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HIV and mpox: a rapid review

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Abstract

In this review, we discuss the history and epidemiology of mpox, prevention strategies, clinical characteristics and management, severity of mpox among persons with advanced HIV, and areas for future research relevant to persons with HIV.

Keywords

AIDS; HIV; monkeypox; monkeypox virus; mpox; opportunistic infection

Introduction

Mpox is a zoonotic disease caused by *Monkeypox virus* (MPXV), an enveloped double-stranded DNA virus that belongs to the same Orthopoxvirus genus of the *Poxviridae* family as *Variola virus*, the causative agent of smallpox. Historically, mpox was mainly a self-limited zoonotic illness, affecting mostly young adults and children in rural rainforest areas in West and Central Africa [1]. The MPXV virus is comprised of two variants, also known as clades: Clade I, formerly the Congo Basin or Central African clade, and Clade II, formerly the West African clade. Clade II is further composed of two subclades, Clade IIa and Clade IIb. In May 2022, an unprecedented multinational outbreak was first recognized, caused by Clade IIb virus. As of 19 July 2023, over 88 500 cases have been reported in 111 countries [2]. People with HIV (PWH) have been disproportionately affected, accounting for around 40–50% of people diagnosed with mpox [3,4]. Severe and fatal illness has also disproportionately affected PWH, especially PWH with advanced or uncontrolled infection [5–8]. Herein, we review the epidemiologic evolution of mpox, the clinical course of mpox for PWH, and treatment and prevention strategies for this population.

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Conflicts of interest

There are no conflicts of interest.

Mpox epidemiology

Impact of smallpox elimination

Smallpox eradication remains one of the greatest achievements in the history of public health, and the eradication effort helped advance much of our early knowledge about mpox. In fact, the first patient identified with mpox in 1970 in the Democratic Republic of the Congo (DRC) was initially suspected of having smallpox, which has similar clinical presentation as mpox sans lymphadenopathy [9].

The WHO launched its plan to eradicate smallpox in 1959, escalating efforts with the creation of the WHO's smallpox eradication unit in 1967 [10]. The last endemic case of smallpox was identified in Somalia in 1977, and the WHO declared the global eradication of smallpox in 1980 [10]. With smallpox eradicated, the Global Commission for the Certification of Smallpox Eradication recommended that smallpox vaccination was no longer necessary [11]. One downstream effect of the successful smallpox eradication campaign is that an increasing proportion of the population has never received a smallpox vaccine and is immunologically naive to orthopoxviruses. This decline in population-level immunity has been implicated in increased mpox incidence rates observed in the DRC in recent years, in addition to a combination of environmental and ecological changes, animal or human movement, improvements in disease detection and diagnosis, and genetic changes in the virus [12,13].

Early mpox outbreaks

Monkeypox virus was first identified in 1958 during two outbreaks of nonfatal pox-like illness among cynomolgus monkeys in Copenhagen that had been transported from Singapore and co-housed with nonhuman primates originating from West Africa [14]. In September 1970, the first case of mpox in humans was reported in a 9-month-old child diagnosed in the DRC [9,15]. From 1970–1979, 54 additional cases of mpox were identified in humans, primarily in forested areas of western and central Africa [16].

Following the WHO's declaration of smallpox eradication in 1980 and the direction of resources to strengthen mpox surveillance efforts, an additional 350 human cases were detected through 1986. Nearly all of these cases were in the DRC, where intensive targeted surveillance was conducted [16]. The primary routes of transmission were suspected to be through direct exposure to skin, especially skin abrasions or mucous membranes, and possibly through respiratory inhalation of infectious particles [17,18]. Person-to-person transmission was only suspected in 28% of cases, and the longest chain of human-to-human transmission was estimated to be four generations [17]. The secondary attack rate for mpox among unvaccinated household contacts was approximately 9%, far lower than that observed in smallpox (37–88%), which declined to only 1% for vaccinated household contacts [16,17,19]. Based upon this finding, Jezek and Fenner [17] estimated that prior smallpox vaccination provided approximately 85% protection against MPXV acquisition. The case fatality rate for Clade I mpox was approximately 10%, with all deaths occurring in unvaccinated children 8 years or less of age [18]. Overall, Clade I has demonstrated greater virulence in humans and nonhuman primates, with case fatality rates in unvaccinated

persons of approximately 11% compared with less than 1% for Clade II, which particularly affects immunocompromised individuals [18,20,21].

Mpox continued to be a disease limited to only the African continent, with sporadic outbreaks and/or cases in West and Central Africa and consistent reporting of cases in DRC, until 2003. That year, an outbreak of 47 confirmed and probable Clade II cases were reported across six US states, and all persons were infected after contact with pet prairie dogs [22]. Outbreak investigators determined that infections originated from a shipment of small mammals from Ghana that were housed near prairie dogs, which were later purchased as pets [23]. The US cases experienced less severe illness than those in the DRC, with no deaths and only two severely ill individuals [23].

Since 2018, sporadic, imported cases have continued to occur in travelers returning to the United States and United Kingdom, with no to minimal onward transmission [13,24–26]. Although MPXV has been identified in many mammal species, most are likely secondary hosts, and the animal reservoir host remains unknown [27–29].

2022 Multinational Clade IIb mpox outbreak

The recent multinational mpox outbreak was first recognized in Europe during May 2022. The United Kingdom reported six cases of human mpox among gay, bisexual, same-gender-loving, and other men who have sex with men (collectively referred to as MSM) during 13–16 May 2022; none reported travel to Africa or contact with imported animals [30]. Many early cases occurred in people who had attended gay pride-related events during the spring in several European countries [4,31]. Nontravel-related cases of locally acquired mpox were subsequently reported from numerous countries more broadly. On 17 May 2022, the Massachusetts Department of Health announced the first suspected case of mpox associated with the global outbreak in a US resident [32]. On 23 May 2022, CDC launched an emergency response, and by mid-summer 2022, both the WHO (July 23) and the US Department of Health and Human Services (August 4) declared the multinational mpox outbreak a public health emergency [33,34]. In the United States as of 10 May 2023, 30 395 cases of mpox and 42 deaths have been reported [35].

The 2022 mpox outbreak has been notable for the rapid and unprecedented surge in number of cases compared with prior outbreaks. Several factors may have contributed to the rapid growth, including the virus's initial entry into a global network of sexually active MSM, the waning of herd and individual immunity conferred by smallpox vaccination, and increased recognition of and testing for the virus [36]. Cases in the United States peaked in August 2022, with the declines attributed to a combination of factors, including vaccination, behavior change, and infection-acquired immunity [37].

Multiple lineages of MPXV were detected in the United States during the early months of the multinational Clade II outbreak [38]. These ongoing introductions of additional MPXV strains raise concerns for the possibility of future outbreaks and highlight the need for continued mpox surveillance.

Demographic characteristics of persons with mpox in the United States

In the United States mpox outbreak, MSM, Black or African American persons, and Hispanic/Latino persons have been disproportionately affected. Persons belonging to these groups have also been disproportionately affected by HIV [39]. Among the 29 939 United States, mpox cases reported as of 31 December 2022, 93% occurred in adult male individuals, among whom 60% were Black/African American or Hispanic/Latino men [40]. Among the 38 mpox-associated deaths in the United States as of March 2023, 87% were non-Hispanic Black or African American persons, and 94% of 33 decedents with available data had HIV [7]. The epidemiology of the mpox outbreak has highlighted continued disparities in HIV prevention and care services as well as in sexual and general health services in the United States, which are likely driven by social and structural factors, including systemic racism.

Demographic characteristics of persons with mpox worldwide

Globally, among persons from 1 January 2022 through 29 January 2023 with available demographic information, 73 560 (96%) of 76 293 were male, and the median age was 34 years [interquartile range (IQR) 29–41] [41]. Of 29 854 men providing data on sexual orientation, 87% self-identified as MSM. Among 35 329 persons with known HIV status, 48% were PWH [41]. The Americas had a higher proportion of PWH compared with Europe (52 vs. 38%), whereas all other regions (Africa, Western Pacific, Eastern Mediterranean, and South-East Asia) each reported fewer than 50 cases with known HIV status [41]. Sexual transmission (69%) was the most reported mode of transmission [41]. The most common transmission setting was small gatherings with sexual contact (e.g. a night club, private party, or sauna), accounting for 66% [42]. Less frequently reported were household (11%) and large events (5%) [41].

Sexual transmission of mpox

The frequent report of exposures during sexual contact; the high prevalence of anogenital lesions at diagnosis; and the high co-occurrence of sexually transmitted infections (STIs) such as gonorrhea, syphilis, and chlamydia suggest that direct sexual contact is the primary route of transmission during the 2022 multinational mpox outbreak [3,4,42–44]. STIs are typically defined as diseases caused by an infectious microorganism transmitted from an infected person to another through exposure to bodily fluids (e.g. blood, semen, saliva, or vaginal, rectal, or urethral fluids) predominantly during oral, anal, or vaginal contact during sexual activity; transmission can also occur via direct skin-to-skin contact through macroabrasions or microabrasions of epithelia or mucous membranes. In this regard, mpox can be described as sexually transmissible, meaning that although its primary means of survival does not require sexual relations, transmission occurs efficiently during intimate sexual contact, with or without penetrative sexual intercourse [42]. Notably, prior to the 2022 multinational Clade IIb mpox outbreak, the potential for sexual transmission of orthopoxviruses had been previously established with documentation of the transmission during the course of close, intimate contact of vaccine-strain vaccinia virus [45–47].

Viral DNA has been detected by PCR in a wide variety of human anogenital samples, including penile, anal, vaginal, vulvar, and cervical lesions as well as sexual fluids

like semen. Of note, replication-competent (i.e. potentially infectious) virus has thus far only been isolated within the first 3 weeks after illness onset from skin lesion swabs, oropharyngeal swabs, anorectal swabs, urethral swabs, conjunctival swabs, and semen [48–55].

Transmission networks

Prior to 2022, most studies on mpox transmission were performed in West and Central Africa [10,17,18,36,56–61]. The longest documented transmission chains extended four to eight generations, and most were attributed to close contact, particularly sharing a household [10,17,18,36,56–61]. Close contact in the household could implicate various routes of acquisition involving activities including sharing a bed, sexual contact, caregiving, and children's play, to name a few [36,61]. However, experience during the 2022 outbreak underscores the remarkable efficiency of direct cutaneous and mucosal inoculation that occurs during sexual contact.

The majority of mpox infections during the 2022 multinational outbreak were transmitted among men during male-to-male sexual contact. Epidemiologic models developed during the outbreak suggested that dense, multicontact networks may have led to sustained transmission, furthering opportunities for multinational spread [62]. Additionally, using a dynamic network modeling framework, CDC modeled that one-time partnerships, may have disproportionately contributed to the transmission of MPXV during the outbreak [63].

However, heterosexual sexual transmission, transmission to children through close nonsexual skin-to-skin contact with a caregiver, transmission through needlestick with a skin lesion-contaminated sharp, and through body piercing and tattooing have been documented [64–68]. Transmission may also occur through contact with materials or fomites that have become contaminated with infected material in the household or patient care environment, such as clothing or linens contaminated with infectious material from body fluids or sores. Occupational exposures in absence of full or sufficiently effective personal protective equipment (PPE) have been reported [69,70].

MPXV can also cross the placenta from person to fetus, which can lead to congenital mpox [71]. During the global outbreak, one case of perinatal transmission has been reported, but pregnancy has not always resulted in transmission to the baby [72,73].

Mpox prevention

Mpox prevention includes both biomedical and behavioral strategies. Vaccination is the principal biomedical intervention for both preexposure and postexposure prophylaxis against mpox. Globally, there are currently three options available for mpox vaccination with varying availability: ACAM2000, a replicating vaccinia virus-based second-generation smallpox vaccine; MVA-BN, a replication-deficient modified vaccinia virus Ankara (MVA) third-generation smallpox vaccine. and LC16, a partially replicating vaccinia virus-based third-generation smallpox vaccine [74,75]. ACAM2000 (Emergent Bio-Solutions) and MVA-BN (Bavarian Nordic) are available in multiple countries, while the availability of LC16 is limited to Japan (KM Biologics) [74]. Both ACAM2000 and LC16 are administered

as a single dose using a bifurcated needle-scarification method and should be used with caution in any person who is immunocompromised, including from HIV, because of the replicating nature of these vaccines [74,75].

JYNNEOS (also known as Imvamune in Canada and Imavanex in Europe) is the tradename of the MVA-BN vaccine formulation available in the United States [76,77]. This two-dose vaccine can be administered subcutaneously or intradermally and has been used widely for preexposure and postexposure prophylaxis against mpox during the 2022 multinational mpox outbreak, including for PWH [77]. As of 25 July 2023, over 1.2 million doses have been administered in the United States [78]. Case-control studies evaluating vaccine effectiveness have ranged from 36–75% for one dose and 66–86% for two doses of vaccine [79–81]. JYNNEOS has been shown to be well tolerated and immunogenic for PWH with a $CD4^+$ count at least 100 cells/μl at the time of vaccination [82].

As postexposure prophylaxis, vaccination with JYNNEOS can prevent mpox if given within 4 days of exposure and may help to reduce the severity of mpox if given during the 4–14 days after exposure [83]. For persons with severe immunocompromise, vaccination beyond 14 days after an exposure can be considered as the benefits of potentially reducing disease severity may outweigh the very small risks of vaccination [83]. Other biomedical postexposure prophylaxis options, including tecovirimat and vaccinia immune globulin (VIGIV), can be considered on a case-by-case basis for persons with mpox exposure and significant T-cell dysfunction [77].

CDC recommends JYNNEOS be offered as preexposure prophylaxis against mpox to all persons with HIV and to MSM with multiple sex partners or with a recent STI diagnosis, among other indications [83]. Disparities in mpox incidence and vaccination persist. An analysis that combined United States mpox incidence and vaccination data highlighted the greater unmet vaccination need experienced by Black or African-American (vaccination-to-case ratio 8.8) and Hispanic/Latino (vaccination-to-case ratio 16.2) men compared with white men (vaccination-to-case ratio 42.5) [40]. Among PWH attending an HIV clinic in the Southeast, White clients were 1.46 times more likely to have received a vaccine compared with Black or African-American clients [84]. In San Francisco, disparities in mpox vaccination of PWH have been additionally documented among transgender women and persons experiencing homelessness [85]. Continued work using equity-based strategies is needed to improve equitable access and uptake of HIV, mpox, and other STI prevention and treatment services.

CDC recommends using a multipronged approach to promote nonstigmatizing, sex-positive, harm-reduction behavioral strategies [86] that include the following: avoiding close contact with people who have a rash that looks like mpox, avoiding contact with objects and materials that a person with mpox has used, washing hands often, limiting the number of sex partners and using other strategies for safer sex, and not attending social gatherings when feeling sick or if experiencing a rash [86]. Some evidence suggests that behavior change in response to the mpox outbreak did occur, which may have helped control transmission [63,88–90]. In a survey of MSM in August 2022, approximately one-half of respondents reported that since learning about the mpox outbreak, they had reduced their

number of sex partners, number of one-time sexual encounters, and their use of dating apps [89]. In a survey of people with HIV during August–December 2022 in Washington, DC, being vaccinated against mpox was associated with reporting other behavioral preventive behaviors [90].

CDC recommends applying a syndemic approach that includes screening for HIV and other STIs when evaluating a person for mpox [91]. Persons have been newly diagnosed with HIV, including with advanced HIV, while being evaluated or treated for mpox during the US outbreak [7,92]. Continued efforts are needed to achieve equitable access and uptake of mpox and HIV testing, prevention, and treatment services. Collaboration between public health and clinical programs for mpox, HIV, and other STIs, as well as creation of co-located, integrated programs, might help improve rates of diagnoses and linkage to care and may help prevent future outbreaks of mpox and further transmission of HIV and other STIs [85,92]. Partnerships with organizations that support MSM and prominent advocates or influencers may also help amplify prevention messaging and efforts [93].

Clinical characteristics and management of mpox

Signs and symptoms of mpox

Classically, mpox disease starts with a prodrome of fever that may be accompanied by headache, malaise or fatigue, and/or lymphadenopathy. Lesions typically occur a few days after the onset of at least one prodromal sign or symptom, and evolve through the following stages: macular, papular, vesicular, pustular, and finally crusts (scabs). The classic lesions of mpox are usually hard, deep, well circumscribed, umbilicated, and can be painful. Typically, all lesions appear synchronously and progress from stage to stage every 1–2 days over approximately 2 weeks. In a report of 40 persons with mpox in Nigeria during 2017–2018, PWH were more likely to have a longer duration of mpox illness, larger and more confluent lesions, secondary bacterial infections, and genital ulcers [94].

The signs and symptoms of mpox observed during the 2022 multinational Clade IIb mpox outbreak have differed from classic mpox in a number of ways (Table 1) [95,96]. These differences may be because of MPXV itself, the higher proportion of cases associated with sexual contact, the larger number of cases, which may have resulted in greater detection of atypical presentations, or a combination of these potential causes. As noted earlier, initial lesions have predominated in the anogenital area, and additional crops of lesions may appear and progress asynchronously. Overall rash burden has also been lower and prodromal signs and symptoms of illness may be absent or occur after onset of rash. Anogenital lesions have been common. Some cases of illness have involved single lesions or few lesions limited to a single area of the body, whereas other cases have experienced the classic generalized progression [4]. During the 2022 multinational mpox outbreak, most persons experienced mild, self-limited disease, but severe manifestations did occur, most commonly among persons with advanced HIV [6].

Mpox among PWH

During the 2022 multinational mpox outbreak, PWH with well controlled HIV infection and who were engaged in care have had comparable severity of mpox illness and outcomes as people without HIV [4,43,97]. A meta-analysis comparing mpox outcomes in PWH and without HIV suggested that PWH had comparable anatomic distribution of mpox skin rash but higher odds of proctitis and diarrhea [98]. PWH with low $CD4^+$ cells counts ($CD4^+$ <350 cells/μl) or poorly controlled HIV have been at greater risk of disseminated disease [99], more severe clinical outcomes [3,31,100–103], and higher mortality [104–106]. In an international case series of mpox patients with HIV and $CD4^+$ less than 350 cells/μl, Mitjà *et al.* observed that the severity of mpox illness increased progressively with decreasing CD4 cell count [105]. Severe manifestations included involvement of the respiratory tract (pulmonary nodules, pleural effusions, lymphadenopathy affecting airways), genitourinary tract (genital edema, urinary obstruction, necrotizing genital lesions), neurologic system (encephalitis, confusion), and eyes (periorbital cellulitis, conjunctivitis, keratitis), among other organ systems. Persons with advanced HIV also experienced particularly severe bacterial superinfections, including sepsis, abscesses, and necrotizing cellulitis, as well as severe skin manifestations, including widespread, coalescing, and necrotic lesions.

Studies have found that PWH with $CD4^+$ cell counts less than 350 cells/μl have a greater risk for hospitalization because of mpox [8,107] than people without HIV. In one convenience sample of 103 patients hospitalized for mpox, almost 90% had HIV of whom 88% had $CD4^+$ cell counts less than 200 cells/μl; PWH represented 91% of deaths [108]. Supplemental Table 1, http://links.lww.com/QAD/C957 summarizes published literature with clinical data comparing persons with and without HIV, including abstracts from the Conference on Retroviruses and Opportunistic Infections in 2023.

The disproportionate morbidity and mortality of mpox among PWH have highlighted gaps in the HIV care and treatment cascade. In case series and epidemiologic studies, among PWH presenting with severe disease or who have died, substantial numbers of persons have either been diagnosed for the first time with HIV that is advanced, or have known HIV but were not taking ART [7,108–110]. Studies have highlighted the importance of HIV testing for all patients presenting with symptoms concerning for mpox [3,111–113]. Additional syndemic strategies, such as incorporating mpox vaccination and testing in status-neutral care models, or HIV cluster detection and response activities [114], may serve to advance Ending the HIV Epidemic (EHE) goals while lowering the population of PWH at risk for severe mpox.

Mpox as an opportunistic infection

The emergence of severe mpox among PWH during the 2022 multinational Clade IIb mpox outbreak bears a striking resemblance to the emergence of opportunistic infections early in the HIV epidemic in the 1980s. Opportunistic infections in the context of HIV have been defined as infections that are more frequent or more severe because of HIV-mediated immunosuppression [115]. As noted above, mpox produces substantially greater morbidity and prolonged disease in people with advanced (i.e. $CD4^+$ cell count <350 cells/μl) or untreated HIV infection. Although the overall mortality rate for clade II infection is low

(<1%), a global case series of mpox in people reported mortality rates among people with advanced HIV up to 15% [5]. The fact that mpox-related deaths have occurred almost exclusively among PWH highlights the ongoing need for continued aggressive, comprehensive strategies for HIV testing, prevention, linkage to care, and treatment services to prevent HIV infection or disease progression that will also mitigate the impact of mpox [116].

Treatment considerations

Basic mpox prevention and treatment guidelines have been generally consistent across the United States, WHO, and other regions (e.g. United Kingdom, Canada, and European Union) [115,117–121]. In general, severity of mpox should determine the need for and type of treatment. As previously noted, for many people, including people with well controlled HIV, mpox is a self-limited illness that resolves spontaneously without antiviral therapy. However, PWH with uncontrolled infection or who have $CD4^+$ cell counts less than 350 cells/μl, or who are otherwise severely immunocompromised (e.g. cancer treatment), may merit earlier or even preemptive treatment because they can experience prolonged severe illness with serious sequelae [115,117].

Although there are currently no treatments specifically approved for mpox, investigational therapies have been made available to treat human mpox during the 2022 mpox outbreak [115,117]. These include tecovirimat (TPOXX; ST246) and brincidofovir (BCV: Tembexa), two Food and Drug Administration (FDA)-approved therapeutics for smallpox. Tecovirimat is a virostatic agent, which inhibits the Orthopoxvirus VP37 envelope-wrapping protein. Brincidofovir, a prodrug of cidofovir, competitively inhibits DNA polymerase to block viral DNA synthesis. Both brincidofovir and tecovirimat have been used for mpox treatment in the United States under investigational new drug (IND) protocols. These drugs were approved under the FDA 'animal rule' and their effectiveness in treating human mpox remains unclear [115,117]. Brincidofovir has safety concerns and contraindications for some individuals; therefore, tecovirimat has been the recommended first-line drug during the 2022 outbreak [117]. Tecovirimat resistance has been documented during the current outbreak, primarily in severely immunocompromised patients receiving extended course(s) of the drug [122]. Vaccinia immune globulin intravenous (VIGIV) is an adjunctive therapy that can be used in severe cases where the development of a robust antibody response may be impaired; in the United States, VIGIV is available under an expanded access IND protocol [117]. Other treatments include intravenous cidofovir, which should not be used simultaneously with brincidofovir [115,117]. Data are not available on the effectiveness of cidofovir or VIGIV to treat mpox in people with HIV [115,117].

PWH not taking ART at the time of mpox diagnosis should be started as soon as possible to optimize their immune response [115,117]. Immune reconstitution inflammatory syndrome (IRIS) following initiation of ART has been raised as a potential concern [105]. Studies are underway to better elucidate any risks or concerns related to possible IRIS [123].

Looking forward

Important knowledge gaps remain regarding mpox prevention and control efforts. Further research is needed to determine the clinical efficacy of vaccines and antivirals, the optimal duration of antiviral treatment as well as how and when to use these treatments in combination, and the durability of immunity after both MPXV infection and vaccination, especially among persons with advanced HIV. Clinical correlates of immunity have yet to be established to guide if, and if so then when, booster vaccination might be needed.

CDC and others are conducting analyses of vaccine effectiveness and the durability of vaccine-derived immunity that will include assessment by route of administration (i.e. subcutaneous vs. intradermal). Three clinical trials are evaluating the use of tecovirimat for the treatment of mpox: the NIH-funded Study of Tecovirimat for Human Mpox Virus (STOMP) trial that includes an open-label arm with immunocompromised participants, the Placebo-controlled Randomized Trial of Tecovirimat in Nonhospitalised Mpox Patients (PLATINUM) trial in the United Kingdom, and the PALM-007 trial in the DRC where Clade I mpox virus predominates [124–126]. In addition, CDC has partnered with NIH to study the possible role of IRIS or other immune dysregulation in PWH with mpox in the Virologic and Immunologic Characteristics of Severe Mpox Among Persons with Advanced HIV (VIRISMAP) study [123].

In conclusion, mpox can be described as both a sexually transmissible infection and an opportunistic infection, with potential to cause severe disease among persons with advanced HIV. The ongoing US mpox outbreak has highlighted the need for equitable access to and uptake of comprehensive HIV prevention and care and other sexual healthcare, including prevention and management of mpox.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Table 1.

Notable differences in the signs and symptoms of illness from classic mpox compared with illness due to the 2022 multinational Clade IIb outbreak strain.

Sign/symptom	Classic	2022 outbreak
Prodrome (e.g. fever, headache, malaise or fatigue, lymphadenopathy)	At least one sign or symptom appears before rash	Variable: signs and symptoms may be absent or occur after rash appears
Lesion distribution	Multiple lesions distributed diffusely and centripetally often involving palms and soles	Fewer or even single lesions that can be limited to only one anatomic area with a more centrifugal distribution
Anogenital lesions	Uncommon	Common: often presenting symptom
Lesion progression	Lesions appear and progress synchronously	Lesions may appear in asynchronous crops that progress separately