Mpox in People Living with HIV

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Abstract (190/200 words)

Purpose of review: The 2022 global outbreak of mpox disproportionally affected people living with HIV (PLWH). We review the data on the presentation, treatment, and prevention of mpox in PLWH.

Recent findings: Most PLWH with mpox had a mild and self-limiting illness, no different to people without HIV. A higher rate of rectal symptoms has been reported among PLWH and those with advanced HIV disease were at higher risk of severe disease, hospitalisation, and death. Treatment with antivirals was widely used in hospitalised patients without any randomised control trial data to support its use and without any data specifically in PLWH. Use of smallpox vaccines to prevent mpox is safe in PLWH regardless of CD4 count. There is limited data on efficacy in those with lower CD4 counts and on long-term protective efficacy.

Summary: PLWH should be offered vaccination against mpox in line with national guidelines. PLWH should be individually risk-assessed for severe mpox, based on their CD4 count and co-morbidities and ideally recruited into treatment trials to build an evidence base on efficacy. HIV and other sexually transmitted infection testing should be offered to all people diagnosed with mpox.

Keywords

HIV, mpox, sexually transmitted infection, tecovirimat, MVA-BN

Introduction

Mpox (previously known as monkeypox) is an infectious disease caused by the monkeypox virus (MPXV), a double-stranded DNA virus and member of the orthopoxvirus genus [1]. This genus includes variola, the causative organism of smallpox, and vaccinia, which can cause a smallpox-like illness but is used to make live-attenuated vaccines that have been used to prevent smallpox, and more recently mpox [2]. First described in 1970, in the Democratic Republic of Congo, mpox has caused sporadic cases and outbreaks mostly confined to the endemic regions of West and Central Africa [3-5]. MPXV is divided into two phylogenetic clades with clade I endemic to Central Africa and typically causing more severe disease [1, 4, 6]. Clade II is endemic to West Africa and associated with a milder illness as seen in the 2017-2018 mpox outbreak in Nigeria [3, 6, 7]. Until 2022, returning travellers represented the majority of mpox cases seen outside endemic regions [8].

On May 14 2022, two confirmed cases of mpox not linked to travel to an endemic region were reported in the UK [9]. This was followed by an exponential rise in global mpox case reports [10, 11]. The World Health Organization (WHO) declared the rapid rise of mpox cases in non-endemic countries a public health emergency of international concern on July 23 2022 [12]. As of August 2023, more than 89,000 mpox cases and 157 deaths have been reported from 114 countries [11]. Almost all (96%) cases were in men; 82.8% identifying as gay, bisexual or other men-who-have-sex-with-men (GBMSM) [11]. Phylogenetic analyses found the majority of cases were from the clade IIb, B.1 lineage [11]. Unlike previous outbreaks of mpox, 89% of cases were in non-endemic regions [10, 11]. Also unique to the 2022-23 mpox outbreak was the HIV prevalence of between 27-60% [11, 13-17]. The disproportionate burden of disease in people living with HIV (PLWH) highlights the need to better understand mpox in this population. This review will summarise recent evidence on the clinical presentation, treatment, and prevention of mpox in PLWH.

Clinical Presentation & Severity

Clinical presentation of mpox typically occurs after a 5–24-day incubation period [1, 18]. Symptoms begin with a prodrome of fever, malaise, lymphadenopathy, and headache. Defervescence usually occurs around day 3 when the characteristic skin eruption appears, starting as a maculopapular rash which progresses to vesicles and then pustules [1]. Complications of mpox include secondary bacterial infections, bronchopneumonia, gastrointestinal involvement, encephalitis, and ocular infections which can result in corneal scarring [6]. Children and those with oropharyngeal lesions were at higher risk of severe mpox requiring hospitalisation during previous outbreaks [19].

The symptomatology of the 2022 outbreak varied from that reported previously in the literature. Up to 50% of people did not experience fever or the classic prodrome [14, 20]. Characteristic skin lesions were almost always present (figure 1); however, most lesions were anogenital (figure 2) with some patients having a solitary genital lesion [14, 18, 20, 21]. Rectal pain or proctitis as the sole presenting feature for mpox was first noted in this outbreak [14, 18, 22]. Oropharyngeal presentations were common and ranged from solitary lesions (figure 3) to epiglottitis, pharyngitis, and peri-tonsillar abscess [14, 18, 23-25]. Severe oropharyngeal symptoms could compromise the upper airway necessitating intubation [26]. Ocular manifestations of mpox included ocular vesicles, keratitis, and conjunctivitis with pseudomembrane formation [27-29]. Penile oedema, arthropathy, myocarditis and central nervous system manifestations were also described [18, 30-33]. Hospitalisation occurred in 10-14% of cases with severe pain (30%) and secondary bacterial infections (26%) being the most common reasons for admission [14, 22, 31].

The high prevalence of HIV in the 2022 outbreak population raised questions about susceptibility and transmission in PLWH. Previously, PLWH were believed to be more at risk of severe disease based on limited data and mostly in people not on ART and with low CD4 counts [3, 31]. Thornhill et al. reported an international series of 528 cases, concluding that the clinical presentation of mpox was similar irrespective of HIV status (PLWH n=218/528; median CD4 cell count 680 cells/mm^3; 95% undetectable

HIV viral load) [14]. Similarly, Catala et al. found no association between HIV status and severity of disease in their series of 185 cases (PLWH n=78/185; median CD4 >600 cells/mm^3; 90% undetectable) [34]. More advanced HIV disease likely contributed to the contrasting severity of historical mpox cases compared to this outbreak [11].

Bragazzi et al. reviewed published data from six clusters in the US, Europe and Australia and found an undetectable HIV viral load to be protective against severe disease [35]. An international case series in PLWH reported by Mitja et al. included only those with CD4 count <350 cells/mm^3. All deaths occurred in those with a CD4 count <200 cells/mm^3, and a high viral load further increased the risk [31]. Severe complications including necrotising skin lesions, lung involvement, and secondary bacterial infection were more common in those with a CD4 count <100 cells/mm^3 [31]. Hospitalisation rates increased with declining CD4 counts and rising viral load [31]. Overall, deaths from mpox in PLWH are rare and associated with low CD4 counts [31, 35, 36]. In response to this, the British HIV Association suggests PLWH with a CD4 <200 cells/mm^3, persistently detectable HIV viral load or a recent HIV related illness be considered at higher risk of severe mpox [37].

Data were collated by the US Centers for Disease Prevention and Control (CDC) from 8 states. From May-July 2022, 1969 persons with mpox were reported; 38% PLWH. Compared to HIV-negative people, PLWH were more likely to experience rectal pain (34% vs 26%) and bleeding (19% vs 12%) and require hospitalisation (8% vs 3%) [17]. This cohort had 78% with a CD4 count >350 cells/mm^3 and 82% with an undetectable HIV viral load. Hospitalisation among PLWH was more common in those with detectable viral loads and CD4 counts <350 cells/mm^3, although rectal symptoms were not related to degree of immunosuppression [14, 21, 31, 38-41].

Our current understanding of the pathogenesis and immunology of MXPV was reviewed by Lum et al. [42]. In common with other viral infections such as herpes simplex and varicella zoster virus, more severe disease would be expected in those with severely impaired cell-mediated immune responses. A person with HIV and B-cell lymphoma who had recently undergone chemotherapy (CD4 count 54 cells/mm^3 and undetectable HIV viral load), had very extensive cutaneous lesions, rectal and oropharyngeal involvement and died with multi-organ failure within 21 days [43]. The chemotherapy regime was not listed but was likely a T-cell depleting regimen. Mitja et al. described an immune reconstitution inflammatory syndrome (IRIS) in 25% of people with mpox at the time of HIV seroconversion who initiated anti-retroviral therapy (ART) [31]. Of the people experiencing an mpox-related IRIS, 57% died [31]. Despite these observations the association between CD4 T-cell response and severity of mpox is unclear [42]. Further work is needed to better understand the relationship between mpox and HIV related immune suppression.

Transmission & Concurrent Sexual Transmitted Infections

Human-to-human transmission of MPXV is described as primarily through contact with virus containing lesions and respiratory droplets [6]. In the 2022 outbreak, mpox spread through sexual networks, behaving like other sexually transmitted infections (STI) [44]. Viral loads were found to be higher in skin, throat and anal samples compared to blood, semen and urine in a French study which included 44% PLWH [13]. Serial quantitative polymerase chain reaction (PCR) assays in ambulatory mpox patients showed that skin lesions were more consistently positive, compared to oropharyngeal and blood samples [45]. This is consistent with skin-to-skin transmission, rather than body fluids or respiratory droplets, as the primary route of transmission.

The high prevalence of HIV among mpox cases suggests that all people with symptoms of mpox should be tested for HIV if their status is not already known [31, 46]. All newly diagnosed people with HIV should start on ART [47] with consideration of the risk of IRIS in the context of severe mpox [31]. Reports from the US and Europe found that 30-50% people diagnosed with mpox had a concurrent STI [14, 16-18, 32]; STI screening is recommended in the WHO guidance [48]. Syphilis was diagnosed in 18% of people with mpox in a US series. [49] UK mpox proctitis guidelines have advised consideration of empirical treatment for rectal gonorrhoea, chlamydia and herpes [50]. It remains unclear how mpox and other STIs interact in terms of transmission and pathogenicity, particularly in the context of proctitis.

Treatment

Most people with mpox will recover without treatment or specialist medical interventions [8]. All mpox patients should be offered supportive treatment such as topical and systemic analgesia for skin, oral and rectal lesions and monitoring for signs of bacterial superinfection. There is currently no licensed antiviral treatment for mpox however tecovirimat, cidofovir and brincidofovir have been used. These antivirals are approved by US regulators for use in smallpox based on animal models [2, 51].

Tecovirimat

Tecovirimat was the most widely used drug for mpox in PLWH [31]. It prevents viral release from cells by inhibiting the VP37 viral envelope protein [52]. Tecovirimat can be given orally or intravenously twice a day for 14 days, with a longer course considered in those with severe or ongoing symptoms [26, 46]. Tecovirimat was granted authorisation under exceptional circumstances by European and UK regulators for use in mpox. The UK license was for hospitalised people meeting the criteria for or at risk of 'severe or complicated disease', which included PLWH. The US CDC also issued recommendations to consider CD4 count and viral load in deciding to use tecovirimat [53]. Nonetheless the evidence for efficacy is limited and includes data from animal studies showing improved survival [51].

Tecovirimat was well tolerated in PLWH during the 2022 outbreak and an analysis by O'Laughlin et al. of 369 people treated with tecovirimat found no difference in outcomes or adverse events according to HIV status [54]. Uncontrolled studies including case reports and series have reported resolution of lesions 3-7 days after tecovirimat initiation [51, 54-59]. Mitja et al. described the use of tecovirimat in people with advanced HIV in their international case series [31]. Five people died with disseminated, progressive mpox despite prolonged tecovirimat treatment. In three of the five, there was tecovirimat resistance with the FL13L mutation [31]. Several randomised controlled trials are now being conducted, including in ambulatory patients.

Although generally well tolerated, tecovirimat has the potential for drug interactions with ART. By day 14 of tecovirimat, bictegravir levels were reduced by 50%, but still sufficient to maintain viral suppression [60]. Rilpivirine, doravirine and maraviroc levels can also be reduced by tecovirimat; careful viral load monitoring should be maintained and dose adjustment considered [60]. This may also be a concern for those on long-acting injectable ART with rilpivirine and cabotegravir. There are no significant drug interactions with other commonly used integrase inhibitors, nucleoside and non-nucleoside reverse transcriptase inhibitors. [61]

Cidofovir & Brincidofovir

Cidofovir is currently licensed for the treatment of CMV, but animal and in vitro studies have suggested activity against poxviruses [62, 63]. Administered intravenously, cidofovir is associated with nephrotoxicity. Brincidofovir, an oral analogue of cidofovir, has less renal toxicity and an improved safety profile [2]. Both are broad spectrum antivirals which inhibit DNA polymerase [63]. Although used in some cases of severe mpox, there is no clear evidence of efficacy [26, 31].

Vaccinia Immune Globulin

Vaccinia immune globulin (VIG) is licensed in the USA for the treatment of severe vaccinia [64]. Vaccines used to combat smallpox and mpox are based on vaccinia and rely on the cross reactivity of the immune response. VIG contains high titre antibodies from people vaccinated against smallpox [2].

It is given intravenously as a single dose but can be repeated. Animal studies showed VIG had activity against other orthopoxviruses in immunosuppressed and immune competent animals [64]. Ahmed et al. found that 2022 MPXV isolates had 84% genetic similarity to vaccinia and that immune responses generated from vaccinia-based vaccine were cross-reactive with MPXV [65].

Vaccination

The modified vaccinia Ankara-Bavarian Nordic vaccine (MVA-BN, marketed as Imvanex, and JYNNEOS in the US) is a third-generation replication defective smallpox vaccine with a better adverse effect profile than early live vaccines. It is licensed for the prevention of smallpox in the UK, US and Europe [5, 66]. The licensed indication has been extended to include mpox [2, 5]. While earlier smallpox vaccines were not recommended for PLWH with CD4 count <200 cells/mm^3 there is no restriction with MVA-BN [53, 67]. UK guidelines recommend a two-dose schedule of the MVA-BN vaccine [5, 66]. People with a CD4 count <200 cells/mm^3 or immune suppressed for another reason, should receive two 0.5ml subcutaneous doses [66]. Those with a suppressed HIV viral load and CD4 count >200 cells/mm^3 can receive 0.1ml intradermal fractionated or 0.5ml subcutaneous doses interchangeably. To maximise the number of people that could be vaccinated with limited global supplies, fractionated intradermal doses of 0.1ml have been given based on evidence from an immunogenicity study which showed non-inferiority of this dose, but did not separately analyse PLWH [68].

The MVA-BN vaccine has shown protection in primate animal studies using lethal doses of MPXV [1]. Greenberg et al. demonstrated comparable safety and immunogenicity in HIV-negative people and PLWH with good CD4 counts (>350 cells/mm^3) [69], while Overton et al. found the same, with a trend towards lower antibody titres with lower CD4 counts [70]. There is a lack of trial data on effectiveness or immunogenicity in PLWH with CD4 counts <100 cells/mm^3 , although there are no additional safety concerns [66].

There is some real world data on the effectiveness of vaccination for the prevention of mpox in PLWH. Payne et al. used data on 9544 people with mpox, together with state-based vaccine uptake data in the US to estimate mpox incidence according to vaccine history. Mpox incidence in unvaccinated people was 9.6 times higher than those who received 2 doses and 7.4 times higher than those who received one dose [71]. The authors found no difference between the subcutaneous and intradermal route of administration. Although PLWH were included, data were not reported by HIV status. A large case-control study, adjusting for health-seeking behaviour and other factors, found a lower estimate of vaccine effectiveness of 35.8% after one dose and 66% after two doses [72]. Data on the use of post-exposure vaccination in PLWH is limited. One single-centre study found 4% of people vaccinated a median of 11 days post-exposure went on to the develop mpox [73]; HIV status was not reported.

Although uncommon, mpox infection after vaccine or prior infection have been reported. Hazra et al. described 37 individuals with mpox after either a previous mpox infection (n=8), or after vaccination (n=29). In those with a second mpox episode, this was generally less severe than the first [74]. There were no deaths or cases of bacterial superinfection and only one of the 37 required hospitalisation. Of the 37 individuals, 8 were PLWH and they had a similar outcome. A study of immunological responses after mpox infection found an early expansion of activated CD4 and CD8 T cells that persisted over time, regardless of HIV status [75]. The authors suggest that it may not be necessary to vaccinate people after mpox infection as almost all will develop a poxvirus-specific cell-mediated response [75]. The long-term effectiveness of vaccination needs further assessment to establish if or when repeat vaccination may be necessary.

Conclusion

The 2022 mpox outbreak saw a rapid rise and then decline in mpox cases in non-endemic countries, predominantly among GBMSM. PLWH were disproportionately affected and had higher rates of rectal symptoms. Advanced HIV disease was a risk factor for severe mpox, hospitalisation, and death. The high rates of concurrent STIs underline the importance of STI testing, and the high prevalence of HIV in mpox cases means HIV testing is essential. For those with HIV, ensuring that they are on HIV treatment will reduce the severity of cases. Although case numbers have declined, further outbreaks may occur. High vaccination coverage should reduce the spread, but may lead to a shift towards milder disease, leading to under-recognition and ongoing sexual transmission. For people living in endemic countries, greater access to vaccination is important to prevent outbreaks and reduce health inequalities. Clinical trials are still needed to establish the efficacy of treatments, although the decline in cases may make these more difficult to conduct. PLWH should be included in both treatment and prevention trials to confirm the safety and efficacy in the population most affected in the recent outbreak.

Key Points

- The 2022 global mpox outbreak disproportionately affected people living with HIV (PLWH).
- Mpox in PLWH is usually self-limiting with severe symptoms and death seen only in those with advanced HIV (CD4 <200 cells/mm^3).
- Anti-viral treatment and vaccination were widely used in PLWH without serious adverse effects.
- Randomised control trial evidence for the efficacy of treatment and prevention interventions for mpox are needed in PLWH.

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* Of special interest

** Of outstanding interest

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Figure 1

Figure 2

Figure 3