

Monkeypox: Clinical Presentation, Diagnosis and Treatment

VDH Monkeypox Symposium

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Monkeypox: Clinical

- Monkeypox begins with fever, headache, muscle aches, and exhaustion after an incubation of 7-14 days (range 5-21 days).
- Classically, within 1 to 3 days *after* onset of fever, patient develops a rash, often beginning on the face then spreading to other parts of the body, hands/feet.
- Lesions are typically all at the same stage.

Monkeypox 2022




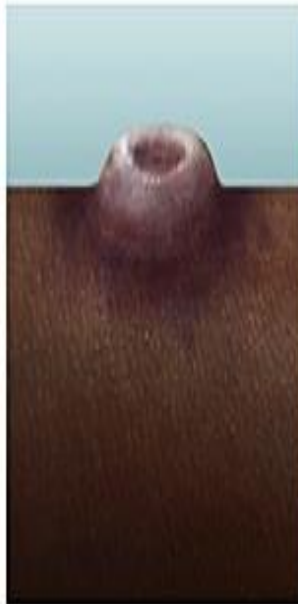






- In the recent outbreak, lesions in many cases started in the genital region (penis, mouth or anal region) before spreading to the extremities.
- First lesions have been noted to appear in area of inoculation and may precede fever.
- Patients remain infectious until scabs have fallen off and skin heals.
- Illness typically lasts for 2–4 weeks.

Monkeypox 2022

Study of 181 Spanish patients with Monkeypox:

- 78% had anogenital lesions; 25% with proctitis (mainly with anal-receptive sex), also more likely to have systemic Sx.
- 8% with penile edema.
- 43% oral and perioral lesions; 10% with tonsillitis (mainly with oral-receptive sex).
- 1-2 lesions in 12%, 3-20 lesions in 80%.
- Localized lymphadenopathy: 85%.

Tarin-Vicente E. Lancet Pub. Online 8/8/2022.

STAGE:	Macules	Papules	Vesicles	Pustules	Scabs
Darker skin pigmentation					
Lighter skin pigmentation					
DAY:	1-2	1-2	1-2	5-7	7-14

Clinicians should be aware of how lesions may present on the spectrum of skin pigmentation.

Perianal, Anal, and Rectal Lesions



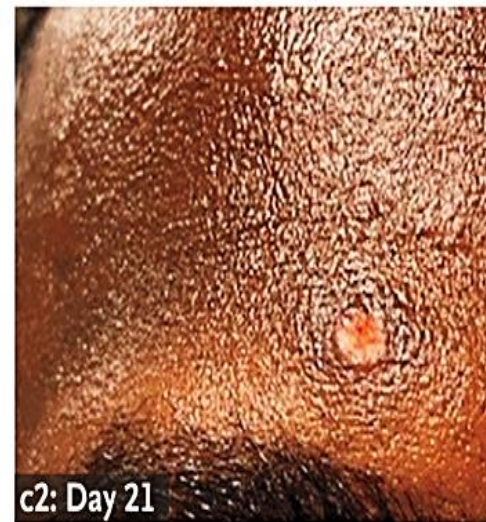
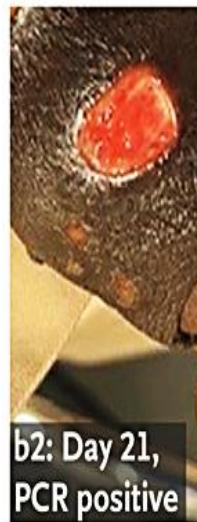
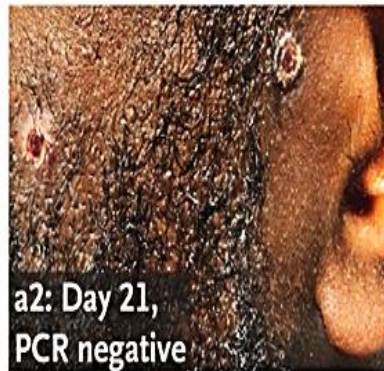
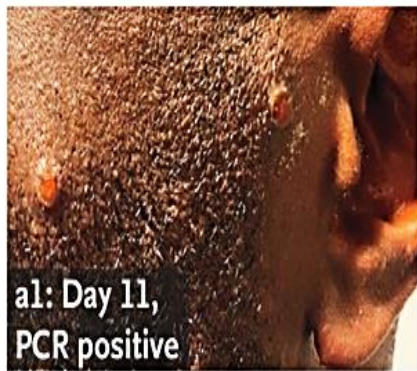
Oral and Perioral Lesions







A Evolution of Cutaneous Lesions



Day -4

Condomless sexual
contact in MSM

Days 4-6

Feeling unwell; additional
lesions develop

Day 0

Single genital lesion
treated with IM penicillin
as suspected syphilis

Day 11

Confirmed monkeypox:
facial and genital lesions
PCR positive

Day 21

Follow-up 1: facial lesions PCR negative,
genital lesions PCR positive

Day 28

Follow-up 2: genital lesions
PCR negative



MPX in Immunocompromised

- CDC has been consulted for patients with severe MPX, most had HIV with CD4 count < 200:
- Coalescing or necrotic skin lesions, some requiring extensive surgical debridement or amputation.
- Severe necrotizing lymphadenopathy.
- Urethral, bowel strictures and scar formation.
- Urethritis, penile necrosis.
- Corneal ulcerations.

CDCHAN-00475 9/29/22.

Mpox: Severe Disease

- Large number of lesions that become confluent, necrotic.
- Lymphadenopathy that becomes necrotizing or obstructive (airways, etc).
- Multiorgan involvement; encephalitis, myocarditis, ocular.
- Scarring lesions and strictures; pharynx with dysphagia, vaginal, anorectal strictures.
- Bacterial superinfections, sepsis.

Asymptomatic Monkeypox

- 200 MSM visiting an STD clinic without clinical Monkeypox had MPVX PCR on 200 anal swabs, 6.5% (+).
- All 13 who were initially asymptomatic were contacted, none reported symptoms c/w MPX.
- 2 later presented with symptoms, an anal rash in one and pharyngitis and fever in the other.

Ferre M. Ann Int Med 2022 doi: 10.7326/M22-2183

Monkeypox and HIV

- Multiple studies around the world have found that ~40% of MPX cases are also HIV (+).
- 96% on ART, 95% with viral suppression.
- HIV status has *not* impacted the incubation, clinical features, lesion number or time to crusting.
- In general, well controlled HIV is not an indication for tecovirimat, but should be considered for CD4 < 200, persistent viremia or AIDs dx within last 6 months.

Monkeypox and HIV

- 382 Mpox cases from 19 countries, 91% PLWH, median CD4 211, 50% with VL <200.
- For those with a CD4 <100 vs. >300, necrotizing skin lesions (54 vs 7%), lung disease (29 vs 0%), death (25% vs 0) are all more common.
- Mortality was 27% with CD4 <100, 4% with CD4 101-200, 0 with CD4 >200.
- 25% who started or reinitiated ART developed Immune Reconstitution Inflammatory Syndrome (IRIS). Mitja O. Lancet 2/2023.

Mpox Deaths

- As of 3/2023, 30,000 confirmed cases of Mpox; 38 deaths (1.3/1,000 cases) in U.S.
- 95% MSM, 87% African American.
- Median interval from onset to death: 68 days.
- 94% with AIDS, all had CD4 <100, 96% <50.
- 27 had data on Rx, 25 received tecovirimat (60% within 3d), 18 of 24 vaccinia IG, 9 of 22 cidofovir, 6 of 15 brincidofovir.
- 73% had received at least one dose of JYNNEOS.

Riser A. MMWR2023;72:404-10.

Monkeypox and HCWs

Monkeypox and HCWs

- 313 Colorado HCPs exposed to patients with MPX, 23% wore all recommended PPE, but only 4% in primary and urgent care settings.
- 50% with high-risk exposure and 40% with intermediate risk exposure received JYNNEOS.
- None became infected.
- 256 global cases among HCPs, only 3 cases felt to be occupationally acquired.

Smallpox Vaccine as PEP

- For smallpox, post exposure prophylaxis with vaccination within 2-3d gives almost complete protection.
- Within 7d, 90% protection.
- Can be considered within 2 weeks.
- Ring vaccination controlled smallpox.
- JYNNEOS likely to provide similar protection from Mpox for HCW and household non sexual contacts (2-8% infected).

Monkeypox and HCWs

- Testing of 60 hospital surfaces in 4 respiratory isolation rooms that had housed 6 MPX patients.
- 93% of surface samples were (+), PPE was (+) in 33% of samples, including visors and gloves.
- 25% of air samples were (+), 3 of 4 before/during bedding change (2018 infection in HCW assoc. with bedding change).
- 2 of 4 samples with viral cultures were (+), including an air sample and anteroom floor swab.

Monkeypox Diagnosis

Monkeypox: Diagnosis

- Laboratory testing includes a *non-variola Orthopoxvirus* PCR (detects vaccinia, Cowpox and Mpox viruses) and an *Orthopoxvirus* test.
- Chickenpox is caused by a herpesvirus, Varicella Zoster Virus, also known as HHV-3, closely related to Herpes simplex.

Mpox Testing: VDH DCLS

- VDH Division of Consolidated Laboratory Services (DCLS) is a Laboratory Response Network (LRN) Advanced Laboratory in Richmond.
- Testing is by real-time PCR.
- Requires prior approval from VDH; contact your local health department epidemiologist.
- 2 - 4 dry swabs of lesions on different body parts, place in separate dry, sterile tubes (do not use viral or universal transport media).

VDH Local HD Epidemiologist

- Go to VDH website, VDH District Directory where each local health department (LHD) and staff are listed.

LHD Epidemiologists

- NPHD

Michelle Burnette 757-683-8384, cell 757-434-5809

- CPHD

Lisa Engel 757-382-8642, cell 757-435-6078

- VBHD

Anna Beringer 757-518-2649, cell 757-438-0173

Mpox Testing: VDH DCLS

- Refrigerate specimens within 1 hour of collection, ship refrigerated on ice packs.
- Package specimens with both a primary and a secondary container.
- Include a completed DCLS Test Request Form.
- Send via routine DCLS courier.
- Turnaround time is 5-6 hours from the start of testing, will be run daily on receipt of sample.

Mpox Testing: VDH DCLS

- Mpox positive tests at DCLS are considered presumptive, confirmatory and Clade specific testing is performed by CDC within 5 -7 days of receipt of specimen.
- If 2 swabs are not received from the initial collection, recollection of specimens may be required for confirmatory testing at CDC.

VDH DCLS

- VDH Division of Consolidated Laboratory Services (DCLS):
 - Dr. LaToya Griffin-Thomas: Bioterrorism/Special Pathogens Testing Lead 804-648-4480, x281
 - Destiny Hairfield: Bioterrorism Response Principal Scientist 804-648-4480, x154

Monkeypox and HCWs

- ED Nurse used a needle to unroof a lesion, needlestick through glove when recapping.
- Received 1st of 2 JYNNEOS doses 15 hours after the needlestick.
- 10 days later developed a single lesion that developed at the site of the needlestick, resolved completely over 19 days.

Mendoza R. MMWR 10/17/2022.

Monkeypox and HCWs

- 2 healthcare nurses developed monkeypox 5 days after collecting samples from a patient.
- PPE (except gloves) were worn during the interview, hands were sanitized and latex gloves were donned prior to sample collection; no skin-to-skin contact.
- Infection most likely occurred from contaminated fomites in the patient's home.

NPHD STD Clinic

- Much more efficient method is to refer suspected Mpox cases to local health department STD clinic.
- Family Planning, PrEP and Sexual Health:
Monday through Friday: 8:30am to 3:00pm.
757-683-2735
- Appointments are encouraged and will be honored. Walk-in slots are sometimes available.

Mpox Testing

- Testing for Mpox is also available from Labcorp, Quest, Aegis Sciences, Sonic Healthcare and Mayo Clinic.
- Sentara sends specimens to Quest which requests one sample in VTM or UTM, if varicella zoster virus PCR is requested, submit a separate sample. Needs to be refrigerated. 3 - 4 day turn around.

Monkeypox False (-) PCR

- MPXV PCR target is the *tumor necrosis factor (TNF) receptor* in both the CDC West African and generic MPXV PCR tests.
- 3 cases reported from California had significant deletions in the *TNF receptor gene* resulting in false negative results.
- PCR based on non-variola orthopoxvirus (NVO) will be correctly identified.

STD Screening for MPOX Cases

- 40% with monkeypox have had another STD in the last year, 10% have had 3.

All Mpox cases should be screened for other STDs:

- ✓ Urine NAAT for GC and Chlamydia (~70% of infections may be missed with urine NAAT only).
- ✓ Rectal NAAT for GC and Chlamydia.
- ✓ Pharyngeal NAAT for GC.
- ✓ Syphilis serology.
- ✓ HIV, if (+), CD4 and HIV RNA.

Frequency of STD screening for MSM?

- STD testing should be done at least annually, but more frequent 3-6 month testing should be considered for :
 - HIV (+).
 - Persons taking PrEP.
 - MSM with multiple sex partners.

Frequency of STD screening for MSM?

- Models from Australia have demonstrated that increasing syphilis screening frequency from two times a year to four times a year resulted in a relative decrease of 84% from peak prevalence.
- Quarterly syphilis screening averted more than twice the number of syphilis cases compared with semiannual screening.
- Quarterly chlamydia and gonorrhea screening was associated with an 83% reduction in incidence.



Monkeypox Treatment

Monkeypox Treatment

Siegrist E. Clin Infect Dis 2023;76:155-64.

Rao A. MMWR 2023;72:232-43.

Monkeypox Treatment

- No FDA approved treatments for Mpox.
- Tecovirimat, brincidofovir and vaccinia immune globulin are available from the Strategic National Stockpile. Cidofovir (Vistide) available by Rx.
- Drugs are FDA approved to treat smallpox and have shown efficacy against animal poxviruses.
- Available as expanded access Investigational New Drug (IND) protocol: tecovirimat and VIGIV or single-patient emergency use IND (e-IND) for brincidofovir.

Monkeypox: Treatment

- **Tecovirimat** (TPOXX) is treatment approved for human smallpox, preferred Rx for Mpox.
- Inhibits activity of the protein VP37, which prevents creation of virions that can be released from an infected host cell, preventing replication and dissemination of virus.
- Studies of MPV infections in primates and rabbitpox found markedly higher survival rates in treated animals.

Tecovirimat Efficacy: HIV

- Retrospective, propensity score matched study of early tecovirimat in PLWH (within 7d of Sx onset) vs. later or untreated.
- Mpox disease progression occurred in 3 of 56 (5%) in the early group vs. 15 of 56 (27%) in the late or no Rx group (OR 13).

Aldred B. JAMA Int Med 2024; E1-E5.

Tecovirimat Efficacy: HIV

- Median CD4 was lower in the early Rx group (314 vs. 433), CD4 < 200 (25% vs. 16%).
- 61% met criteria for Rx before d7, but were not treated.
- 36% in the late or no Rx group eventually received tecovirimat, median 10d after Sx onset.

“Findings support starting tecovirimat in all PWH as soon as an Mpox dx is suspected.”

Aldred B. JAMA Int Med 2024; E1-E5.

Tecovirimat: Who to Treat?

- Severe illness requiring hospitalization.
- Ocular, oral or genital involvement.
- Immunocompromised, esp. HIV with $CD4 < 200$.
- Children < 8 years old, esp. < 1 y.o.
- Pregnant/breastfeeding.
- Atopic dermatitis, eczema, psoriasis and others.

In general, well controlled HIV is not an indication to treat, but could be considered for $CD4 < 200$, persistent viremia or AIDs dx within last 6 months.

Tecovirimat

- Dose: 200 mg capsule bid x 14d and IV formulation (cyclodextrin may accumulate with CrCl <30).
- Should be taken with a high fat meal (600 calories and 45 gm fat or more).
- Available under an EA-IND (Expanded Access Investigational New Drug) after approval by VDH/CDC.

STOMP Trial

- CDC strongly recommends enrollment in clinical trials: Study of Tecovirimat for Human Pox (STOMP). www.stomptpoxx.org/main
855-876-9997
- STOMP is an NIAID-funded clinical trial led by the ACTG to evaluate tecovirimat with a randomized placebo arm and an open label arm for immunocompromised.
- Patients can self enroll for *suspected or confirmed* Mpox remotely by phone, testing done locally.

EA IND

- Expanded Access (EA) Investigational New Drug (IND) done online at VDH or CDC for *suspected or documented* Mpox:
- Google VDH Mpox: go to For Healthcare Providers: Treatment Guidance, scroll down to TPOXX ordering:
- Tecovirimat (TPOXX) IND Registry for Providers/Facilities
- Form takes about 10 minutes, IRB is prepopulated using CDC IRB.

Tecovirimat

- TPOXX Provider Treatment Interest Form
- Tecovirimat can be shipped directly to patient, provider or facility from VDH Central Pharmacy in Richmond.
- Shipping same day if request before 3:00 pm.

If problems or questions, contact:

Alexis Page, PharmD Pharmacy Supervisor VDH

Office: 804-298-3053 Cell: 804-219-9531

Tecovirimat: Required Forms

- Informed Consent (5 pages).
- Patient Intake Form (3 pages).
- FDA Form 1572 (2 pages).
- Clinical Outcome Form (4 pages).
- Serious Adverse Events Form (3 pages).
- Optional: lesion photos, lesion samples for resistance testing, pharmacokinetic samples for tecovirimat levels, patient diary.

Tecovirimat Resistance

- Tecovirimat has a low barrier to viral resistance, single amino acid change in the VP37 protein can lead to high level resistance.
- In cell culture studies, multiple single amino acid substitutions were associated with high level phenotypic resistance (≥ 10 -fold increase in EC50).
- >5,000 samples have been evaluated to date by CDC, with 0.5% resistance mutations detected, refer for testing if new lesions after 7d Rx.

Tecovirimat and ART

- Tecovirimat is metabolized by UGT1A1 and UGT1A4 and is a weak inducer of CYP3A4.
- Potential decreased levels of rilpivirine. If on rilpivirine, increase dose (add 25 mg) during Rx with tecovirimat and for 2 weeks after.
- Do not start Cabenuva (cabotegravir/rilpivirine) within 2 weeks of tecovirimat and if already on Cabenuva add rilpivirine 25 mg. If not available, return to ARVs before Cabenuva started.

Mpox Rx: Additional Measures

- Treatment in addition to Tecovirimat can be considered with:
- Disease progression while receiving tecovirimat or initial improvement followed by worsening.
- Concern for tecovirimat resistance.
- Allergic, unable to receive/tolerate tecovirimat.

➤ CDC Clinical Consultation Team:

poxvirus@cdc.gov

After hours: CDC Emergency Ops Center: 770-488-7100.

Brincidofovir (Tembexa, CMX001)

- Brincidofovir is a prodrug of cidofovir, selectively inhibits OPXV DNA polymerase.
- Brincidofovir can be added to tecovirimat, one 200 mg tablet weekly for 2 weeks, one animal study suggests synergy (AAC 2007;51:4118-24.)
- Side effects: diarrhea, N/V, abdominal pain, neutropenia.
- Do not coadminister with protease inhibitors.
- Less toxic than Cidofovir (Vistide); serious renal toxicity was seen during Rx of CMV disease. (don't use together with brincidofovir).

Brincidofovir e-IND

- Requires single-patient emergency use IND:
DDI.EIND@fda.hhs.gov
301-796-3400

After hours:

CDER-EIND@fda.hhs.gov

- CDER Emergency Coordinator 301-796-9900.

Cidofovir (Vistide)

- Cidofovir is FDA approved for Rx of CMV retinitis.
- Prodrug that must enter cells to be phosphorylated by cellular enzymes to the active form, CDV diphosphate (CDV-pp) with a prolonged intracellular half life, allowing weekly dosing.
- CDV-pp is incorporated into growing DNA strand slowing synthesis and inhibits DNA polymerase.
- Dose limiting nephrotoxicity, reduced by probenecid and 1 L NS infusion.

VIGIV

- Vaccinia Immune Globulin Intravenous (VIGIV): provides passive immunity through OPXV-specific Abs collected from pooled human plasma of persons immunized with smallpox vaccine.
- Consider in patients where a robust Ab response may be impaired (requires EA IND protocol).
- Dose: 6,000-9,000 units/kg as a single dose IV.
- For severely immunocompromised, second dose 3-4 days later has been suggested.
- Has been associated with corneal scarring in an animal study of vaccinia keratitis.

Ocular Monkeypox

- Trifluridine (Viroptic) is a thymidine analog that interferes with DNA synthesis with selective toxicity to OPXVs.
- One drop every 2h in affected eye when awake for first 2 weeks (max. 9 drops), then 4 times daily for additional 2 weeks.

Monkeypox Consultation

CDC Clinical Consultation Service:

eocevent482@cdc.gov

- CDC Emergency Operations Center:

770-488-7100

Mpox: Diagnosis and Treatment

- **Diagnosis:** Testing via VDH DCLS, approval from LHD epidemiologist, swabs of lesion in sterile tube, refrigerated, transported to LHD for courier to Richmond or commercial lab testing (Sentara uses Quest) or refer patient to LHD for testing.
- **Treatment:** *suspected or confirmed* severe disease, immunocompromised, esp. HIV (+) with CD4 <200 or increased VL.
- Refer to TPOXX trial or complete EA IND.

Preventing Monkeypox: Personal Measures

Monkeypox Prevention

- **Take a temporary break** from activities that increase exposure to monkeypox until you are two weeks after your second dose of vaccine. This will greatly reduce your risk.
- **Limit** your number of sex partners to reduce your likelihood of exposure.
- **Avoid** spaces like back rooms, saunas, sex clubs, or private and public sex parties, where intimate, often anonymous sexual contact with multiple partners occurs.

Monkeypox Prevention

- Make a habit of exchanging contact information with any new partner to allow for sexual health follow-up, if needed.
- Talk with your partner about any monkeypox symptoms and be aware of any new or unexplained rash or lesion on either of your bodies, including the mouth, genitals, or anus.

Monkeypox Prevention

- Condoms (latex or polyurethane) may protect from exposure to monkeypox.
- However, condoms alone may not prevent all exposures to monkeypox since the rash can occur on other parts of the body.
- Gloves (latex/polyurethane/nitrile) might also reduce the possibility of exposure.
- Gloves must cover all exposed skin and be removed carefully to avoid touching the outer surface.

Monkeypox Prevention

- Do not touch another person's rash or scabs.
- Do not share eating utensils, cups, clothing, bedding, towels, or personal grooming devices.
- Wash your hands with soap and water or use an alcohol-based hand sanitizer after contact with infected people or animals.
- Wear a mask in situations where you may have *lengthy* or *close* face-to-face contact with people who may be infected.

Monkeypox Prevention

American Men's Internet Survey in 8/2022 found that MSM, since learning about the MPX outbreak:

- 48% had reduced their number of sex partners.
- 50% reduced one-time sexual encounters.
- 50% reduced sex with partners met on dating apps or at sex venues.

Delaney K. MMWR 8/26-22.

Monkeypox Prevention

- Change your behavior.
- Men with more than one sex partner in the preceding 3 weeks had 5 times the risk of being infected with MPX.
- One-time sex accounted for 50% of MPX cases.
- Decreasing one-time partnerships by 40% decreased the risk of getting MPX by ~25%.

Spicknall I. MMWR 8/26/22.

Monkeypox Infection: Preventing Spread to Others

Monkeypox Prevention

- If you or your partner has or recently had monkeypox symptoms, or you have a new or unexplained rash anywhere on your body, do not have sex and see a healthcare provider.
- If you do not have a healthcare provider or insurance, go to your local public health department.
- Be aware that in some cases, symptoms may be mild, and some people may not even know they have monkeypox.

Monkeypox Prevention

- If you or a partner has monkeypox or think you may have monkeypox, the best way to protect yourself and others is to avoid sex of any kind (oral, anal, vaginal) and kissing or touching each other's bodies—while you are sick.
- **Especially avoid touching any rash.**
- Do not share things like towels, fetish gear, sex toys, and toothbrushes.
- Abstinence during active infection and for up to 8 weeks after recovery (UK recommendation).