Diagnosis and Clinical Approach to Monkeypox: Perspectives of a HIV physician

Webinar organized by WHO SEARO

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• November 16, 2022
Viruses are all different and classified by the genetic material they contain.

MPX is member of the Poxviridae family of viruses called Orthopoxvirus and is a double-stranded DNA virus. This subset includes the smallpox (variola, now eradicated), vaccinia and cowpox viruses.

- **Monkeypox**  →  **DNA virus**
- **HIV**  →  **Retrovirus (RNA virus but makes RNA into DNA in host)**
- **SARS-CoV-2, poliovirus, measles virus**  →  **RNA virus**
Emergence of Monkeypox — West and Central Africa, 1970–2017

• Monkeypox first described in 1958 where two outbreaks occurred in monkeys used for research
• Monkeys not major carriers of disease
• Closely related to smallpox, mass smallpox vaccine programs protected humans against monkeypox
• Smallpox eradicated in 1980 worldwide (1970 in US) so smallpox vaccine programs gradually ceased in 1970s
• Countries in Central & West Africa became susceptible to “endemic” outbreaks increasing in the past decade
ARS question: Prior to this current outbreak of MPX in the US, what was the prior next biggest outbreak associated with?

1. Travel to Nigeria
2. Infected prairie dogs
3. Injection drug use
4. School outbreak
5. Rave party
“Endemic” outbreaks (continued)

- Thought usually transmitted to humans from bite or touching infected animal (mainly rodents- rats, mice, squirrels)
- In US, MPX usually seen in returning travelers (e.g. two cases in 2021 Nigeria)
- In 2003, outbreak in US in Midwest (71 people) from interacting with pet prairie dogs – interacted with infected animals Ghana
- New - Nigeria reports that sexual transmission may have been occurring there since 2019, likely among men-who-have-sex-with-men, new light

CDC MMWR 2003; CDC MMWR 2021
“Non-endemic” outbreak of monkeypox

• ~759,000 cases in 110 countries; first case reported to WHO on May 12 so 5 months now, 50 deaths

• Early cases in UK, then rest of Europe, Canada/Australia then US, all coming down with highest rates now in Latin America

<table>
<thead>
<tr>
<th>79,411</th>
<th>50</th>
<th>110</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed cases</td>
<td>Deaths</td>
<td>Countries reporting cases</td>
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</tbody>
</table>

WHO reporting

www.monkeypox.global.health
Epidemiology of this MPX outbreak

- 79,000 cases
- Overwhelmingly gay and bisexual men
- 98-99% male
- Seems to be from sexual contact – skin to skin and close respiratory contact
- Cases slowing worldwide, especially in US/UK/ Europe (vaccine, natural immunity, behavior change)
- Rare (31 in US) cases in children
- 50 deaths (11 investigated in US, all severely immunocompromised)

Pfeiffer. CDC MMWR August 19, 2022
US outbreak (n=28,999 on 11/14/22): CA and NY have highest number of cases
India confirms first case of monkeypox in WHO South-East Asia Region

15 July 2022 | News release | SEARO

New Delhi | 15 July 2022

The first case of monkeypox in WHO South-East Asia Region has been reported from India, in a 35-year old man who arrived from the Middle East earlier this week.
Confirmed cases of Monkeypox
from 1 Jan 2022, as of 15 Nov 22

[Map showing confirmed cases of Monkeypox around the world]
### Total Monkeypox cases, by WHO region

From 1 Jan 2022. Data as of 15 Nov 2022

<table>
<thead>
<tr>
<th>Region of the Americas</th>
<th>Total Confirmed Cases</th>
<th>Total Probable Cases</th>
<th>Total Deaths</th>
<th>Cases in past week</th>
<th>7-day % change in cases</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>52,875</td>
<td>1,495</td>
<td>30</td>
<td>1,025</td>
<td>−19%</td>
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</table>

| European Region        | 25,465                | 0                    | 5            | 83                 | 63%                     |

| African Region         | 982                   | 0                    | 14           | 24                 | 0%                      |

| Western Pacific Region | 216                   | 0                    | 0            | 0                  | −100%                   |

| Eastern Mediterranean Region | 72               | 0                    | 1            | 0                  | 0%                      |

| South-East Asia Region | 31                    | 0                    | 1            | 0                  | −100%                   |

| Total                  | 79,641                | 1,495                | 51           | 1,132              | −16%                    |

1 Using most recently complete international standard week (Monday - Sunday)
India confirms Asia's first monkeypox death

By Jose Devasia and Chris Thomas

Monkeypox in India: Heterosexual contact seen in 3 out of 5 cases in Delhi, says ICMR

3 min read. Updated: 26 Aug 2022, 07:15 AM IST

Livemint
ARS question: What is the approximate rate of HIV infection among cases in this MPX outbreak?

1. 5%
2. 10%
3. 20%
4. 30%
5. 40%
What are symptoms?

- Largest case report (n=528), 16 countries, median age 38, 98% gay/bisexual men, 75% White, 41% had HIV
- Skin lesions 95% -most common anatomical sites anus and genital regions (73%)
- Can be singular or multiple – uncomfortable
- Ranging from flat to blisters to crusted lesions- most have fewer than 10 lesions
- Mouth lesions in 5%
- Common systemic features included fever (in 62%), lethargy (41%), muscle aches (31%), headache (27%), and big lymph nodes (56%), symptoms that frequently preceded the rash.
- Same symptoms if HIV negative or positive
MONKEYPOX

VISUAL EXAMPLES OF MONKEYPOX RASH

Admitted as inpatient due to very severe rectal pain,

Photo Credit: UK Health Security Agency
Epidemiologic and Clinical Characteristics of Monkeypox Cases — United States, May 17–July 22, 2022

- May 17–July 22, 2022
- 2,891 U.S. monkeypox cases reported by 43 states, Puerto Rico DC
- 99% men; (available data)
- 94% same sex activity
- 41% White; 28% Latino; 26% Black (changing)
- 41% HIV
- 42% without prodrome
- 46% genital lesions

Kathryn G. Curran, PhD¹; Kristen Eberly, MPH¹; Olivia O. Russell, MPH²; Robert E. Snyder, PhD³; Elisabeth K. Phillips, MPH³; Eric C. Tang, MD³; Philip J. Prager, MD1,3; Melissa A. Sanchez, PhD3; Lisa Hay, MPH4; Stephanie F. Cohen, MD4; Elana K. Say, PhD5; Sharon Yin, MPH5.
Monkeypox cases: High rates of other STDs and HIV

- Never have an orthopoxvirus & HIV temporally overlapped before
- High rates of other STDs and HIV in this large (>1900 cases in US) evaluation
People with HIV had more severe rectal pain likely more lesions.
Herpes, syphilis, molluscum contagiosum all STDs that can spread by other means as well (close contact)
Rapid communication

Isolation of viable monkeypox virus from anal and urethral swabs, Italy, May to July 2022

Davide Moschese¹, Giacomo Pozza², Davide Mileto³, Andrea Giacomelli², Miriam Cutrera³, Maria Vittoria Cossu¹, Maddalena Matone¹, Martina Beltrami², Federica Salari³, Spinello Antinori⁴, Alessandra Lombardi³, Giuliano Rizzardini¹

View Affiliations
Vaccine effectiveness

- Jynneos vaccine approved for smallpox and monkeypox; ACAM2000 had more side effects
- What we have right now (DRC study showed 85% efficacy but not well designed, wide CIs) although monkeypox vaccine being developed
- Quebec and UK rolled out faster & clear reduction in cases in those settings first (also likely natural infection, behavior change)
- If goes into general population as STD, will need more widespread vaccination but decreasing
- 5 doses from 1: Intradermal administration – many antigen presenting cells in skin- strategy expounded in times of resource scarcity
What do we know about the vaccine?

Most convincing evidence that smallpox vaccine protects against monkeypox is rise in latter 30 years (1 generation) after mass smallpox vaccination campaigns ceased

• ACAM2000- smallpox vaccine
• Jynneos- smallpox and monkeypox vaccine
The Transmission Potential of Monkeypox Virus in Human Populations

P E M Fine,* Z Jezek,† B Grab† and H Dixon†

Fine P E M (Department of Tropical Hygiene, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK), Jezek Z, Grab B and Dixon H. The transmission potential of monkeypox virus in human populations. *International Journal of Epidemiology 1988, 17: 643–650.

Data on monkeypox in Zaire over the five years 1980–1984 are analysed to assess the protection imparted by past smallpox vaccination and the transmission potential of the virus in unvaccinated communities. Attack rates in individuals with and without vaccination scars indicated that smallpox vaccination (discontinued in 1980) imparted approximately 85% protection against monkeypox. It is predicted that monkeypox virus will continue to be introduced into human communities from animal sources, and that the average magnitude and duration of monkeypox epidemics will increase as vaccine-derived protection declines in the population. On the other hand, current evidence indicates that the virus is appreciably less transmissible than was smallpox, and that it will not persist in human communities, even in the total absence of vaccination. The findings thus support the recommendation of the Global Commission for the Certification of Smallpox Eradication to cease routine smallpox vaccination in monkeypox endemic areas, but to encourage continued epidemiological surveillance.
WHO: Monkeypox cases drop 21%, reversing month-long increase

Declining monkeypox cases shows virus 'can be eliminated,' WHO boss says
1,067,367
Doses Administered in the 57 U.S. Jurisdictions Reporting Data as of November 8, 2022.

Total JYNNEOS Vaccine Doses Administered and Reported to CDC
ARS question: Approximately now many doses do you think need to be administered in the US of the Jynneos vaccine?

1. 500,000
2. 1 million
3. 1.2 million
4. 2 million
5. 3.2 million
How many doses do we need to give out in US?

Not known exactly but $1.2 \text{ million} \times 2 + 648,500 \times 2 = \sim 3.7 \text{ million}$

Notable gains have been made in increasing pre-exposure prophylaxis (PrEP) use for HIV prevention in the U.S. Preliminary CDC data\(^1\) show that in 2020, about 25% of the 1.2 million people for whom PrEP is recommended were prescribed it, compared to only about 3% in 2015.

Complete data set available [here](#)
HHS Facilitates Agreement to Accelerate Delivery of Additional Smallpox and Monkeypox Vaccines Using New U.S. Production Line

The U.S. Department of Health and Human Services (HHS) has facilitated an agreement between Bavarian Nordic and Grand River Aseptic Manufacturing (GRAM), a Michigan-based pharmaceutical contract manufacturer, to establish the first fill and finish line for the JYNNEOS vaccine in the U.S.

To support the current monkeypox outbreak and future smallpox preparedness, the Biomedical Advanced Research and Development Authority (BARDA), within the HHS Administration for Strategic Preparedness and Response (ASPR), has ordered 5.5 million vials of JYNNEOS from Bavarian Nordic to be filled, finished and delivered from U.S. government-owned bulk vaccine stored in Denmark. Under the procurement, Bavarian Nordic agreed to complete a technology transfer that would allow for 2.5 million of those vials to be filled and finished by a U.S.-based contract manufacturer.
TESTING: Two swabs if possible, be aware of rare “false” negative

09/02/2022: Lab Alert: MPXV TNF Receptor Gene Deletion May Lead to False Negative Results with Some MPXV Specific LDTs

CDC is aware of three Monkeypox virus (MPXV) cases in California in which preliminary data show a significant deletion in the tumor necrosis factor (TNF) receptor gene. This gene is the target for the CDC West African MPXV and Generic MPXV real-time PCR tests. At this point, the TNF receptor gene deletion is rare. Molecular laboratory developed tests (LDTs) designed using the CDC published primers and probes that specifically target Monkeypox virus did NOT detect the virus because of the TNF receptor gene deletion in these specimens. These cases were still correctly diagnosed because they were also tested with an LDT that was developed based on CDC's published non-variola Orthopoxvirus (NVO) test.

https://www.cdc.gov/locs/2022/09-02-2022-lab-alert-MPXV_TNF_Receptor_Gene_Deletion_May_Lead_False_Negative_Results_Some_MPXV_Specific_LDTs.html
Tecovirimat: Approved for smallpox

- **FDA approved 2018** under the 'animal rule' as a smallpox therapeutic (for bioterror event)
  - inhibits viral packaging and transport to cell surface for production
  - safety demonstrated in a human study
  - headache (17.0% teco, 14.4% PBO) and nausea (5.6% each) were seen  
    Grossenbach et al., NEJM 2018

- **No MPX efficacy trial data**
  - Some non-human primate data on protection against lethal smallpox and monkeypox challenges
  - Evidence for lower and less lengthy period of viremia and respiratory shedding

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**FDA approves the first drug with an indication for treatment of smallpox**

3 For Immediate Release: July 13, 2018

The U.S. Food and Drug Administration today approved TPOXX (tecovirimat), the first drug with an indication for treatment of smallpox. Though the World Health Organization declared smallpox, a contagious and sometimes fatal infectious disease, eradicated in 1980, there have been longstanding concerns that smallpox could be used as a bioweapon.

**Original Article**

Oral Tecovirimat for the Treatment of Smallpox

Douglas W. Grossenbach, Ph.D., Kady Honeychurch, Ph.D., Eric A. Rose, M.D., Jarasvech Chinsangaram, D.V.M., Ph.D., Annie Frimm, B.S., Biswajit Maiti, Ph.D., Candace Lovejoy, B.S., Ingrid Meara, M.S., Paul Long, B.S., and Dennis E. Hruby, Ph.D.
Tecovirimat: Pre-2022 Evidence for MPX

- Adler et al., 2022, Lancet ID
  - Report on n=7 UK residents diagnosed with MPX 2018-2021, (4M, 3F) in Liverpool and Newcastle, 4 acquired abroad, spread to additional 3 in UK
  - n=3 treated with brincidofovir 200mg PO qWeek: all had raised LFTs and ceased therapy
  - n=1 treated with tecovirimat 600mg PO BID x14d on day 5
    - shorter viral shedding & hosp. course, no new lesions 24h after start, recovered
Tecovirimat: 2022 Clinical Studies

- During 2022 MPX epidemic, no EUA → using it in IND Mode
  - USA: extensive paperwork, regulatory oversight by CDC
  - Revisions have been made to streamline this but not an EUA therapy

- First large case series: NEJM
  - n=528 patients 4/2022-7/2022 in 16 countries
    - 98% gay/bisexual men, 75% White, 41% HIV-positive
    - Symptoms/clinical presentations spanning spectrum
  - Only 5% received a therapeutic
    - 2% tecovirimat, 2% IV or topical cidofovir, <1% Vaccina Ig
    - Outcomes not described except n=1 with severe epiglottitis who recovered fully after tecovirimat treatment
• CDC MMWR case series from USA: 9/16/22
  – n=549 patients 5/2022-8/2022 in USA cities treated with tecovirimat under US EA-IND protocol
  – Most informative report to date
    • 98% male, median age 36.5 years
    • 39% non Hispanic white, 35% Hispanic/Latino, 18% Non Hispanic Black or African American
    • 50% HIV-positive
    • 9.5% had Jynneos, 1.5% had prior MPX or smallpox vaccination (total =11%)
    • Median time from symptom onset to tecovirimat start = 7 days (IQR 5-10)
Tecovirimat: 2022 Clinical Studies

• CDC MMWR USA case series

Benefits observed
• Median time from initiation to improvement = 3 days (data on n=255)
  • similar among HIV+ and HIV-negative
• Recovery by time of post-treatment assessment: 72.6% (data on n=317)
• 90% had lesions crusted/healing

Adverse effects
• Adverse events in 3.5% (data on n=340)
  – HA (n=3), nausea (n=2), visual changes (n=2), weakness (n=2), psychiatric hospitalization (n=1)
• 6.9% hospitalized for median 4 days (data on n=369)
• New lesions at time of post-treatment followup: 2.2% (data on n=137)

Slide made by Vivek Jain MD

• Tecovirimat safe
• Efficacy remains unclear
Compassionate use:

- Lesions in sensitive or high risk sites (near eye, urethral meatus, or causing pain)
- Severe pharyngeal or rectal pain
- High number of lesions (>50-100)
- Rapidly progressing lesions
- Immunocompromising condition including HIV with unsuppressed viremia and/or low CD4+ T cell count
Other therapies for severe MPX

- **Supportive care**
  - **Most patients fully recover**
  - **Symptomatic treatment (Sitz baths, gabapentin, selected opiates)**

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<thead>
<tr>
<th>Severe disease</th>
<th>Illness complication</th>
<th>At high risk for severe disease</th>
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</thead>
<tbody>
<tr>
<td>• Sepsis</td>
<td>• Secondary infection</td>
<td>• HIV with high VL or low CD4</td>
</tr>
<tr>
<td>• Hospitalization</td>
<td>• Proctitis with tenesmus</td>
<td>• Severe immunocompromise</td>
</tr>
<tr>
<td>• Evidence of viremia</td>
<td>• Uncontrolled pain</td>
<td>• Age &lt; 8</td>
</tr>
<tr>
<td>• Lesion location/type</td>
<td>• Rectal bleeding</td>
<td>• Pregnant/breastfeeding</td>
</tr>
<tr>
<td>• Eye</td>
<td>• Gastroenteritis</td>
<td>• Significant active exfoliative dermatologic conditions</td>
</tr>
<tr>
<td>• Mouth/Pharynx</td>
<td>• Pneumonia</td>
<td>• Increased risk for stricture/fisulta (e.g. IBD)</td>
</tr>
<tr>
<td>• Rectum</td>
<td>• Encephalitis</td>
<td></td>
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<tr>
<td>• Urethra</td>
<td></td>
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<td>• Vagina</td>
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Slide made by Tim Wilkin MD
Why a clinical trial?

SAFETY and Human Efficacy

Why We Need A Clinical Trial

1. Learn if the drug works and is safe
   - **Important to gain support for local and worldwide distribution**
2. Learn if the virus develops resistance to the drug
3. Understand what markers tell us that the drug is working so we can identify future promising drugs
4. If it doesn’t work, we are spending time and money that could be used to find drugs that do
STOMP – ACTG A5418

Study of Tecovirimat for Human Monkeypox Virus (STOMP)

Eligible Participant

Eligible for Randomization

Not Eligible for Randomization
- Severe disease
  - Ocular involvement, hospitalization, deep lesions requiring surgical intervention, potentially disfiguring lesions on the face
- Those with severe immunodeficiency, severe inflammatory skin conditions
- Pregnant and breastfeeding people
- Children

Yes

No

Randomized 2:1

Arm A Tecovirimat
Arm B Placebo
Arm C Open-Label Tecovirimat

Progression or Ongoing Pain

Slide made by Tim Wilkin MD
Schedule of Evaluations

Arms A+B
- Tecovirimat or Placebo

Arm C
- Tecovirimat

Exam, Swabs, Blood:
- d_1
- d_8
- d_15
- d_22
- d_29

STI Screen
- d_29
- d_57

Study Diary every day thru Day 29
Lesion self-assessment, Pain Scale, Eq-5d-5L

Daily reminder for diaries

Modified schedule for those <18 years of age

Randomized arm can move to open label tecovirimat for disease progression or severe pain (day 5 or later)

Slide made by Tim Wilkin MD
Conclusion

• Not new and Africa has received no vaccines or therapeutics
• Should we reclassify as STD?
• Vaccines seem to be working
• Therapeutics- New ACTG study indicated to give tecovirimat final approval