Update su infezione da Monkeypox (Mpox) virus

Lorenzo Zammarchi

Dipartimento Medicina Sperimentale e Clinica, Università degli Studi di Firenze

SOD Malattie Infettive e Tropicali, Azienda Ospedaliero Universitaria Careggi – Firenze

2022-23 Mpox (Monkeypox) Outbreak: Global Trends

World Health Organization

Produced on 19 December 2023

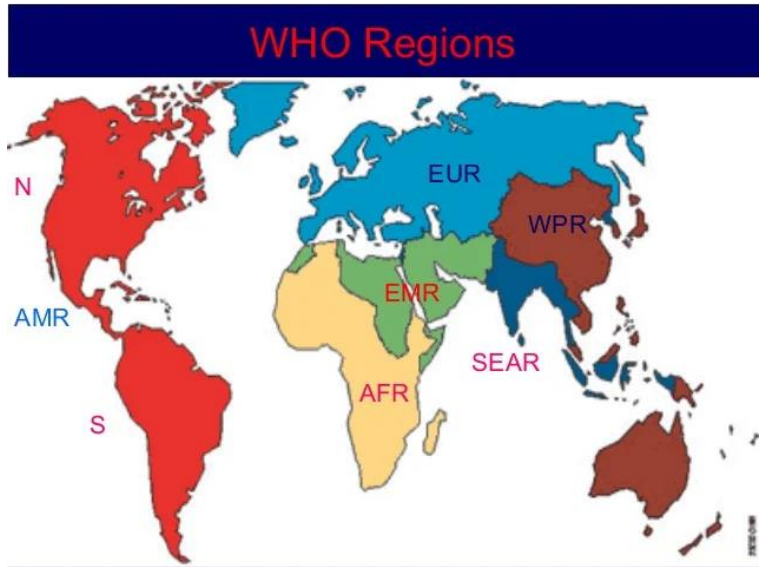
Key Figures

November 2023

906	4	26
Confirmed cases	Deaths	Countries reporting cases

Overall

92 783	171	116
Confirmed cases	Deaths	Countries reporting cases



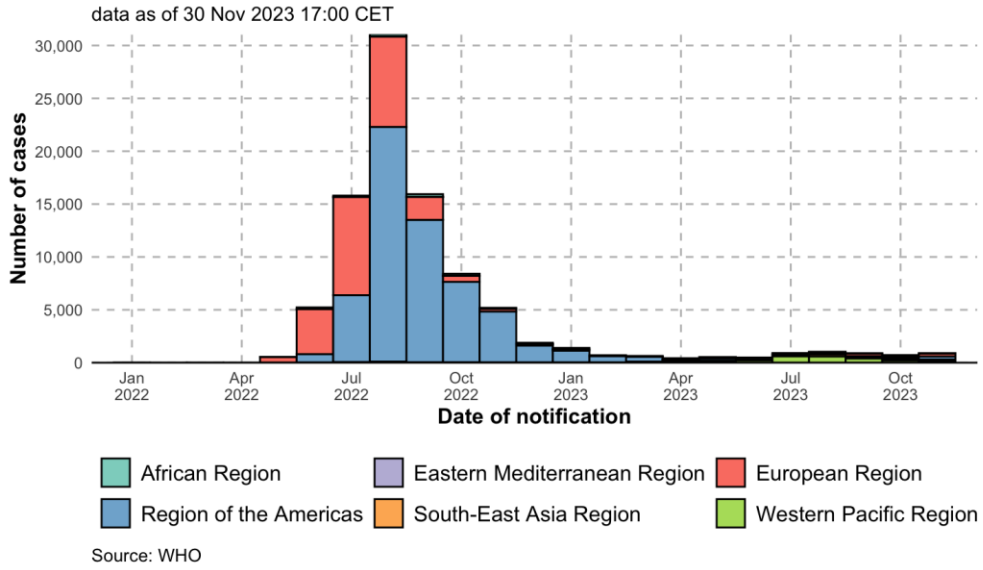
Overview

- Ongoing outbreak of mpox continues to primarily affect MSM
- No signal suggesting sustained transmission beyond these networks

- **Global Risk** according to the WHO Committee (July 2023)
  - Newly affected countries: low
  - Countries with historical mpox transmission: moderate
  - The overall global risk for MSM: moderate

Global situation update

- **November 2023:** the number of monthly new cases ↑ **25.7%** (906 cases)
- **One country (Oman)** reported the first case
- Majority of NEW cases:
  - Americas (34%)
  - European Region (28.6%)

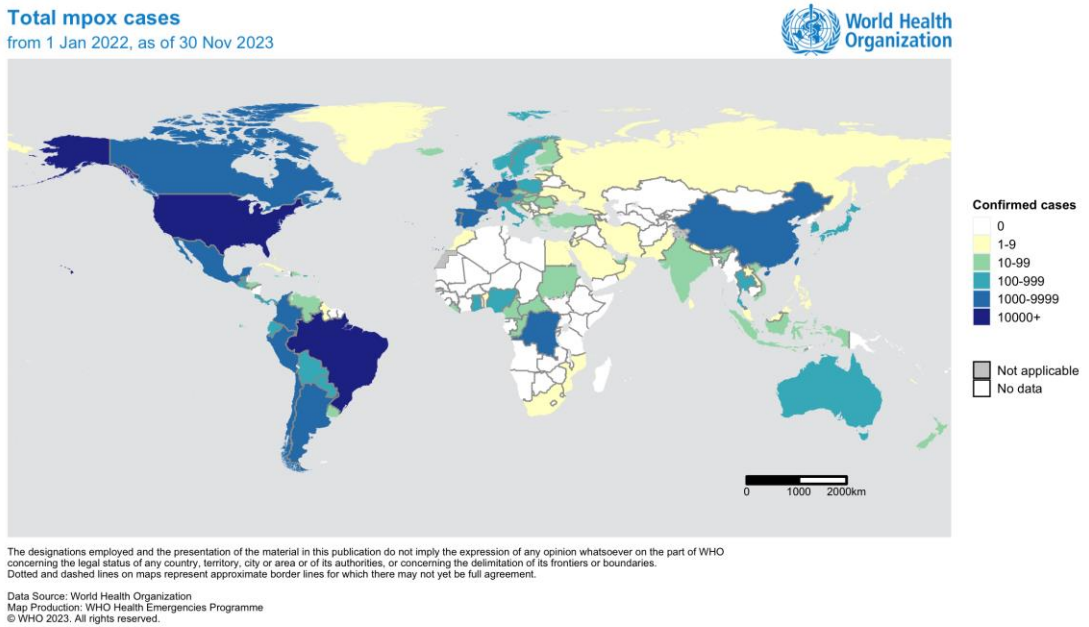


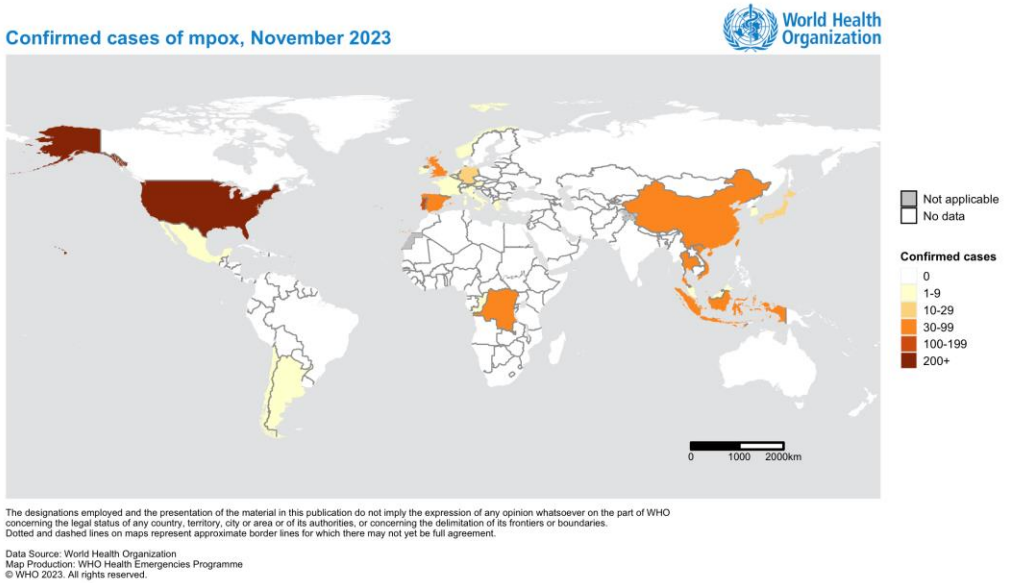
Global situation update

- Top 10 countries (81.4% of cases):

1. United States of America (n = 31 070)
2. Brazil (n = 10 967)
3. Spain (n = 7 684)
4. France (n = 4 164)
5. Colombia (n = 4 090)
6. Mexico (n = 4 071)
7. The United Kingdom (n = 3 867)
8. Peru (n = 3 812)
9. Germany (n = 3 779)
10. China (n = 2 024)

….. Italy (n= 989)



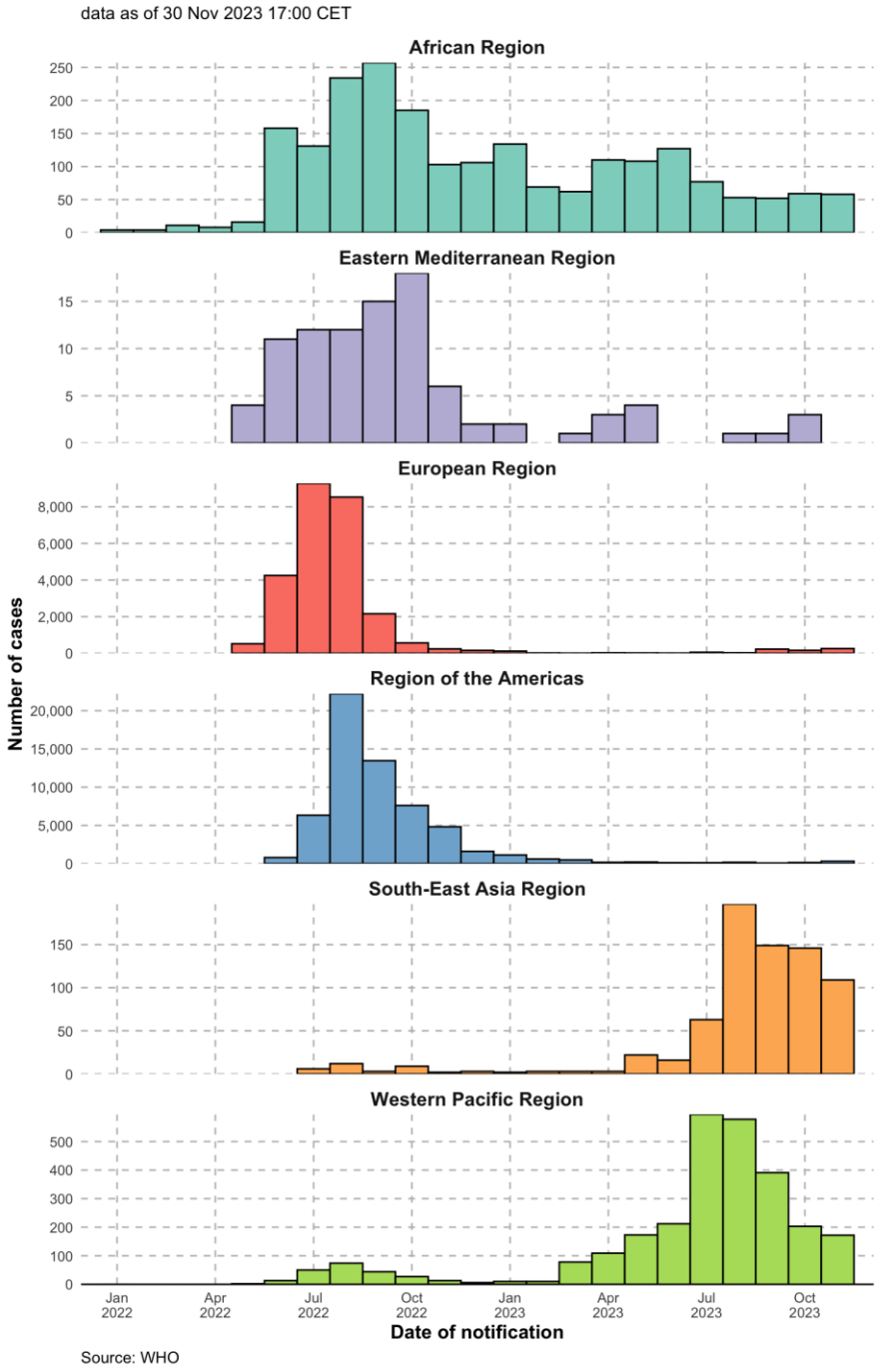


Recent trends (last six months)

- On average: 828 cases have been observed monthly

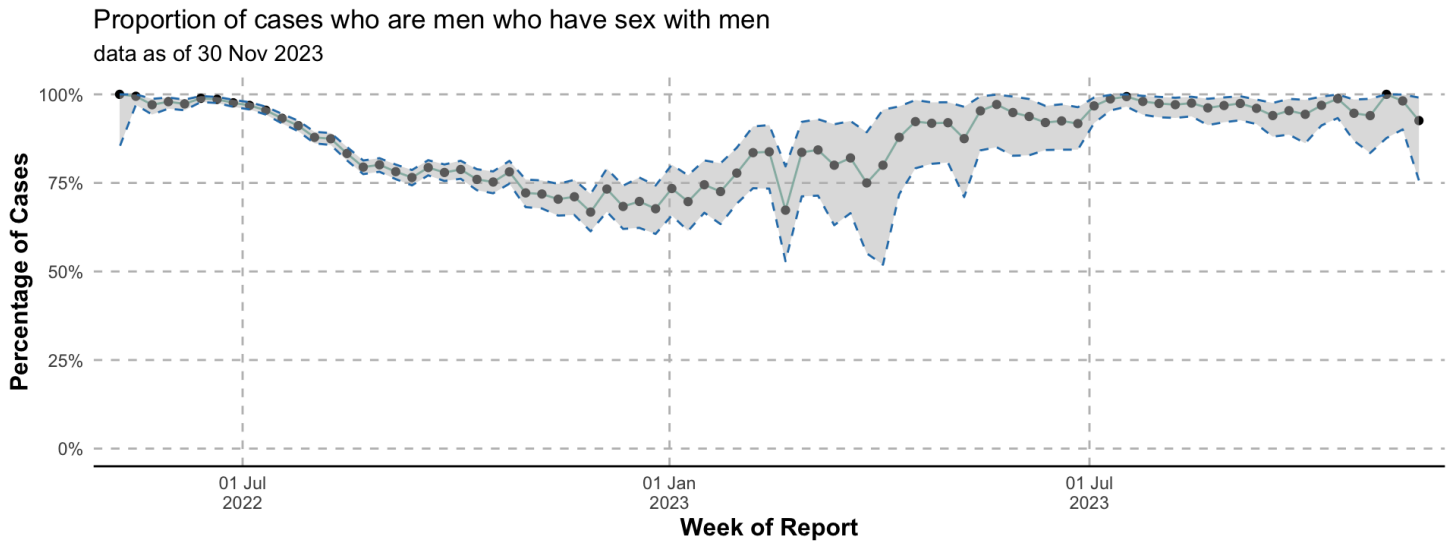
- Most affected regions:

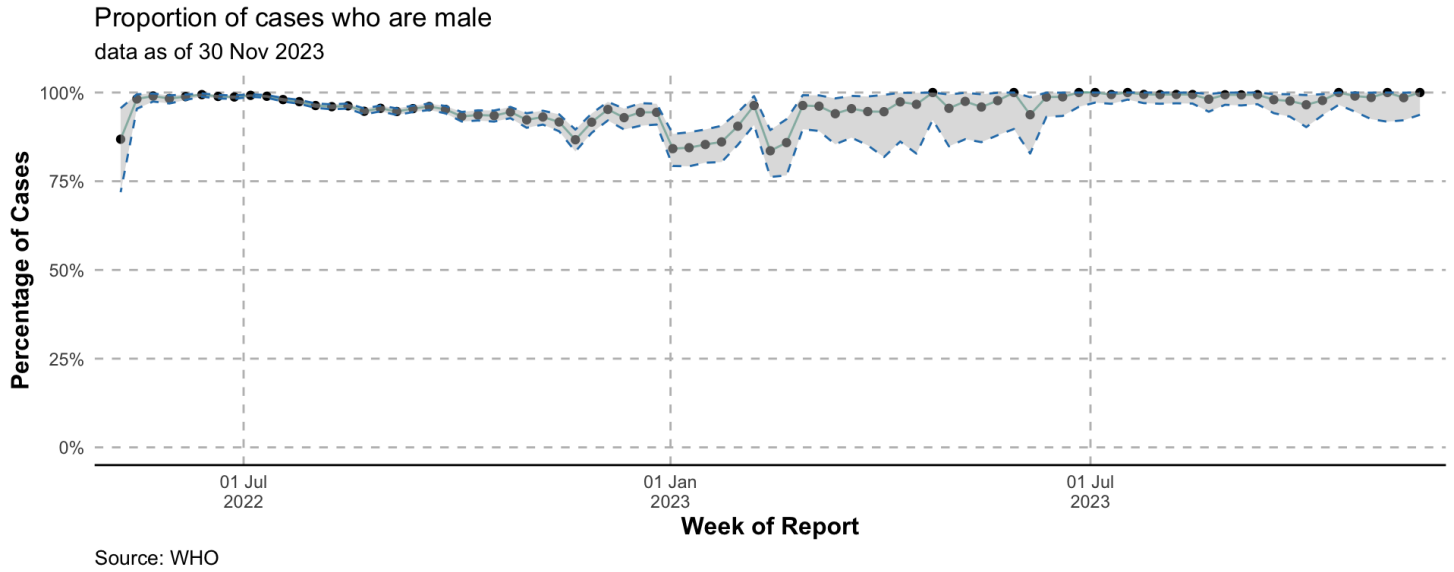
1. Western Pacific Region: 2151 cases, 3 deaths
2. Americas: 955 cases, 19 deaths
3. European Region: 752 cases, 0 deaths



-Proportion of cases who are MSM

-Proportion of cases who are male





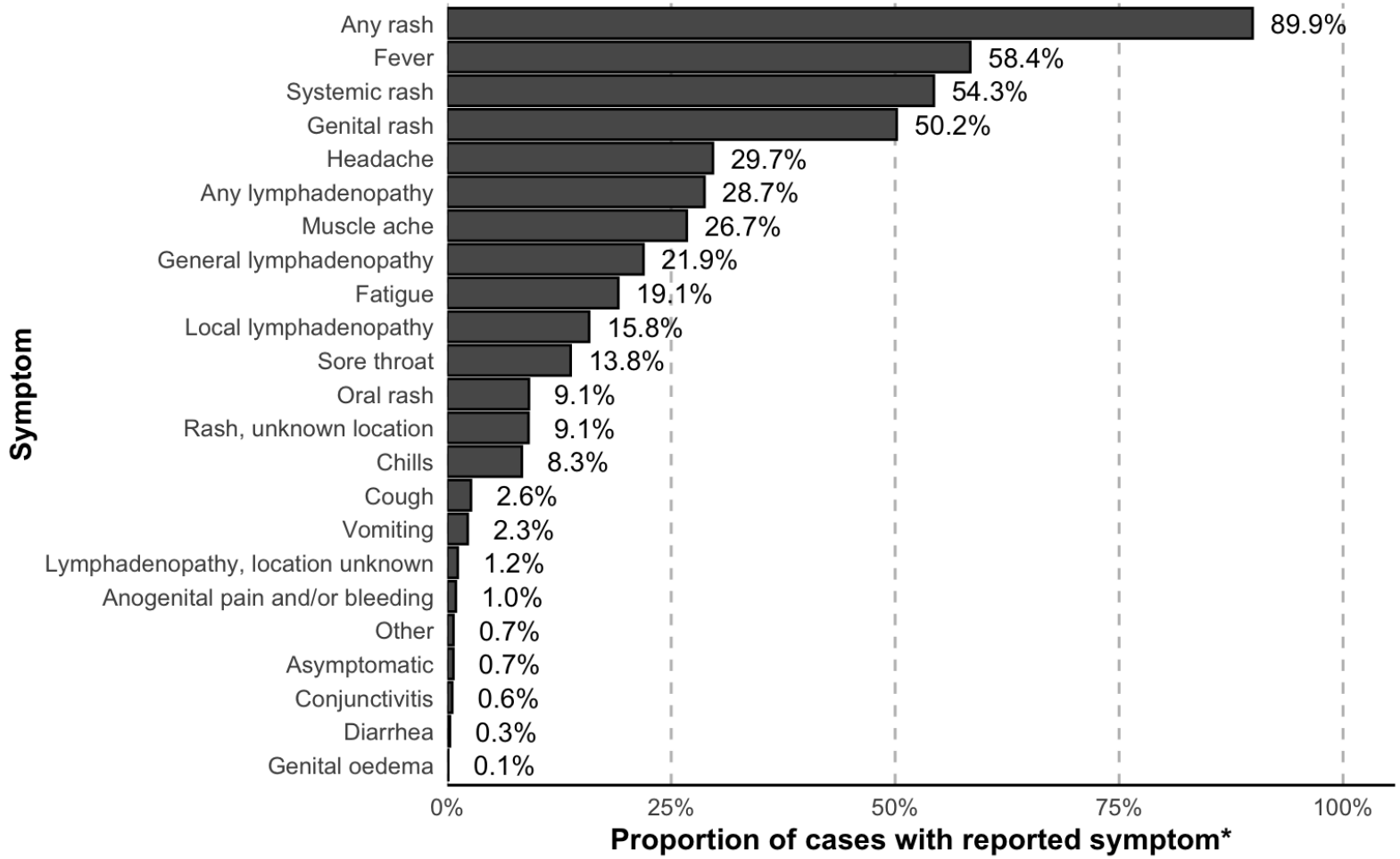
Case profile

- 96.4% male
- 85.1% MSM
- 52.1% HIV positive
- Median age is 34 years (IQR: 29 - 41)
- Males between 18-44 years old account for 79.4% of cases
- **83.1% probably sexually transmitted**
- **65.3% Party setting with sexual contacts**
- **10.9% hospitalization**
- **0.3% died**

Case profile

- **3.6%** (n=3121) female:
  - 74% from the **Region of the Americas ; 14% from European Region**
  - 51% via **sexual encounters**
- **1.3%** (n=1149) aged **0-17**
  - 61% from **Region of the Americas**
- **55 pregnant or recently pregnant.**
  - **12 hospitalized**
  - 0 **admitted to ICU**
  - **0** died.
  - The most common mode of transmission was **sexual encounter (4/9 cases where route was known)**.
- **1 263 health workers** (most were exposed in the community)

Clinical features



Source: WHO
*36,723 cases with at least one reported symptom from a country where at least two unique symptoms reported used as denominator

Italia (bollettino 10 gennaio 2024)

Al 30/12/2022 erano stati segnalati 946 casi.
Nel 2023: +43 casi

Bollettino di MERCOLEDì 10 gennaio 2024

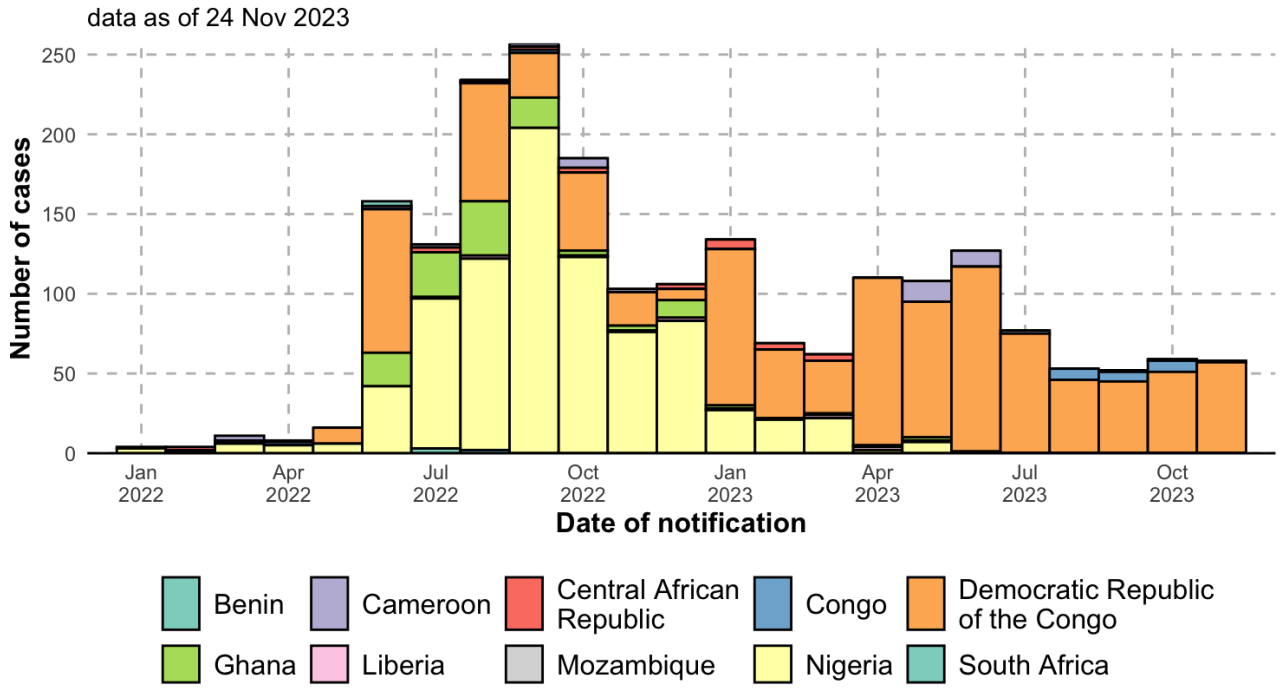
DATI NAZIONALI	
Casi confermati	989
Incremento rispetto all'ultima rilevazione *	17
Casi collegati a viaggi all'estero	258
Età mediana in anni (range)	37 (14-71)
Genere	975 M; 14 F

DATI REGIONALI		
Regioni	Casi confermati	Incremento rispetto all'ultima rilevazione *
Lombardia	427	12
Lazio	165	1
Emilia - Romagna	89	0
Veneto	68	1
Campania	48	1
Toscana	48	0
Piemonte	36	1
Liguria	29	0
Puglia	21	0
Friuli - Venezia Giulia	17	0
Sicilia	16	0
Marche	9	1
Sardegna	6	0
Abruzzo	5	0
PA. Trento	3	0
PA. Bolzano	2	0
Basilicata	0	0
Calabria	0	0
Molise	0	0
Umbria	0	0
Valle d'Aosta	0	0

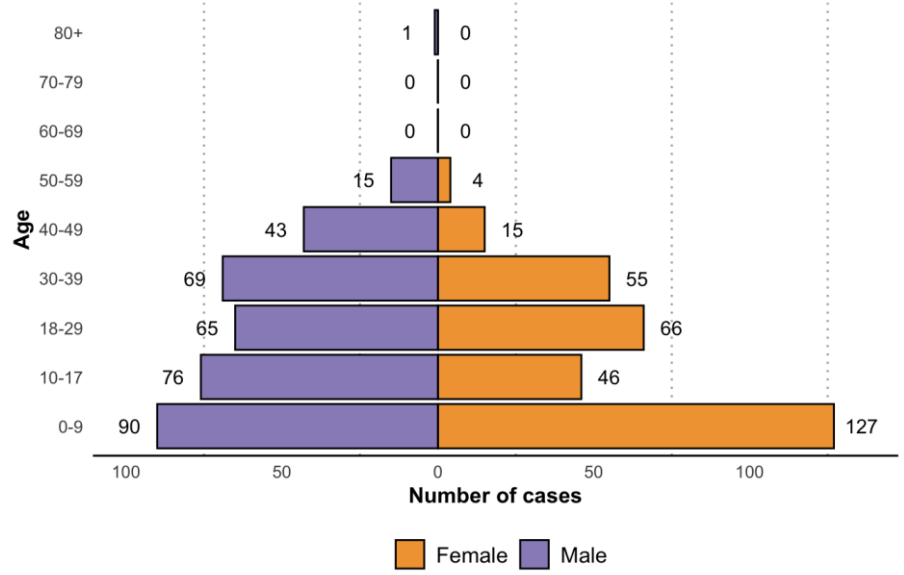
*(? novembre 2023)

Situation in Africa

- In 2023:
- 2,126 confirmed cases
- 22 deaths
- Patients with detailed data (n=672):
  - 53.4% male - 46.6% female
  - The median age is 17 (IQR: 7 - 32)
  - 50.4% aged 0-17
  - 17.7% aged 0-4

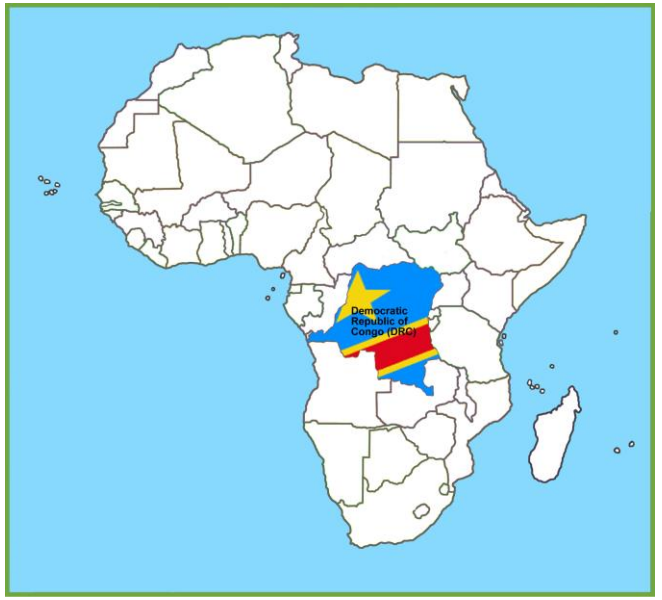


Source: WHO



Source: WHO
672 cases with age-sex data

Situation in The Democratic Republic of the Congo

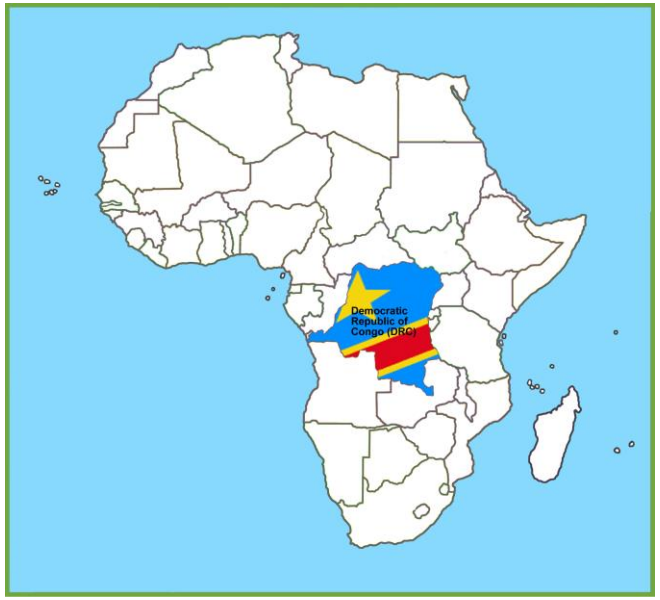


- In 2023:
  - 13 357 suspected cases (only 10% are tested)
  - 607 suspected deaths (CFR 4.5%)
  - 70% of cases and deaths in children <15y
- Only MPXV clade I reported
- No confirmed cases of MPXV clade IIb (dominant in the current global outbreak)
- In April 2023 transmission through sexual contact of MPXV clade I was documented for the first time in the Democratic Republic of the Congo

DISPATCHES

Clade I–Associated Mpox Cases Associated with Sexual Contact, the Democratic Republic of the Congo

Emile M. Kibungu, Emmanuel H. Vakaniaki, Eddy Kinganda-Lusamaki, Thierry Kalonji-Mukendi, Elisabeth Pukuta, Nicole A. Hoff, Isaac I. Bogoch, Muge Cevik, Gregg S. Gonsalves, Lisa E. Hensley, Nicola Low, Souradet Y. Shaw, Erin Schillberg, Mikayla Hunter, Lygie Lunyanga, Sylvie Linsuke, Joule Madinga, Martine Peeters, Jean-Claude Makangara Cigolo, Steve Ahuka-Mundeke, Jean-Jacques Muyembe, Anne W. Rimoin,[1] Jason Kindrachuk,[1] Placide Mbala-Kingebeni,[1] Robert S. Lushima;[1] International Mpox Research Consortium



- Patient 1 had 9 new sexual partners: 3 developed suspected symptoms and were confirmed with MPXV infection
- 36 additional sexual partners were identified and 1 was diagnosed to be infected
- All 5 identified cases were infected with the same MPXV clade I

Kibungu EM et al EID 2023

Morbidity and Mortality Weekly Report

The CDC Domestic Mpox Response — United States, 2022–2023

Jennifer H. McQuiston, DVM[1]; Christopher R. Braden, MD[2]; Michael D. Bowen, PhD[1]; Andrea M. McCollum, PhD[1]; Robert McDonald, MD[3]; Neal Carnes, PhD[4]; Rosalind J. Carter, PhD[5]; Athalia Christie, DrPH[6]; Jeffrey B. Doty, MS[1]; Sascha Ellington, PhD[7]; S. Nicole Fehrenbach, MPP[8]; Adi V. Gundlapalli, MD, PhD[9]; Christina L. Hutson, PhD[1]; Rachel E. Kachur, MPH[3]; Aaron Maitland, PhD[10]; Christine M. Pearson[1]; Joseph Prejean, PhD[4]; Laura A. S. Quilter, MD[3]; Agam K. Rao, MD[1]; Yon Yu, PharmD[8]; Jonathan Mermin, MD[11]

- >30,000 U.S. mpox cases reported,
- >140,000 specimens were tested
- >1.2 million doses of vaccine were administered,
- >6,900 patients treated with tecovirimat, antiviral medication with activity against orthopoxviruses
- Black and Hispanic persons represented 33% and 31% of mpox cases
- Of 42 fatal cases: 94% immunocompromised because HIV ; 87% Black persons

McQuiston JH et al MMWR 2023

Mpox in people with advanced HIV infection: a global case series

Oriol Mitjà, Andrea Alemany*, Michael Marks*, Jezer I Lezama Mora, Juan Carlos Rodríguez-Aldama, Mayara Secco Torres Silva, Ever Arturo Corral Herrera, Brenda Crabtree-Ramirez, José Luis Blanco, Nicolo Girometti, Valentina Mazzotta, Aniruddha Hazra, Macarena Silva, Juan José Montenegro-Idrogo, Kelly Gebo, Jade Ghosn, María Fernanda Peña Vázquez, Eduardo Matos Prado, Uche Unigwe, Judit Villar-García, Noah Wald-Dickler, Jason Zucker, Roger Paredes, Alexandra Calmy, Laura Waters, Cristina Galvan-Casas, Sharon Walmsley, Chloe M Orkin, on behalf of SHARE-NET writing group*

Inclusion criteria: HIV positive <350 CD4/mmc with mpox

- 382 cases from 19 centers
- 107 (28%) hospitalized
- 27 (25%) died (all with CD4<200)
- Among people with CD4 counts of less than 200 cells per mm3, more deaths occurred in those with high HIV viral load.
- An immune reconstitution inflammatory syndrome to mpox was suspected in 21 (25%)
- Three individuals had laboratory confirmation of tecovirimat resistance.

	Total (n=382)	CD4 <100 cells per mm³* (n=85)	CD4 100–200 cells per mm³ (n=94)	CD4 201–300 cells per mm³ (n=128)	CD4 >300 cells per mm³ (n=75)
Mpox rash presentation					
Peak number of skin lesions	15 (8–35)	30 (15–100)	20 (12–35)	12 (6–20)	10 (4–15)
Rash duration in days	23 (18–33)	31 (21–45)	26 (19–40)	21 (16–28)	21 (15–30)
Mpox organ complications†					
Dermatological skin lesions distant from the point of entry					
Overall	94 (25%)	49 (58%)	20 (21%)	18 (14%)	7 (9%)

Mpox as AIDS-defining event with a severe and protracted course: clinical, immunological, and virological implications

Carmela Pinnetti, Eleonora Cimini, Valentina Mazzotta, Giulia Matusali, Alessandra Vergori, Annalisa Mondi, Martina Rueca, Sandro Batzella, Eleonora Tartaglia, Aurora Bettini, Stefania Notari, Marika Rubino, Massimo Tempestilli, Carlo Pareo, Laura Falasca, Franca Del Nonno, Alessandra Scarabello, Marta Camici, Roberta Gagliardini, Enrico Girardi, Francesco Vaia, Fabrizio Maggi, Chiara Agrati, Andrea Antinori

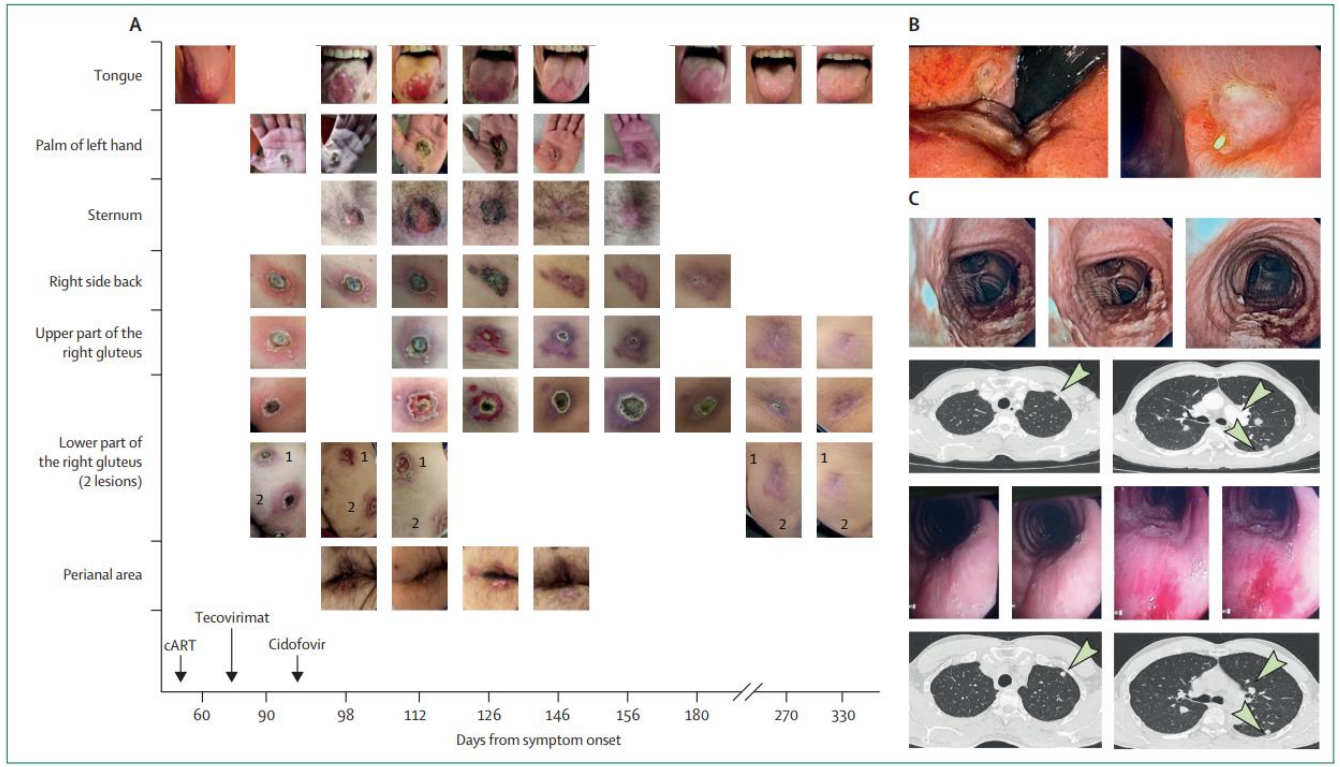


Figure 1: **Timeline of clinical presentation, endoscopic picture, and radiological images**
(A) Evolution over time of lesions on the tongue, left palm, sternum, right dorsum and gluteus, and perianal area. (B) Severe proctitis was documented at proctoscopy performed 2 days before the first

Pinnetti C et al LID 2023

Morbidity and Mortality Weekly Report

Interim Clinical Treatment Considerations for Severe Manifestations of Mpox — United States, February 2023

Agam K. Rao, MD[1]; Caroline A. Schrodt, MD[1]; Faisal S. Minhaj, PharmD[1,2]; Michelle A. Waltenburg, DVM[3]; Shama Cash-Goldwasser, MD[2]; Yon Yu, PharmD[4]; Brett W. Petersen, MD[1]; Christina Hutson, PhD[1]; Inger K. Damon, MD, PhD[3]

Indication to treatment:

- **Severe disease** (hemorrhagic disease; a large number of lesions such that they are confluent; necrotic lesions; severe lymphadenopathy that can be necrotizing or obstructing (such as in airways); involvement of multiple organ systems and associated comorbidities (for example, pulmonary involvement with nodular lesions; sepsis; encephalitis; myocarditis; ocular or periorbital infections); or other conditions requiring hospitalization
- **Involvement of anatomic areas which might result in serious sequelae**
- **People who are at high risk** for severe disease:
  - **Severe immunocompromised**
  - **Pediatric populations**, particularly patients younger than 1 year of age
  - **Pregnant or breastfeeding people**
  - **People with a condition affecting skin integrity**

- **Tecovirimat (po/iv)**
- **Brincidofovir**
- **Cidofovir**
- **Vaccinia Immune Globulin**
- **Ophthalmic trifluridine**

Rao AK et al MMWR 2023

Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV

The information in the brief version is excerpted directly from the full-text guidelines. The brief version is a compilation of the tables and boxed recommendations.

July 24, 2023

Mpox

- Added new mpox chapter covering the epidemiologic, diagnostic, prevention, and treatment considerations for people with HIV.

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.

*People with HIV at high risk for severe mpox

- not virologically suppressed or
- have CD4 counts <350 cells/mm3

*Severe mpox:

- hemorrhagic disease
- a large number of lesions such that they are confluent
- Sepsis
- Encephalitis
- ocular or periorbital infections
- other conditions requiring hospitalization.

Management of Mpox in Persons with HIV

Epidemiology and prevention

- An outbreak of Mpox (formerly known as Monkeypox) outside West/Central Africa is ongoing since May 2022. In the context of the current outbreak, sexual intercourses have been the major route of transmission. It has disproportionally affected MSM, particularly people with HIV and PrEP users
- Counselling should be offered to these persons to reduce the risk of Mpox transmission
- Close contacts of an individual with Mpox should be identified and monitored according to local guidelines
- See Vaccination for recommendations regarding Mpox preventive and post-exposure vaccination
- Individuals recently diagnosed with Mpox should be tested for concomitant STIs. See also STI

Clinical features and diagnosis

- Fever, lymphadenopathy and enanthema in prodromal phase, followed by cutaneous lesions (most frequently vesiculopustular, but multiple morphologies may occur). Atypical presentations, such as single genital ulcer, proctitis and anorectal involvement, or conjunctival involvement may occur
- Aggressive disseminated infection with large necrotizing skin/mucosal lesions and multisystemic involvement (pulmonary, ocular or central nervous system manifestations; secondary cutaneous or bacteriaemic superinfection) may occur in individuals with immunosuppression, including persons with advanced/uncontrolled HIV infection (CD4 T cells<200 cells/mm³, having most cases <100 cells/mm³)
- Definitive diagnosis requires Mpox DNA detection by PCR on cutaneous lesion/crust swab. PCR on oropharyngeal/conjunctival/rectal swab may be useful in atypical presentations. See also WHO guidelines and CDC guidelines

Management and treatment

- All individuals with Mpox should be offered appropriate symptomatic treatment (pain and fever management, care of skin lesions)
- Isolation measures for confirmed cases and effective contact-tracing should be implemented to reduce the risk of Mpox spreading, according to local guidelines
- Non-severe cases without immunosuppression or other high-risk clinical manifestations and able to self-isolate at home may be managed conservatively. Close monitoring of clinical conditions and early recognition of complications (e.g.: bacterial superinfection; difficult breathing; deterioration of general conditions) should be ensured
- Severe cases or cases at high-risk of severe disease, defined as persons with any of the following:
  - CD4 T cells <200 cells/mm³ (see also CDC guidelines)
  - fulminant disseminated infection (confluent, necrotic skin lesions; pulmonary or CNS complications; sepsis)
  - mucosal or genital lesions with the potential for causing strictures
  - ocular involvement
  - lymphadenopathy causing difficulties in breathing/oral intake
  - skin and deep tissues bacterial superinfection
  - severe, uncontrolled pain
  - pre-existing skin conditions affecting skin integrity
  - pediatric, pregnant or breast-feeding populations
  - other conditions requiring hospitalization

  Should be evaluated for hospitalization and initiation of antiviral treatment (see also WHO guidelines and CDC guidelines)

Therapeutic considerations for severe cases

Severe cases and persons at risk of severe disease should be admitted for close monitoring. In immunocompromised patients, it is critical to optimize immune function to maximize chances of recovery. To date, effectiveness of antiviral therapies in Mpox has not been systematically evaluated, but preliminary data suggest that their use may be beneficial in severe cases. See also MMWR-Interim clinical treatment considerations for Mpox

First-line therapy	Dose	Comments
Tecovirimat	Oral dosing: • 40-120 kg: 600 mg bid • >120 kg: 600 mg tid • To be administered with high-fat meal IV dosing: • 35-120 kg: 200 mg every 12 hours over 6 hours • > 120 kg: 300 mg every 12 hours over 6 hours • Do not administer IV formulation in patients with CrCl< 30mL/min, and use caution in people with milder degrees of renal impairment Treatment duration: 10 to 14 days	• Tecovirimat has been approved for the treatment orthopox viruses infections (including Mpox) based on animal studies. Studies to assess benefit of tecovirimat treatment in people with Mpox are ongoing. Data on special population (pregnant women; pediatric patients) are limited. • Tecovirimat may reduce RPV levels. Consider additional drug-drug interactions when prescribing tecovirimat; See also Anti-infective/ART interaction table

Additional therapeutic options

Several agents have been proposed as adjunctive or alternative therapies for Mpox.

- Brincidofovir and cidofovir are effective against other poxviruses, and anecdotical data suggest that they could be effective against Mpox. The use of these agents may be considered in patients not eligible to or failing first-line therapy with tecovirimat. In addition, either brincidofovir or cidofovir may be considered in combination with tecovirimat as first-line therapy for severely immunocompromised patients.
- Vaccinia immune globulin intravenous (VIGIV) can be considered for severely immunocompromised patients unable to mount an effective immune response. Caution should be applied in administering VIGIV in patients with corneal involvement. See also MMWR-Interim clinical treatment considerations for Mpox
- Topical application of trifluridine could be considered in patients with ocular involvement

Considerations for ART start

- Cases of clinical deterioration attributable to immune reconstitution inflammatory syndrome (IRIS) have been observed in persons with advanced HIV infection antiretroviral-naïve or re-initiating ART. Monitor carefully for signs of IRIS after ART introduction

EACS European AIDS Clinical Society

12 GUIDELINES

Version 12.0

October 2023

English

JAMA Internal Medicine | Original Investigation

Early Tecovirimat Treatment for Mpox Disease Among People With HIV

Bruce Aldred, MD; Robert H. Lyles, PhD; Jane Y. Scott, MD; Daniel J. Gromer, MD; Amalia Aldredge, MD; Kimberly A. Workowski, MD; Zanthia Wiley, MD; Boghuma K. Titanji, MD, PhD; Brittany Szabo, PA-C; Anandi N. Sheth, MD, MSc; Paulina A. Rebolledo, MD; Minh Ly Nguyen, MD; Vincent C. Marconi, MD; Colleen F. Kelley, MD, MPH; Sheetal Kandiah, MD; Aley Kalapila, MD, PhD; Jesse T. Jacob, MD; Betsy Hall, FNP-C; Jonathan A. Colasanti, MD, MSPH; Emily J. Cartwright, MD; Valeria D. Cantos, MD

Aldred B et al JAMA Int Med 2024

Table. Matched Cohorts of Persons With HIV and Mpox Who Received Early Tecovirimat vs Late or No Tecovirimat

Covariate or exposure	No. (%)		P value[a]
	Early tecovirimat cohort (n = 56)	Late or no tecovirimat cohort (n = 56)	
Demographics			
Age, median (IQR), y	35 (30-42)	36 (32-43)	.60
Gender			
Cisgender men	54 (96.4)	54 (96.4)	>.99
Other[b]	2 (3.6)	2 (3.6)	
Race			
Black	46 (82.1)	49 (87.5)	.60
Other[c]	10 (17.9)	7 (12.5)	
HIV indices			
HIV viral load, cells/mL			
<200	33 (58.9)	34 (60.7)	>.99
>200	23 (41.1)	22 (39.3)	
Median CD4	314	433	

Progession of disease

- 3/56 (5.4%) in the early tevovirimat
- 15/56 (26.8%) in the late or no tecovirimat

Paired OR 13.00 [95% CI 1.71-99.40]; p=0.002

*progression to severe Mpox or development of additional severe Mpox criteria

Severe Mpox disease according to CDC criteria:

- hemorrhagic disease
- a large number of lesions such that they are confluent
- sepsis
- encephalitis
- ocular or periorbital infections
- other conditions requiring hospitalization.

RESEARCH

Tecovirimat Resistance in Mpox Patients, United States, 2022–2023

Todd G. Smith, Crystal M. Gigante, Nhien T. Wynn, Audrey Matheny, Whitni Davidson, Yong Yang, Rene Edgar Condori, Kyle O'Connell, Lynsey Kovar, Tracie L. Williams, Yon C. Yu, Brett W. Petersen, Nicolle Baird, David Lowe, Yu Li, Panayampalli S. Satheshkumar, Christina L. Hutson

- Least 7,563 patients have received tecovirimat for mpox treatment in the United States
- Tecovirimat is an inhibitor of VP37 (also know as F13 protein)
- Single nucleotide alterations to the orthopoxviral F13L gene cause resistance to tecovirimat
- **Frequency of resistant viruses remains relatively low (<1%)** compared with the total number of patients treated with tecovirimat
- **Most resistant isolates were associated with severely immunocompromised mpox patients on multiple courses of tecovirimat treatment**

Smith T et al EID 2023

Grazie per l’attenzione