creating a reservoir of disease in the animal population. This reservoir is believed to have been the source of the sporadic human outbreaks that have occurred in certain African countries since the first cases were identified in the 1970s until the recent 2022 multinational mpox outbreak.[1] Two distinct clades of mpox virus have been described in different geographic regions of Africa; Clade I (previously called Congo Basin clade) was classically associated with more severe disease and more human-to-human transmission than Clade II (previously called West African clade).[2,3] Historically, risk for serious infection and death has been greatest for children <8 years of age as well as developing fetuses infected perinatally.[4]

The epidemiology of Clade II mpox has evolved as human cases of mpox outside of Africa have been identified.[5] The first notable mpox outbreak occurred in the United States in 2003 and was associated with the importation of small African mammals; transmission occurred through direct contact or contaminated fomites.[6] Mpox also re-emerged in countries like Nigeria, which saw a large outbreak in 2017 and 2018 after decades without human cases.[7,8] However, from 2018 until May 2022, all cases involved persons traveling from endemic areas to other nations, including the United Kingdom (4 cases), Singapore (1 case), Israel (1 case), and the United States (2 cases).[9-14]

In May 2022, a large multinational outbreak of Clade II mpox was recognized. Multiple lineages of mpox virus were detected in the United States during the early months of the outbreak, suggesting multiple introductions of mpox worldwide and raising concerns for future outbreaks.[15] The majority of infections in 2022 were transmitted sexually through intimate contact with one or more mpox lesions on the skin or mucosal surfaces of people with mpox infection.[16] Infections have disproportionately affected gay, bisexual, same-gender-loving, and other men who have sex with men (MSM). Notably, infections in women and children and occupational infections transmitted to health care personnel through injury with contaminated sharps also have been reported.[17-25] Among MSM, coinfection with HIV and other sexually transmitted infections (STIs) has been common.[17] Across reports, around 40% to 50% of cases have been in people with HIV, and around 15% to 30% of cases have been diagnosed concomitantly with gonorrhea, syphilis, chlamydia, or other STIs.[17,18,26,27] Severe and fatal cases have disproportionately been reported in people with HIV, especially among people with advanced or uncontrolled HIV.[28-39] Although the overall mortality rate for Clade II infection is low (<1%), mortality among people with advanced HIV has been higher.[8,36-39]

Clinical Manifestations

In outbreaks prior to 2022, mpox cases had been characterized by prodromal symptoms of fever, headache, lymphadenopathy, myalgias, or fatigue followed by a distinctive rash that progresses synchronously from macules to papules, vesicles, pustules, and, ultimately, crusted lesions. In prior

outbreaks, some cases among people with HIV were identified; these cases involved longer duration of illness, larger size of lesions, more frequent secondary bacterial infections, and presence of genital ulcers.[8,38]

In the 2022 multinational mpox outbreak, the clinical manifestations associated with Clade II infection were distinct in several respects.[18,40] Prodromal symptoms have been mild or absent and have not always preceded the rash.[40] Rash commonly occurs as anogenital or oropharyngeal/perioral lesions, with rash involving the limbs, face, and trunk also occurring.[18,40] Lesions can be single or multiple and limited to a single body site and also can progress in varying stages.[18,40] Inguinal, cervical, and/or axillary lymphadenopathy may be present, similar to historic outbreaks, but not as reliably as with classic presentations.[40]

Most patients, including those with well-controlled HIV, experience self-limiting disease and recover with supportive care alone.[41] For a subset of patients, infection can be more severe.[41] Pharyngeal involvement can result in tonsillitis or pharyngitis associated with odynophagia or dysphagia.[18] Anorectal involvement has caused tenesmus, proctitis, and rectal bleeding, which can be severe.[18,42] Inflammation from genital lesions can produce dysuria occasionally complicated by significant paraphimosis/phimosis or urethritis that limits the ability to urinate.[39,43,44] Severe gastrointestinal manifestations, such as enteritis or colitis, and anogenital involvement can necessitate hospitalization for enhanced symptom control, including pain management.[18,39,44] Lesions have led to stricture and scar formation, causing urethral or bowel obstruction.[39,44] Ocular involvement from autoinoculation can result in conjunctivitis, blepharitis, keratitis, corneal ulcer with possible scarring, and, in rare cases, loss of vision.[45-47] Bacterial superinfections (e.g., staphylococcal skin and soft tissue infections) can also occur.[39] Other reported manifestations have included nodular pulmonary disease, encephalitis and transverse myelitis, myocarditis and pericarditis, septic arthritis, viral "cold abscesses," and genital necrosis.[39,48,49]

During the current outbreak, cases among pediatric patients and pregnant people have been less common and have not yet been associated with severe disease.[50,51] People who are significantly immunocompromised, most commonly from poorly controlled HIV (CD4 T lymphocyte [CD4] cell count <350 cells/mm^3 and especially <50 cells/mm^3), have experienced more severe infections, including increased likelihood of hospitalization and disseminated disease, likely because their weakened immune systems are unable to clear the virus.[28-39] These more severe manifestations can include coalescing or necrotic lesions involving areas of skin (including genitalia) that require surgical debridement and that can continue to progress despite initiation of medical treatment for mpox (see Treating Disease below).[52] Patients' illness can continue to worsen if immune function is not restored, resulting in death.[39]

Diagnosis

Clinical presentation with symptoms such as a characteristic rash associated with mpox lesions is strongly suggestive of mpox.[53] However, diagnosis of mpox based solely on clinical presentation can be challenging due to the protean appearance of mpox lesions. Mpox lesions can mimic lesions seen in other infections such as herpes zoster, as well as STIs such as syphilis, herpes simplex, and molluscum contagiosum. For this reason, and due to the high frequency of coinfection with STIs seen during the multinational 2022 Clade II mpox outbreak, a broad differential diagnosis is encouraged for all people undergoing evaluation for mpox, and screening for STIs, including HIV, is recommended.[17]

Mpox is typically confirmed by the presence of mpox virus DNA in a clinical specimen using the polymerase chain reaction (PCR).[16,53] The recommended specimen is skin lesion material, which can include swabs of a lesion's surface, lesion exudate, or lesion crusts. In the absence of a lesion on epithelialized skin, specimens from mucosal (e.g., oropharynx, saliva, anorectum) lesions or tissues can support diagnosis of mpox. Unroofing or aspiration of lesions is neither required nor recommended and has led to occupational infections from injuries with contaminated sharps; vigorous swabbing of lesion surfaces alone is sufficient.[22,23,54] Testing is available through state public health laboratories and multiple commercial laboratories.

The diagnosis of mpox can also be established by serologic testing demonstrating detectable levels of anti-*Orthopoxvirus* immune globulin M antibody during the period of 4 to 56 days after rash onset in the absence of recent mpox vaccination.[53] If there is high clinical suspicion for mpox and inconclusive or negative testing via PCR or antibody testing, additional testing—such as next-generation sequencing, viral culture to demonstrate the presence of replication-competent virus, biopsy with immunohistochemical staining to demonstrate the presence of viral antigen, or electron microscopy to demonstrate the presence of characteristic viral particles—can be used to confirm the diagnosis, but these diagnostic technologies have varying availability.[53]

Preventing Exposure

Strategies to prevent mpox exposure are similar for people with and without HIV.[55] Regardless of vaccination, people with HIV at risk for mpox should avoid skin-to-skin or other close intimate contact (including sex) with people who may have constitutional symptoms or a rash suspicious for mpox, avoid contact with contaminated surfaces or objects (including linens) used by a person with mpox, and perform frequent hand hygiene after touching rash material or surfaces that may have had contact with rash material **(AIII).** Condoms or other barrier methods may provide additional protection during sex or other intimate activity. During active mpox outbreaks when rates of community transmission may be high, it is recommended that people (including people with HIV) be counseled about the value of reducing their number of sexual partners and limiting visits to venues where group sex or other prolonged skin-to-skin contact is possible **(CIII).**

Recommendations regarding the use of personal protective equipment and other infection control practices when clinically managing patients with mpox can be found at the CDC web page on Infection Prevention and Control of Mpox in Healthcare Settings. Of particular note, sharps should not be used to unroof lesions when collecting diagnostic samples. Self-inoculation with sharps contaminated with mpox via penetrating wound injuries has been the leading cause of health care-associated infections.[22-25]

Preventing Disease

Recommendations for Preventing Mpox Infection
Vaccination Before Mpox Exposure • Indications o Mpox vaccination should be offered to all people with HIV who have potential for mpox exposure or anticipate potential exposure to mpox per CDC interim clinical considerations (BII). o Mpox vaccination should be provided to any other people with HIV who request vaccination (CII).

- Vaccination
  - MVA-BN vaccine, sold in the United States as JYNNEOS, is the preferred vaccine before mpox exposure and is safe to use in people with HIV; administer JYNNEOS in two doses (0.1 mL ID or 0.5 mL SQ) 28 days apart (AII).
  - Administration of live, replicating vaccinia vaccines (i.e., ACAM2000) to pregnant or immunocompromised people, including people with HIV, is contraindicated (AII).

Vaccination Following Mpox Exposure

- Indications
  - For unvaccinated people with HIV who experience a known or presumed exposure, post-exposure vaccination is recommended as soon as possible, ideally within 4 days after exposure; however, administration 4 to 14 days after exposure may still provide some protection against mpox and should be offered (BII).
- Vaccination
  - JYNNEOS is the preferred vaccine following mpox exposure and is safe to use in people with HIV; administer JYNNEOS in two doses (0.1 mL ID or 0.5 mL SQ) 28 days apart as soon as possible and within 14 days after exposure to mpox (AII).
  - Administration of live, replicating vaccinia vaccines (i.e., ACAM2000) to pregnant, breastfeeding, or immunocompromised individuals, including people with HIV, is contraindicated (AII).

Alternative Post-Exposure Prophylaxis

- On a case-by-case basis and in consultation with an infectious disease expert, people with HIV who have advanced immunosuppression or a contraindication to vaccination can consider—
  - Tecovirimat 600 mg PO every 12 hours (people weighing 40 kg to <120 kg) or every 8 hours (patients weighing ≥120 kg) for 14 days (CIII), *or*
  - VIGIV 6,000–9,000 units/kg IV single dose (CIII)
- NOTE: There are no clinical data regarding the effectiveness of mpox post-exposure prophylaxis with these agents.

Key: CDC = Centers for Disease Control and Prevention; ID = intradermal; MVA-BN = modified vaccinia Ankara-Bavarian Nordic; IV = intravenous; PO = orally; SQ = subcutaneous; VIGIV = vaccinia immune globulin intravenous

Vaccination is the principal biomedical means of preventing mpox. Mpox vaccination should be offered to all people with HIV who have potential for mpox exposure or anticipate potential exposure to mpox per Centers for Disease Control and Prevention (CDC) interim clinical considerations **(BII).** Additionally, mpox vaccination should be provided to any other people with HIV who request vaccination **(CII).** For unvaccinated people with HIV who experience a known or presumed exposure, post-exposure vaccination is recommended as soon as possible, ideally within 4 days after exposure; however, administration 4 to 14 days after exposure may still provide some protection against mpox and should be offered **(BII).** At this time, vaccination recommendations are in the context of a rapidly evolving multinational mpox outbreak. For current mpox vaccination recommendations, please see CDC's interim clinical considerations.

People with HIV who are eligible for vaccination against mpox should receive modified vaccinia Ankara (MVA) vaccines **(AII),** a live, non-replicating viral vaccine sold as JYNNEOS in the United States and as IMVANEX or IMVAMUNE elsewhere**.** JYNNEOS consists of two doses given 4 weeks (28 days) apart. CDC's interim clinical considerations for mpox vaccination recommend vaccine administration either subcutaneously or intradermally—both have been found to be effective.[56] For JYNNEOS, if the second dose is not administered during the recommended interval, it should be administered as soon as possible **(CIII).** There is no need to restart or add doses to the

series if there is an extended interval between doses **(CIII).** People who have received smallpox vaccination more than 10 years ago should still receive two doses of JYNNEOS **(CIII).**

Use of live, replicating vaccinia vaccines, such as ACAM2000, is **contraindicated** in immunocompromised individuals, including people with HIV, due to the risk of serious complications from the enhanced replication and dissemination of vaccinia virus **(AII).**[57]

JYNNEOS has been demonstrated to be both safe for people with HIV and equally immunogenic in people with HIV as in people without HIV.[58-60] However, these studies were limited to people who were virologically suppressed and had CD4 counts ≥100 cells/mm^3. Immunogenicity among people with HIV who are not virologically suppressed or have lower CD4 counts remains unknown.

Several studies indicate that JYNNEOS is effective against mpox.[61-67] Matched case control study data indicate that vaccine effectiveness against symptomatic infection ranges from 36-75% after one dose to 66-89% after two doses.[65-67] However, all studies to date have had insufficient data to assess the effectiveness of JYNNEOS against mpox by HIV status or CD4 count, and immunologic correlates of protection have not yet been established.

For people with HIV who have advanced immunosuppression or a contraindication to vaccination, tecovirimat or vaccinia immune globulin intravenous (VIGIV) can be used for mpox post-exposure prophylaxis on a case-by-case basis in consultation with an infectious diseases expert and CDC **(CIII);** however, there are no clinical data regarding the effectiveness of mpox post-exposure prophylaxis with these agents. Per U.S. Food and Drug Administration (FDA) labeling, VIGIV might theoretically impair the efficacy of live attenuated virus vaccines; however, the extent to which it might affect live but non-replicating vaccines, such as JYNNEOS, is unclear.[68] Vaccination with any live virus vaccines should be delayed until 3 months after VIGIV administration **(CIII).**[68] People who received VIGIV shortly after a live virus vaccination should be revaccinated 3 months after administration of the immune globulin **(CIII).**[68]

Treating Disease

Recommendations for Treating Mpox
• People not presently taking ART should initiate treatment as soon as possible (AIII).
*Preferred Therapy for Severe Disease or at Risk for Severe Disease**
• Tecovirimat 600 mg PO every 12 hours (<120 kg) or every 8 hours (≥120 kg) for 14 days (BIII) within 30 minutes of a fatty meal; *or*
• Tecovirimat 200 mg IV every 12 hours for 14 days (<120 kg) or 300 mg IV every 12 hours (≥ 120 kg), if concern exists regarding altered gastrointestinal absorption capacity, the inability to take PO, or the extent of organ systems affected by mpox (BIII).
• NOTE: Patients with severe immunocompromise might benefit from extended treatment (i.e., >14 days) of preferred or adjunctive therapies if new confirmed mpox lesions occur or existing lesions worsen despite treatment.
• NOTE: For severe disease, the Panel recommends early intervention with combination therapy at the time of the first medical encounter, in consultation with CDC or an expert in mpox treatment (CIII).
*Adjunctive Therapy for Severe Disease or at Risk for Severe Disease**

- Cidofovir 5 mg/kg/week IV for two doses with saline hydration before and after therapy and probenecid 2 g PO 3 hours before the dose followed by 1 g PO 2 hours after the dose, and 1 g PO 8 hours after the dose (total of 4 g) (BIII), *or*
  - Cidofovir is contraindicated in patients with a serum creatinine >1.5 mg/dL, a calculated creatinine clearance ≤55 mL/min, or a urine protein ≥100 mg/dL (equivalent to ≥2+ proteinuria). Given the nephrotoxic potential of cidofovir, cautious use of cidofovir with tenofovir is advised. This regimen should be avoided in patients with sulfa allergy because of cross-hypersensitivity with probenecid.
- Brincidofovir 200 mg PO once weekly for two doses (BIII), *or*
- VIGIV 6,000–9,000 units/kg IV single dose (BIII)
  - NOTE: Vaccination with any live virus vaccines should be delayed until 3 months after VIGIV administration (CIII). People who received VIGIV shortly after a live virus vaccination should be revaccinated 3 months after administration of the immune globulin (CIII).
- NOTE: Consultation with local health department and/or CDC should be obtained prior to initiating the above therapies.

Preferred Therapy for Ocular Mpox

- Tecovirimat 600 mg PO every 12 hours (<120 kg) or every 8 hours (≥120 kg) for 14 days (CIII) within 30 minutes of a fatty meal, *and*
- Trifluridine (Viroptic) 1 drop into affected eye(s) every 2 hours when awake (max: 9 drops/day) until reepithelialization, then every 4 hours (min: 5 drops/day) for 7 days or until all periocular lesions have healed (CIII)
  - Prolonged use of trifluridine beyond 21 days might cause corneal epithelial toxicity and should be avoided (AII).
- NOTE: Trifluridine should be used in consultation with an ophthalmologist.

Other Considerations

- CDC offers a clinical consultation service (email eocevent482@cdc.gov), or health care providers may contact the CDC Emergency Operations Center (EOC) at 770-488-7100, where CDC can provide additional guidance to clinicians with patient management questions.
- Patients with mpox benefit from supportive care and pain control that is implemented early in the illness (BIII).

Pregnancy Considerations

- Tecovirimat can be used as a first-line antiviral for people who are pregnant, recently pregnant, or breastfeeding (BIII).
- In animal studies, cidofovir and brincidofovir have been shown to be teratogenic; therefore, these agents are not recommended for use in pregnancy (AIII).

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; CDC = Centers for Disease Control and Prevention; IV = intravenous; the Panel = Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV; PO = orally; VIGIV = vaccinia immune globulin intravenous

* People with HIV who are not virologically suppressed or who have CD4 counts <350 cells/mm^3 are considered at high risk for severe mpox. Severe mpox might manifest as hemorrhagic disease; a large number of lesions such that they are confluent; sepsis; encephalitis; ocular or periorbital infections; or other conditions requiring hospitalization.

For people with well-controlled HIV, mpox is typically a self-limiting illness that resolves spontaneously without antiviral treatment. However, people with HIV who are not virologically suppressed, who have CD4 counts <350 cells/mm^3, or who are otherwise severely immunocompromised can experience prolonged severe illness with serious sequelae and are therefore candidates for antiviral treatment.[41] See the CDC's Mpox Clinical Considerations for more information.

If therapy is considered, oral tecovirimat should be administered as first-line treatment **(BIII).** Tecovirimat, which inhibits the *Orthopoxvirus* VP37 envelope-wrapping protein, is available as an oral capsule or intravenous (IV) injection. The decision to use oral or IV tecovirimat should be based on the severity of illness (e.g., extent of other organ systems affected by mpox, presence of coalescing non-healing lesions), other comorbidities that could contribute to greater severity of illness, expected adherence to the oral formulation, and gastrointestinal absorption capacity.[41] Oral tecovirimat requires intact gastrointestinal absorption and the ability to consume a high-fat meal (600 calories and 25 g fat) to support absorption, which may pose a challenge.[69]

Tecovirimat should be administered early in the course of illness for patients with advanced HIV, along with supportive care and pain control **(BIII).** Studies using a variety of animal models have shown that tecovirimat is effective in treating *Orthopoxvirus* disease.[70-72] Human clinical trials have demonstrated the drug had an acceptable safety profile.[71,73,74] A case report from the United Kingdom has suggested that tecovirimat may shorten the duration of mpox illness and mpox viral shedding.[75] There are ongoing clinical trials to assess the efficacy of tecovirimat to treat mpox.[76-78] Tecovirimat can be provided under an expanded access investigational new drug (IND) protocol or through clinical trials.

IV cidofovir or oral brincidofovir can be used as adjunctive therapy in people with severe manifestations of mpox or at risk of severe manifestations **(BIII).** Cidofovir, which acts via competitive inhibition of DNA polymerase to block DNA synthesis of many DNA viruses, is an FDA-approved antiviral medication for the treatment of cytomegalovirus (CMV) retinitis in people with advanced HIV. Brincidofovir, available orally as a tablet or suspension, is a prodrug of cidofovir that acts similarly and is thought to have less toxicity. Human data are not available on the effectiveness of cidofovir or brincidofovir to treat mpox in people with HIV. However, *in vitro* and animal studies have demonstrated that these drugs are effective against other *Orthopoxviruses*.[79-84] Data from animal models suggest that the combination of tecovirimat and brincidofovir may act synergistically to improve outcomes and could be considered for patients with disseminated infection **(CIII).**[85]

Cidofovir or brincidofovir can be used for people with or at risk for severe disease or people who experience clinically significant progression while receiving tecovirimat, develop recrudescence of disease after an initial period of improvement while receiving tecovirimat, or are otherwise ineligible to receive oral or IV tecovirimat **(BIII).** Brincidofovir is available from federal partners to clinicians who request and obtain a single-patient emergency use IND authorization for treatment of mpox. Clinicians should consider the side effect profiles of both medications when deciding on their use.

VIGIV can be used in severe cases where the development of a robust antibody response may be impaired **(BIII).** Data are not available on the effectiveness of VIGIV to treat mpox in people with HIV. In animal models using non-human primates, vaccine-induced vaccinia antibodies were protective against lethal challenge with mpox virus. The benefit of VIGIV for treatment of severe mpox is unknown. VIGIV is administered under an expanded access IND. Subsequent dosing (i.e., redosing) decisions should be made on a case-by-case basis in consultation with CDC and can be considered when: mpox lesions affect a large percentage of a patient's body surface at the time of diagnosis; new lesions (or expanding borders on existing lesions) emerge several days after VIGIV; lesions affect mobility or are concerning for long-term sequelae, such as sexual dysfunction; or adverse events or contraindications preclude maximal use of other medical countermeasures.[41]

Depending on the severity of immunocompromise and uncontrolled viral replication, these additional therapies to tecovirimat (i.e., VIGIV and brincidofovir or cidofovir) can be considered after balancing the benefits and harms. In severe cases, the Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV recommends early intervention with combination therapy at the time of the first medical encounter, in consultation with CDC or an expert in mpox treatment **(CIII)**.

The role of topical therapy in the treatment of mpox remains unknown. Topical cidofovir has been used for skin lesions with mixed success.[86,87] For ocular involvement, trifluridine, in addition to systemic therapy, can be used in cases of mpox virus conjunctivitis and is recommended in cases of mpox virus keratitis, in consultation with an ophthalmologist **(CIII).**[45,88,89] Prolonged use of trifluridine beyond 21 days might cause corneal epithelial toxicity and should be avoided **(AII).**[90]

Treatments for mpox have the potential for complex and possibly bidirectional interactions with certain antiretroviral agents. Drug–Drug Interactions tables in the Adult and Adolescent Antiretroviral Guidelines describe such interactions and recommendations for therapeutic drug monitoring and dosage adjustments, where feasible.

Special Considerations with Regard to Starting Antiretroviral Therapy

People with HIV not presently taking antiretroviral therapy (ART) should initiate treatment as soon as possible to improve T and B cell function, which have key roles in modulating mpox disease severity and preventing mortality **(AIII).**[41,91-93] In people with advanced HIV (e.g., CD4 count <350 cells/mm^3), those whose HIV viral load is unsuppressed, or those who otherwise merit treatment for mpox, ART should ideally be started at the same time as mpox therapy **(AIII).**

Monitoring of Response to Therapy and Adverse Events (Including Immune Reconstitution Inflammatory Syndrome)

As with other opportunistic infections in people with advanced HIV, dysregulated immune responses, such as immune reconstitution inflammatory syndrome (IRIS), following initiation of ART have been raised as a potential concern.[35] IRIS could lead to paradoxical worsening or a protracted course of mpox disease. Data are insufficient to inform recommendations on identification and management of dysregulated immune responses in the setting of mpox infection in people with advanced HIV. Providing passive immunity with the use of VIGIV and extending the duration of antivirals such as tecovirimat should be considered pending immune recovery **(CIII).** VIGIV has an estimated half-life of up to 3 weeks. If immune reconstitution is slow, repeat dosing should be considered on a case-by-case basis, as noted above **(BIII).**

Monitoring is recommended during and after treatment of mpox to detect toxicity, as well as persistence or recurrence of mpox.

The most common adverse effects of tecovirimat are headache and nausea.[69] After the treating clinician has assessed the risks and benefits and determined that IV tecovirimat is clinically necessary, the IV formulation should be used with caution in patients with severe renal impairment (creatinine clearance [CrCl] <30 mL/min) due to accumulation of an excipient in the IV formulation (hydroxypropyl-beta-cyclodextrin) that has shown potential for nephrotoxicity at very high exposure levels. If the IV formulation is used, closely monitor renal function; if renal toxicity is suspected,

switching to oral tecovirimat, if possible, or an alternative agent can be considered in consultation with CDC.

Adverse effects of cidofovir include dose-related nephrotoxicity, neutropenia, uveitis, and hypotony (low intraocular pressure).[94] The risk of severe renal injury from IV cidofovir can be reduced by prehydration and oral probenecid before and after cidofovir administration. In patients receiving IV cidofovir, analysis of blood urea nitrogen and creatinine levels and urinalysis should be performed before each infusion.[94] Drug administration is **contraindicated** if renal dysfunction or substantial proteinuria is detected (a serum creatinine >1.5 mg/dL, creatinine clearance ≤55 mL/min, or a urine protein ≥100 mg/dL [equivalent to ≥2+ proteinuria]).[94] Particular attention is needed for patients receiving other potentially nephrotoxic medications, including tenofovir disoproxil fumarate.[94] Periodic ophthalmologic examinations are needed to monitor for cidofovir-associated uveitis or hypotony.[94]

Adverse effects of brincidofovir include diarrhea, nausea, and other gastrointestinal adverse events and elevations in hepatic enzymes (e.g., alanine transaminase, aspartate aminotransferase) and bilirubin.[95] Brincidofovir-induced diarrhea may impair absorption of oral tecovirimat. Screening for liver test abnormalities should be performed before starting therapy and repeat testing for follow-up as clinically indicated.[95] Since brincidofovir is usually given only in two doses 1 week apart, monitoring of liver function parameters is generally done before the second dose (Day 8).[95] If serum aminotransferases are elevated and persist above 10 times the upper limit of normal, consider not giving the second dose of brincidofovir.[95] The second and final dose of brincidofovir should not be given on Day 8 if elevation of serum aminotransferases is accompanied by clinical signs and symptoms of liver inflammation or increasing direct bilirubin, alkaline phosphatase, or international normalized ratio.[95] Male patients should be counseled on the risk for irreversible effects on male fertility based on testicular toxicity observed in animal studies **(AII).**[95] Individuals of childbearing potential should use effective contraception and/or condoms during treatment and for at least 4 months after the last dose **(AIII).**[95]

Managing Treatment Failure

Clinical failure of therapy for mpox might be more likely in patients who do not have substantial immune reconstitution after initiation or optimization of ART or who are otherwise severely immunocompromised. Treatment failure can also result from inadequate tecovirimat levels secondary to inadequate gastrointestinal absorption, drug resistance, or nonadherence.

Lesions may continue to develop after a 14-day course of tecovirimat. If clinical manifestations do not improve, symptoms progress despite the use of oral tecovirimat, or there are concerns about gastrointestinal absorption, IV tecovirimat should be initiated if not already being used **(BIII).** In these cases, the addition of other therapeutics, including brincidofovir or cidofovir and VIGIV should also be assessed. Extending the duration of tecovirimat treatment should be done carefully, through short increments of time and close clinical monitoring for safety signals and clinical response **(BIII).**

The use of topical or ablative therapies for progressive hypertrophic lesions has been reported, but their role is still under exploration.[96] Consultation with an infectious diseases specialist, dermatology, and wound care services should be sought. CDC offers a clinical consultation service (email eocevent482@cdc.gov), or health care providers may contact the CDC Emergency Operations Center (EOC) at 770-488-7100, where CDC can provide additional guidance to clinicians with patient management questions.

Tecovirimat has a relatively low barrier to viral resistance. Single amino acid substitutions at various locations in the F13L gene coding the viral VP37 drug target confer substantial reductions in tecovirimat's antiviral activity.[69] Genotypic and phenotypic resistance to tecovirimat has been documented in patients with severe immunocompromising conditions who have disseminated and progressive mpox infection and have received or are undergoing prolonged tecovirimat treatment.[97]

Patients for whom resistance is suspected (e.g., new lesions form after at least 7 days of treatment) or documented can be considered for additional therapeutics, including cidofovir or brincidofovir, and VIGIV. Efforts should be made to restore immune function, such as ensuring people with HIV are receiving effective ART and limiting the use of immunocompromising therapies.[41]

Clinicians may consider sending repeat sample swabs to the CDC to assess for the continued presence of virus and to assess for evidence of potential viral resistance based on genetic sequencing. Formal tecovirimat sensitivity testing results cannot be used to guide treatment decisions for individual patients for two reasons: first, they require culture-based resistance testing techniques that take weeks to perform (i.e., results cannot be returned in a timely manner); and second, reporting of these results is not permitted under Clinical Laboratory Improvement Amendments. However, the results of tecovirimat susceptibility testing are helpful to public health efforts to monitor for the emergence of tecovirimat resistance.

Persistently positive PCR test results are expected until lesions resolve; therefore, subsequent testing of lesion specimens may not be informative unless new lesions or progressive lesions are occurring despite 14 days of tecovirimat treatment. Evaluating trends in PCR cycle threshold (Ct) values may be informative; Ct values ≥35 might suggest that minimal replication-competent virus is present.[98] Certain laboratories may be able to test for presence of viable virus with culture techniques, but these results may not be available in a clinically relevant timeframe.

Other possible reasons for treatment failure may include a dysregulated immune response with associated inflammation or the presence of another opportunistic infection. If viable mpox virus is still detected by culture, viral replication and ongoing infection may be driving the disease process and antiviral medications should be continued. Biopsy of the affected tissue can be performed in cases with new or atypical lesions where it is unclear if the lesions are primarily due to mpox or another infectious cause, including secondary bacterial or fungal infections, and in cases with significant complications (e.g., mucosal or bowel lesions, severe lymphadenopathy, pulmonary nodular lesions, or severe conjunctivitis). Consultation with infectious diseases specialists and CDC is encouraged.

Preventing Recurrence and Reinfection

The durability of immunity after infection with mpox or after vaccination is unknown, including among people with HIV. No clinical correlates of immunity have yet been established to guide when booster vaccination may be needed following infection or a primary vaccination series.

Special Considerations During Pregnancy

Data regarding mpox infection in pregnancy are limited.[99,100] It is unknown if pregnant people, including people with HIV, are more susceptible to mpox or if infection is more severe in pregnancy. Mpox can be transmitted to the fetus during pregnancy or to the newborn by close contact during and after birth. Adverse pregnancy outcomes, including spontaneous pregnancy loss and stillbirth, have

been reported in cases of confirmed mpox infection during pregnancy.[4,101] Preterm delivery and neonatal mpox infection have also been reported.[50]

The signs and symptoms of mpox infection in pregnant people appear similar to those in non-pregnant people, including prodromal symptoms and rash. The approach to diagnosis of mpox in pregnant people is the same as in non-pregnant people.

For people who are pregnant, breastfeeding, or trying to become pregnant and who require vaccination, JYNNEOS should be used because it is non-replication competent **(AIII).** Studies of JYNNEOS vaccine in animals have shown no evidence of harm to the developing fetus.[102] Vaccination with ACAM2000, which contains a replication-competent virus, is **contraindicated** in people who are pregnant or breastfeeding due to risk of pregnancy loss, congenital defects, and vaccinia virus infection in fetuses and newborns and the availability of alternative non-replicating viral vaccine **(AII).**[57]

Treatment for mpox should be offered to people who are pregnant, recently pregnant, or breastfeeding **(AIII).** Tecovirimat can be used as a first-line antiviral for people who are pregnant, recently pregnant, or breastfeeding **(BIII).** Information about the impact of tecovirimat on reproductive development is limited to animal studies, in which no specific fetal effects were observed.[69] It is not known if treatment with tecovirimat during pregnancy prevents congenital mpox. Animal reproduction studies have not been conducted with VIGIV; therefore, it is not known whether VIGIV can cause fetal harm when administered during pregnancy or affect future fertility.[68] However, other immune globulins have been widely used during pregnancy for many years without any apparent negative reproductive effects. In animal studies, cidofovir and brincidofovir have been shown to be teratogenic; therefore, these agents are **not recommended** for use in pregnancy **(AIII).**[94,95]

References

1. Ladnyj ID, Ziegler P, Kima E. A human infection caused by monkeypox virus in Basankusu Territory, Democratic Republic of the Congo. *Bull World Health Organ*. 1972;46(5):593-597. Available at: https://www.pubmed.ncbi.nlm.nih.gov/4340218.

2. Chen N, Li G, Liszewski MK, et al. Virulence differences between monkeypox virus isolates from West Africa and the Congo basin. *Virology*. 2005;340(1):46-63. Available at: https://www.pubmed.ncbi.nlm.nih.gov/16023693.

3. Likos AM, Sammons SA, Olson VA, et al. A tale of two clades: monkeypox viruses. *J Gen Virol*. 2005;86(Pt 10):2661-2672. Available at: https://www.pubmed.ncbi.nlm.nih.gov/16186219.

4. Mbala PK, Huggins JW, Riu-Rovira T, et al. Maternal and fetal outcomes among pregnant women with human monkeypox infection in the Democratic Republic of Congo. *J Infect Dis*. 2017;216(7):824-828. Available at: https://www.pubmed.ncbi.nlm.nih.gov/29029147.

5. Bunge EM, Hoet B, Chen L, et al. The changing epidemiology of human monkeypox-a potential threat? A systematic review. *PLoS Negl Trop Dis*. 2022;16(2):e0010141. Available at: https://www.pubmed.ncbi.nlm.nih.gov/35148313.

6. Centers for Disease Control and Prevention. Update: multistate outbreak of monkeypox—Illinois, Indiana, Kansas, Missouri, Ohio, and Wisconsin, 2003. *MMWR Morb Mortal Wkly Rep*. 2003;52(27):642-646. Available at: https://www.pubmed.ncbi.nlm.nih.gov/12855947.

7. Ogoina D, Yinka-Ogunleye A. Sexual history of human monkeypox patients seen at a tertiary hospital in Bayelsa, Nigeria. *Int J STD AIDS*. 2022;33(10):928-932. Available at: https://www.pubmed.ncbi.nlm.nih.gov/35969500.

8. Yinka-Ogunleye A, Aruna O, Dalhat M, et al. Outbreak of human monkeypox in Nigeria in 2017–18: a clinical and epidemiological report. *Lancet Infect Dis*. 2019;19(8):872-879. Available at: https://www.pubmed.ncbi.nlm.nih.gov/31285143.

9. Vaughan A, Aarons E, Astbury J, et al. Two cases of monkeypox imported to the United Kingdom, September 2018. *Euro Surveill*. 2018;23(38). Available at: https://www.pubmed.ncbi.nlm.nih.gov/30255836.

10. European Centre for Disease Prevention and Control. Rapid risk assessment: monkeypox cases in the UK imported by travellers returning from Nigeria, 2018. 2018. Available at: https://ecdc.europa.eu/sites/portal/files/documents/13-09-2018-RRA-Monkeypox-Nigeria-United-Kingdom.pdf.

11. Erez N, Achdout H, Milrot E, et al. Diagnosis of imported monkeypox, Israel, 2018. *Emerg Infect Dis*. 2019;25(5):980-983. Available at: https://www.pubmed.ncbi.nlm.nih.gov/30848724.

12. Yong SEF, Ng OT, Ho ZJM, et al. Imported monkeypox, Singapore. *Emerg Infect Dis*. 2020;26(8):1826-1830. Available at: https://www.pubmed.ncbi.nlm.nih.gov/32338590.

13. Costello V, Sowash M, Gaur A, et al. Imported monkeypox from international traveler, Maryland, USA, 2021. *Emerg Infect Dis*. 2022;28(5):1002-1005. Available at: https://www.pubmed.ncbi.nlm.nih.gov/35263559.

14. Rao AK, Schulte J, Chen TH, et al. Monkeypox in a traveler returning from Nigeria - Dallas, Texas, July 2021. *MMWR Morb Mortal Wkly Rep*. 2022;71(14):509-516. Available at: https://www.pubmed.ncbi.nlm.nih.gov/35389974.

15. Gigante CM, Korber B, Seabolt MH, et al. Multiple lineages of monkeypox virus detected in the United States, 2021–2022. *Science*. 2022;378(6619):560-565. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36264825.

16. Centers for Disease Control and Prevention. Science brief: detection and transmission of monkeypox virus. Available at: https://www.cdc.gov/poxvirus/monkeypox/about/science-behind-transmission.html.

17. Curran KG, Eberly K, Russell OO, et al. HIV and sexually transmitted infections among persons with monkeypox - eight U.S. jurisdictions, May 17–July 22, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(36):1141-1147. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36074735.

18. Thornhill JP, Barkati S, Walmsley S, et al. Monkeypox virus infection in humans across 16 countries - April–June 2022. *N Engl J Med*. 2022;387(8):679-691. Available at: https://www.pubmed.ncbi.nlm.nih.gov/35866746.

19. Saunders KE, Van Horn AN, Medlin HK, et al. Monkeypox in a young infant - Florida, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(38):1220-1221. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36136958.

20. Aguilera-Alonso D, Alonso-Cadenas JA, Roguera-Sopena M, Lorusso N, Miguel LGS, Calvo C. Monkeypox virus infections in children in Spain during the first months of the 2022 outbreak. *Lancet Child Adolesc Health*. 2022;6(11):e22-e23. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36058226.

21. Alonso-Cadenas JA, Andina-Martinez D, Garcia-Garcia CJ, Gaitero-Tristan J, Garcia-Ascaso MT, Torrelo A. Monkeypox disease in a breastfeeding infant. *Pediatr Dermatol*. 2022. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36180382.

22. Carvalho LB, Casadio LVB, Polly M, et al. Monkeypox virus transmission to healthcare worker through needlestick injury, Brazil. *Emerg Infect Dis*. 2022;28(11):2334-2336. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36121391.

23. Mendoza R, Petras JK, Jenkins P, et al. Monkeypox virus infection resulting from an occupational needlestick - Florida, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(42):1348-1349. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36264845.

24. Choi Y, Jeon EB, Kim T, et al. Case report and literature review of occupational transmission of monkeypox virus to healthcare workers, South Korea. *Emerg Infect Dis*. 2023;29(5):997-1001. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36856759.

25. Caldas JP, Valdoleiros SR, Rebelo S, Tavares M. Monkeypox after occupational needlestick injury from pustule. *Emerg Infect Dis*. 2022;28(12):2516-2519. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36252152.

26. Tarin-Vicente EJ, Alemany A, Agud-Dios M, et al. Clinical presentation and virological assessment of confirmed human monkeypox virus cases in Spain: a prospective observational

cohort study. *Lancet*. 2022;400(10353):661-669. Available at: https://www.pubmed.ncbi.nlm.nih.gov/35952705.

27. Philpott D, Hughes CM, Alroy KA, et al. Epidemiologic and clinical characteristics of monkeypox cases - United States, May 17–July 22, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(32):1018-1022. Available at: https://www.pubmed.ncbi.nlm.nih.gov/35951487.

28. Philpott D, Bonacci R, Weidle P, et al. CD4 count <350 cells/mm^3 increases risk of hospitalization with mpox in PWH. Presented at: Conference on Retroviruses and Opportunistic Infections 2023; 2023. Seattle, WA. Available at: https://www.croiconference.org/wp-content/uploads/sites/2/posters/2023/HIV_gdph_croi_poster-133209603871672583.pdf.

29. Cholli PA, Miller MJ, Paromita P, et al. Characteristics of patients hospitalized with mpox during the 2022 U.S. outbreak. Presented at: Conference on Retroviruses and Opportunistic Infections 2023; 2023. Seattle, WA. Available at: https://www.croiconference.org/wp-content/uploads/sites/2/posters/2023/CROI_Poster_-_Mpox_in_Hospitalized_Patien_(1)-133199180923744122.pdf.

30. Corma-Gómez A, Santos M, Cabello A, et al. Mpox virus infection is more severe in patients with uncontrolled HIV infection. Presented at: Conference on Retroviruses and Opportunistic Infections 2023; 2023. Seattle, WA. Available at: https://www.croiconference.org/wp-content/uploads/sites/2/posters/2023/CROI_Mpox-133211828530842872.pdf.

31. Garcia EA, Lash MK, McPherson TD, et al. Severe mpox among people living with HIV receiving tecovirimat in New York City. Presented at: Conference on Retroviruses and Opportunistic Infections 2023; 2023. Seattle, WA. Available at: https://www.croiconference.org/wp-content/uploads/sites/2/posters/2023/NYCDOHMH_SevereMpox-HIV_CROI2023_0735-133205427984584752.pdf.

32. Garneau WM, Jones JL, Dashler G, et al. Clinical outcomes among in- and outpatients with mpox in an urban health system. Presented at: Conference on Retroviruses and Opportunistic Infections 2023; 2023. Seattle, WA. Available at: https://www.croiconference.org/wp-content/uploads/sites/2/posters/2023/mpox_outcomes_-_garneau-133207198771747332.pdf.

33. Silva M, Coutinho C, Torres T, et al. Impact of HIV infection on mpox-related hospitalizations in Brazil. Presented at: Conference on Retroviruses and Opportunistic Infections 2023; 2023. Seattle, WA. Available at: https://www.croiconference.org/wp-content/uploads/sites/2/posters/2023/CROI_Poster_MpoxHospitalizationsHIV_0905_vers%C3%A3o_final-133209759446392218.pdf.

34. Vo C, Zomorodi R, Silvera R, et al. Demographic and clinical characteristics of mpox within a New York City health system. Presented at: Conference on Retroviruses and Opportunistic Infections 2023; 2023. Seattle, WA. Available at: https://www.croiconference.org/wp-content/uploads/sites/2/posters/2023/CROI_poster_v21_final_-_Chris_Vo-133211560201291269.pdf.

35. Mitja O, Alemany A, Marks M, et al. Mpox in people with advanced HIV infection: a global case series. *Lancet*. 2023. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36828001.

36. World Health Organization. Multi-country outbreak of mpox, external situation report #12 - 14 December 2022. 2022. Available at: https://www.who.int/publications/m/item/multi-country-outbreak-of-mpox--external-situation-report-12--14-december-2022.

37. Nigeria Centre for Disease Control. Weekly Epidemiological Report week 51: 16th–22nd December 2019. Nigeria: Nigeria Centre for Disease Control and Prevention; January 3 2020. Available at: https://reliefweb.int/report/nigeria/ncdc-weekly-epidemiological-report-volume-9-no-51-16th-22nd-december-2019.

38. Ogoina D, Iroezindu M, James HI, et al. Clinical course and outcome of human monkeypox in Nigeria. *Clin Infect Dis*. 2020;71(8):e210-e214. Available at: https://www.pubmed.ncbi.nlm.nih.gov/32052029.

39. Miller MJ, Cash-Goldwasser S, Marx GE, et al. Severe monkeypox in hospitalized patients - United States, August 10–October 10, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(44):1412-1417. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36327164.

40. Centers for Disease Control and Prevention. Health Alert Network (HAN) no. 466: monkeypox virus infection in the United States and other non-endemic countries—2022. 2022. Available at: https://emergency.cdc.gov/han/2022/han00466.asp.

41. Rao AK, Schrodt CA, Minhaj FS, et al. Interim clinical treatment considerations for severe manifestations of mpox - United States, February 2023. *MMWR Morb Mortal Wkly Rep*. 2023;72(9):232-243. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36862595.

42. Lucar J, Roberts A, Saardi KM, Yee R, Siegel MO, Palmore TN. Monkeypox virus-associated severe proctitis treated with oral tecovirimat: a report of two cases. *Ann Intern Med*. 2022;175(11):1626-1627. Available at: https://www.pubmed.ncbi.nlm.nih.gov/35981225.

43. Patel A, Bilinska J, Tam JCH, et al. Clinical features and novel presentations of human monkeypox in a central London centre during the 2022 outbreak: descriptive case series. *BMJ*. 2022;378:e072410. Available at: https://www.pubmed.ncbi.nlm.nih.gov/35902115.

44. Centers for Disease Control and Prevention. Health Alert Network (HAN) no. 475: severe manifestations of monkeypox among people who are immunocompromised due to HIV or other conditions. 2022. Available at: https://emergency.cdc.gov/han/2022/han00475.asp.

45. Cash-Goldwasser S, Labuda SM, McCormick DW, et al. Ocular monkeypox - United States, July–September 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(42):1343-1347. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36264836.

46. Nogueira Filho PA, Lazari CDS, Granato CFH, et al. Ocular manifestations of monkeypox: a case report. *Arq Bras Oftalmol*. 2022;85(6):632-635. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36350927.

47. Kaufman AR, Chodosh J, Pineda R 2nd. Monkeypox virus and ophthalmology-a primer on the 2022 monkeypox outbreak and monkeypox-related ophthalmic disease. *JAMA Ophthalmol*. 2022. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36326768.

48. Pastula DM, Copeland MJ, Hannan MC, et al. Two cases of monkeypox-associated encephalomyelitis - Colorado and the District of Columbia, July–August 2022. *MMWR Morb*

Mortal Wkly Rep. 2022;71(38):1212-1215. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36136957.

49. Fonti M, Mader T, Burmester-Kiang J, et al. Monkeypox associated acute arthritis. *Lancet Rheumatol*. 2022;4(11):e804. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36247685.

50. Khalil A, Samara A, O'Brien P, et al. Monkeypox in pregnancy: update on current outbreak. *Lancet Infect Dis*. 2022;22(11):1534-1535. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36115375.

51. Hennessee I, Shelus V, McArdle CE, et al. Epidemiologic and clinical features of children and adolescents aged <18 years with monkeypox - United States, May 17–September 24, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(44):1407-1411. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36331124.

52. Carrubba S, Geevarghese A, Solli E, et al. Novel severe oculocutaneous manifestations of human monkeypox virus infection and their historical analogues. *Lancet Infect Dis*. 2023. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36702137.

53. Centers for Disease Control and Prevention. Case definitions for use in the 2022 mpox response. 2022. Available at: https://www.cdc.gov/poxvirus/monkeypox/clinicians/case-definition.html.

54. Centers for Disease Control and Prevention. Infection prevention and control of mpox in healthcare settings. 2022. Available at: https://www.cdc.gov/poxvirus/monkeypox/clinicians/infection-control-healthcare.html.

55. O'Shea J, Filardo TD, Morris SB, Weiser J, Petersen B, Brooks JT. Interim guidance for prevention and treatment of monkeypox in persons with HIV infection - United States, August 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(32):1023-1028. Available at: https://www.pubmed.ncbi.nlm.nih.gov/35951495.

56. Centers for Disease Control and Prevention. JYNNEOS vaccine. 2022. Available at: https://www.cdc.gov/poxvirus/monkeypox/interim-considerations/jynneos-vaccine.html.

57. Food and Drug Administration. ACAM2000 [package insert]. 2018. Available at: https://www.fda.gov/media/75792/download.

58. Overton ET, Lawrence SJ, Stapleton JT, et al. A randomized phase II trial to compare safety and immunogenicity of the MVA-BN smallpox vaccine at various doses in adults with a history of AIDS. *Vaccine*. 2020;38(11):2600-2607. Available at: https://www.pubmed.ncbi.nlm.nih.gov/32057574.

59. Overton ET, Stapleton J, Frank I, et al. Safety and immunogenicity of modified vaccinia Ankara-Bavarian Nordic smallpox vaccine in vaccinia-naive and experienced human immunodeficiency virus-infected individuals: an open-label, controlled clinical phase II trial. *Open Forum Infect Dis*. 2015;2(2):ofv040. Available at: https://www.pubmed.ncbi.nlm.nih.gov/26380340.

60. Greenberg RN, Overton ET, Haas DW, et al. Safety, immunogenicity, and surrogate markers of clinical efficacy for modified vaccinia Ankara as a smallpox vaccine in HIV-infected subjects. *J Infect Dis*. 2013;207(5):749-758. Available at: https://www.pubmed.ncbi.nlm.nih.gov/23225902.

61. Centers for Disease Control and Prevention. Preliminary JYNNEOS vaccine effectiveness estimates against medically attended mpox disease in the U.S., August 15, 2022–October 29, 2022. 2022. Available at: https://www.cdc.gov/poxvirus/monkeypox/cases-data/mpx-JYENNOS-vaccine-effectiveness.html.

62. Payne AB, Ray LC, Cole MM, et al. Reduced risk for mpox after receipt of 1 or 2 doses of JYNNEOS vaccine compared with risk among unvaccinated persons - 43 U.S. jurisdictions, July 31–October 1, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(49):1560-1564. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36480479.

63. Bertran M, Andrews N, Davison C, et al. Effectiveness of one dose of MVA-BN smallpox vaccine against mpox in England using the case-coverage method: an observational study. *Lancet Infect Dis*. 2023. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36924787.

64. Arbel R, Sagy YW, Zucker R, et al. Effectiveness of a single-dose modified vaccinia Ankara in human monkeypox: an observational study. *Research Square*. 2022. Available at: https://assets.researchsquare.com/files/rs-1976861/v2/742e7169-1a89-48e6-995c-c17f0276ec90.pdf?c=1663905577.

65. Dalton AF, Diallo AO, Chard AN, et al. Estimated effectiveness of JYNNEOS vaccine in preventing mpox: a multijurisdictional case-control study - United States, August 19, 2022–March 31, 2023. *MMWR Morb Mortal Wkly Rep*. 2023;72(20):553-558. Available at: https://www.pubmed.ncbi.nlm.nih.gov/37200229.

66. Deputy NP, Deckert J, Chard AN, et al. Vaccine effectiveness of JYNNEOS against mpox disease in the United States. *N Engl J Med*. 2023. Available at: https://www.pubmed.ncbi.nlm.nih.gov/37199451.

67. Rosenberg ES, Dorabawila V, Hart-Malloy R, et al. Effectiveness of JYNNEOS vaccine against diagnosed mpox infection—New York, 2022. *MMWR Morb Mortal Wkly Rep*. 2023;72(20):559–563. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10205166.

68. Food and Drug Administration. Vaccine Immune Globulin Intravenous [package insert]. 2005. Available at: https://www.fda.gov/media/78174/download.

69. Food and Drug Administration. TPOXX (tecovirimat) [package insert]. 2018. Available at: https://www.fda.gov/media/75792/download.

70. Merchlinsky M, Albright A, Olson V, et al. The development and approval of tecoviromat (TPOXX®), the first antiviral against smallpox. *Antiviral Res*. 2019;168:168-174. Available at: https://www.pubmed.ncbi.nlm.nih.gov/31181284.

71. Grosenbach DW, Honeychurch K, Rose EA, et al. Oral tecovirimat for the treatment of smallpox. *N Engl J Med*. 2018;379(1):44-53. Available at: https://www.pubmed.ncbi.nlm.nih.gov/29972742.

72. Smith SK, Self J, Weiss S, et al. Effective antiviral treatment of systemic orthopoxvirus disease: ST-246 treatment of prairie dogs infected with monkeypox virus. *J Virol*. 2011;85(17):9176-9187. Available at: https://www.pubmed.ncbi.nlm.nih.gov/21697474.

73. Desai AN, Thompson GR 3rd, Neumeister SM, Arutyunova AM, Trigg K, Cohen SH. Compassionate use of tecovirimat for the treatment of monkeypox infection. *JAMA*. 2022;328(13):1348-1350. Available at: https://www.pubmed.ncbi.nlm.nih.gov/35994281.

74. O'Laughlin K, Tobolowsky FA, Elmor R, et al. Clinical use of tecovirimat (TPOXX) for treatment of monkeypox under an Investigational New Drug protocol - United States, May–August 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(37):1190-1195. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36107794.

75. Adler H, Gould S, Hine P, et al. Clinical features and management of human monkeypox: a retrospective observational study in the UK. *Lancet Infect Dis*. 2022;22(8):1153-1162. Available at: https://www.pubmed.ncbi.nlm.nih.gov/35623380.

76. National Institutes of Health. Study of tecovirimat for human monkeypox virus (STOMP). 2022. Available at: https://clinicaltrials.gov/ct2/show/NCT05534984.

77. National Institutes of Health. Tecovirimat for treatment of monkeypox virus. 2022. Available at: https://clinicaltrials.gov/ct2/show/NCT05559099.

78. National Institute for Health and Care Research. New clinical trial to test treatment for mpox (PLATINUM). 2022. Available at: https://www.nihr.ac.uk/news/new-clinical-trial-to-test-treatment-for-mpox/31352.

79. Rice AD, Adams MM, Wallace G, et al. Efficacy of CMX001 as a post exposure antiviral in New Zealand White rabbits infected with rabbitpox virus, a model for orthopoxvirus infections of humans. *Viruses*. 2011;3(1):47-62. Available at: https://www.pubmed.ncbi.nlm.nih.gov/21373379.

80. Parker S, Chen NG, Foster S, et al. Evaluation of disease and viral biomarkers as triggers for therapeutic intervention in respiratory mousepox - an animal model of smallpox. *Antiviral Res*. 2012;94(1):44-53. Available at: https://www.pubmed.ncbi.nlm.nih.gov/22381921.

81. Baker RO, Bray M, Huggins JW. Potential antiviral therapeutics for smallpox, monkeypox and other orthopoxvirus infections. *Antiviral Res*. 2003;57(1-2):13-23. Available at: https://www.pubmed.ncbi.nlm.nih.gov/12615299.

82. Smee DF. Progress in the discovery of compounds inhibiting orthopoxviruses in animal models. *Antivir Chem Chemother*. 2008;19(3):115-124. Available at: https://www.pubmed.ncbi.nlm.nih.gov/19024628.

83. Stittelaar KJ, Neyts J, Naesens L, et al. Antiviral treatment is more effective than smallpox vaccination upon lethal monkeypox virus infection. *Nature*. 2006;439(7077):745-748. Available at: https://www.pubmed.ncbi.nlm.nih.gov/16341204.

84. Hutson CL, Kondas AV, Mauldin MR, et al. Pharmacokinetics and efficacy of a potential smallpox therapeutic, brincidofovir, in a lethal monkeypox virus animal model. *mSphere*. 2021;6(1). Available at: https://www.pubmed.ncbi.nlm.nih.gov/33536322.

85. Quenelle DC, Prichard MN, Keith KA, et al. Synergistic efficacy of the combination of ST-246 with CMX001 against orthopoxviruses. *Antimicrob Agents Chemother*. 2007;51(11):4118-4124. Available at: https://www.pubmed.ncbi.nlm.nih.gov/17724153.

86. Sobral-Costas TG, Escudero-Tornero R, Servera-Negre G, et al. Human monkeypox outbreak: epidemiological data and therapeutic potential of topical cidofovir in a prospective cohort study. *J Am Acad Dermatol*. 2022. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36455826.

87. Rubio-Muniz CA, Montero-Menárguez J, López-Valle A, et al. Monkeypox: is topical cidofovir a good idea? *Clin Exp Dermatol*. 2022. Available at: https://doi.org/10.1093/ced/llac038.

88. Parkhurst JR, Danenberg PV, Heidelberger C. Growth inhibition of cells in cultures and of vaccinia virus infected HeLa cells by derivatives of trifluorothymidine. *Chemotherapy*. 1976;22(3-4):221-231. Available at: https://www.pubmed.ncbi.nlm.nih.gov/178485.

89. Hyndiuk RA, Seideman S, Leibsohn JM. Treatment of vaccinial keratitis with trifluorothymidine. *Arch Ophthalmol*. 1976;94(10):1785-1786. Available at: https://www.pubmed.ncbi.nlm.nih.gov/823931.

90. Maudgal PC, Van Damme B, Missotten L. Corneal epithelial dysplasia after trifluridine use. *Graefes Arch Clin Exp Ophthalmol*. 1983;220(1):6-12. Available at: https://www.pubmed.ncbi.nlm.nih.gov/6403411.

91. Agrati C, Cossarizza A, Mazzotta V, et al. Immunological signature in human cases of monkeypox infection in 2022 outbreak: an observational study. *Lancet Infect Dis*. 2022. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36356606.

92. Lum FM, Torres-Ruesta A, Tay MZ, et al. Monkeypox: disease epidemiology, host immunity and clinical interventions. *Nat Rev Immunol*. 2022;22(10):597-613. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36064780.

93. Hermanussen L, Grewe I, Tang HT, et al. Tecovirimat therapy for severe monkeypox infection: longitudinal assessment of viral titers and clinical response pattern-a first case-series experience. *J Med Virol*. 2022. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36177717.

94. Food and Drug Administration. Cidofovir [package insert]. 2000. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/1999/020638s003lbl.pdf.

95. Food and Drug Administration. Brincidofovir [package insert]. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214460s000,214461s000lbl.pdf.

96. Scotti B, Piraccini BM, Gaspari V. Hypertrophic verrucous lesions after monkeypox virus infection. *Lancet Infect Dis*. 2022. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36309035.

97. Centers for Disease Control and Prevention. Update on managing monkeypox in patients receiving therapeutics. 2022. Available at: https://emergency.cdc.gov/han/2022/han00481.asp.

98. Paran N, Yahalom-Ronen Y, Shifman O, et al. Monkeypox DNA levels correlate with virus infectivity in clinical samples, Israel, 2022. *Euro Surveill*. 2022;27(35). Available at: https://www.pubmed.ncbi.nlm.nih.gov/36052723.

99. Jamieson DJ, Cono J, Richards CL, Treadwell TA. The role of the obstetrician-gynecologist in emerging infectious diseases: monkeypox and pregnancy. *Obstet Gynecol*. 2004;103(4):754-756. Available at: https://www.pubmed.ncbi.nlm.nih.gov/15051569.

100. Meaney-Delman DM, Galang RR, Petersen BW, Jamieson DJ. A primer on monkeypox virus for obstetrician-gynecologists: diagnosis, prevention, and treatment. *Obstet Gynecol*. 2022;140(3):391-397. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36356237.

101. Jezek Z; Fenner Z. Human monkeypox. *Monographs in Virology*. 1988;17:127-140. Available at: https://www.karger.com/DOI/10.1159/000416465.

102. Food and Drug Administration. JYNNEOS [package insert]. 2022. Available at: https://www.fda.gov/media/131078/download.