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Mpox and HIV—Collision of Two Diseases

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Abstract

Purpose of Review The global outbreak of mpox has brought renewed attention to a previously neglected disease which is particularly severe in people with underlying untreated HIV co-infection. For this population, the disease is progressive, severe, and often lethal. In this review, we examine the pathogenesis of mpox disease and its collision with co-existent HIV infection and discuss key considerations for management as well as emerging clinical dilemmas and areas for future research.

Recent Findings Co-existent untreated HIV infection characterized by severe immunocompromise potentiates the nefarious effects of monkeypox virus infection leading to severe manifestations of mpox. Treating mpox in the context of HIV requires mpox-directed therapies, supportive care, and HIV-specific treatment to restore immune function. Preventative measures for PWH are like those in healthy individuals, but the effectiveness and durability of protection conferred by existing vaccines in PWH remain to be fully characterized.

Summary Mpox is an important opportunistic infection in PWH. Clinicians should be aware of the unique features of the disease in this population and approaches to care and management of mpox in PWH.

Keywords Mpox · HIV · Pathogenesis

Introduction

The summer of 2022 marked an unexpected global surge of mpox, a neglected zoonotic *Orthopoxvirus* infection that had previously only been endemic to countries in West and Central Africa. The outbreak disproportionately impacted the social and sexual networks of men who have sex with men (MSM) and rapidly spread to over 110 countries, with more than 88,000 recorded cases globally [1]. Most cases of the disease in the ongoing outbreak are self-limiting, and mortality has been considerably lower (0.1%) than previously reported in historical African cohorts [2]. Co-infection with HIV, especially in severely immunocompromised individuals who are not on antiretroviral therapy, has emerged as a risk factor for a severe and protracted form of the disease, which can have a more lethal course [3••, 4, 5]. In this review, we provide an overview of mpox in people with HIV, focusing on its immunopathogenesis, clinical management, and preventative measures for people with HIV (PWH). We also highlight unanswered research questions and future directions that need to be considered as we navigate the collision of HIV and mpox.

Virology and Immunopathogenesis of Monkeypox Virus

Virology

Monkeypox virus (MPXV) is a DNA virus that belongs to the *Orthopoxvirus* genus. It is closely related to, but less virulent than, variola virus, which is the causative agent of the now eradicated smallpox disease. MPXV possesses a large double-stranded linear DNA genome, approximately 197 kb in length. Under electron microscopy, virions appear as oval or brick-like structures measuring 200–250 nm. The central

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region of the genome is mostly conserved and is flanked by two variable terminal regions [6, 7]. The central part of the genome encodes structural proteins and essential enzymes, which are delimited by open reading frames (ORFs) sharing up to 96.3% sequence homology with corresponding regions of the variola virus genome [6, 7]. On the other hand, the terminal regions encode host-range and virulence genes, which differ significantly from those of other pathogenic orthopoxviruses. Sequence analyses have identified two distinct clades of the virus [2, 6]. Clade I virus, which is more virulent and associated with case fatality rates of up to 10.6%, is endemic to central Africa. Clade II, endemic to West Africa, is associated with lower case fatality rates ranging from 0.1 to 3.6% and is responsible for the ongoing global outbreak [2].

Immunopathogenesis

Following introduction of the virus into a new host, MPXV rapidly spreads to nearby tissue resident immune cells such as dendritic cells, macrophages, monocytes, and B-cells [7, 8]. Extensive virus replication occurs in lymphoid tissue potentially facilitating dissemination to other organs via lymphatic vessels [7, 8]. The immune-mediated response to monkeypox virus (MPXV) likely plays an important role in the pathogenesis of severe mpox, particularly in individuals with AIDS (see Fig. 1). The immunopathogenesis leading to severe clinical manifestations of mpox has been associated with various factors, including impaired natural killer (NK) cell function [9], lymphopenia [10], inadequate antibody responses [11], virus-induced cytokine storm [12], and the immune evasion properties exhibited by MPXV itself (as discussed in previous reviews [8]).

Lymphopenia is a feature of severe mpox disease [10] and is thought to be a consequence of direct damage to lymphoid tissues caused by MPXV replication. In one prospective cohort [10] comprising individuals with confirmed mpox, a significant proportion of individuals (11%) exhibited reduced CD4 + T cell counts below 500 cells/μL. This reduction in CD4 T cells may be more pronounced in individuals who already have depleted CD4 + T cell reserves due to underlying HIV infection, suggesting a potential synergy between HIV-induced immunosuppression and the development of severe mpox disease.

NK cells play a crucial role in the innate immune response during MPXV infection [8]. In non-human primate

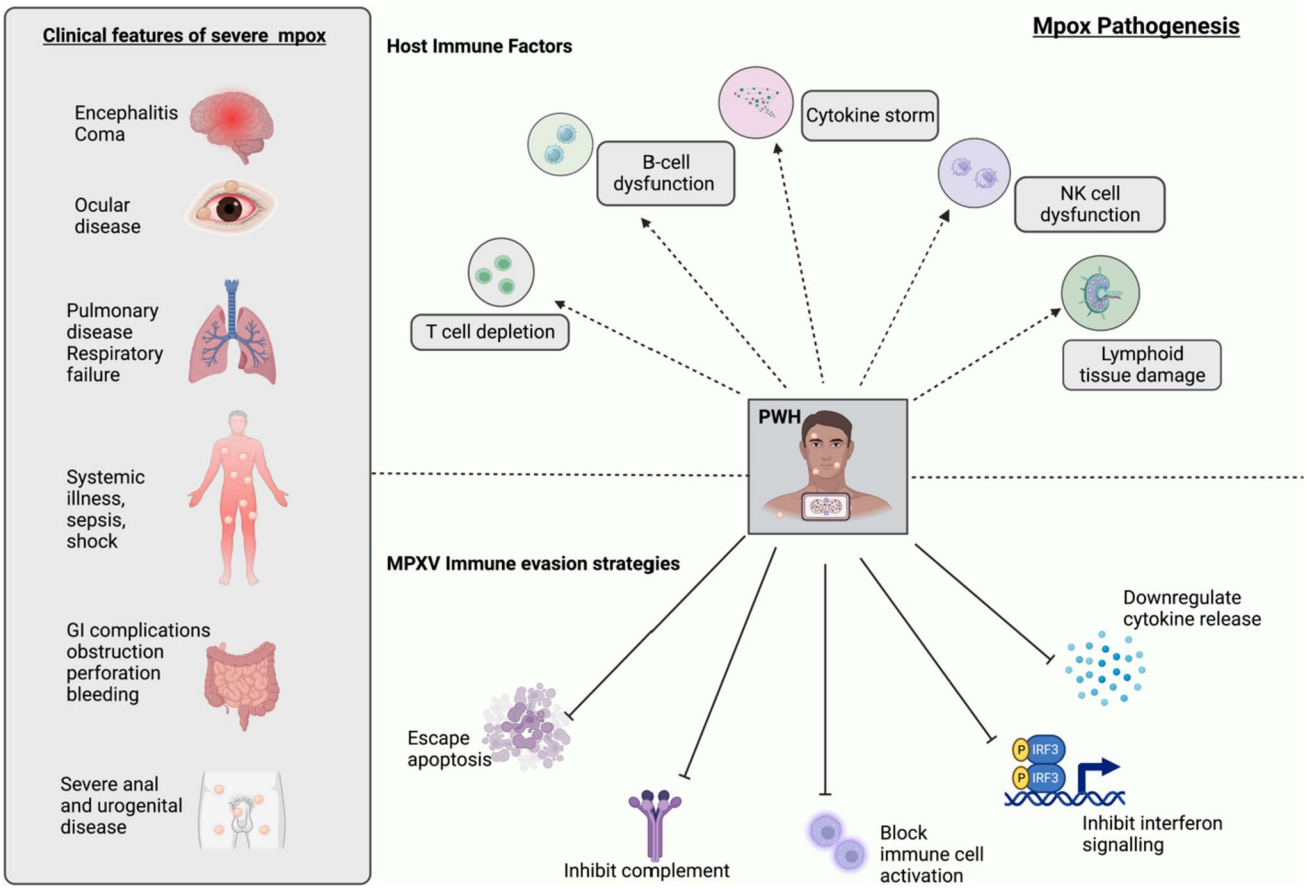

Fig. 1 Immunopathogenesis on mpox in people with HIV

(NHP) models of monkeypox (mpox), MPXV infection and viral replication lead to a rapid expansion of NK cells both in the bloodstream and in lymphoid tissues [9]. The significance of NK cells in clearing MPXV has been demonstrated in studies using genetically modified CAST/EiJ mice, which are more susceptible to orthopoxviruses due to having low numbers of NK cells [13••]. In these studies, the administration of IL-15, a cytokine that induces the proliferation of NK cells, protected the mice from lethal MPXV challenge [13••]. This protective effect was observed even with CD4 + and CD8 + T cell depletion, providing further evidence that the temporary increase in NK cells induced by IL-15 treatment is crucial for MPXV clearance [13••]. There is extensive literature demonstrating the negative impact of HIV-1 viremia on NK cell homeostasis and their antiviral effector functions (reviewed in [14]). It is reasonable to speculate that aberrant NK cell function in the context of uncontrolled HIV-1 viremia may further impede the ability of PWH to control MPXV viral replication leading to a more protracted and severe disease course. Understanding the specific roles of innate immune cells in human MPXV infections may play an important role in identifying biomarkers for disease severity and prognostication.

B-cell function and antibody production play a crucial role in the immune response to *Orthopoxvirus* infections [15, 16]. This was exemplified by the successful eradication of smallpox through a global vaccination campaign [15]. In clinical practice, vaccinia immunoglobulin has proven effective in treating individuals with *Orthopoxvirus* infections or providing passive immunity to close contacts of those infected with smallpox [17]. Orthopoxviruses demonstrate immunologic cross-protection, and vaccines based on *vaccinia* virus can generate protective immunity against MPXV in both humans and in animal models of mpox disease [2]. However, the specific correlates of vaccine-induced immune protection still are not clearly defined.

HIV infection adversely affects B-cell function through direct and indirect mechanisms, leading to increased apoptosis, heightened exhaustion, reduced response to immunization, and other B-cell defects (reviewed in [18]). Follicular helper CD4 + T cells play a critical role in augmenting the recall and differentiation of memory B-cells into antibody-secreting cells [19]. In individuals with HIV, who have depleted CD4 + T cell counts, B-cell responses to antigenic stimulation are often suboptimal [18]. In a non-human primate (NHP) model of MPXV infection, CD4 + T cells were shown to be vital in inducing a protective antibody response against a lethal challenge with MPXV in previously vaccinia-vaccinated rhesus macaques. Furthermore, macaques infected with *Simian Immunodeficiency Virus* (SIV) with CD4 + T cell counts < 300 cells/mm^3 did not develop protective antibodies after vaccination with a vaccinia-based vaccine and subsequently developed a lethal infection upon challenge with MPXV [20••]. This suggests that CD4 + T cells are important modulators of the immune response in mpox disease and provides an additional rationale for why persons with advanced HIV infection may experience severe and sometimes lethal disease. In the 2022 outbreak, persons with well-controlled HIV infection on ART and CD4 + T cell counts > 500cells/mm^3 have similar disease course often a self-limiting illness, as persons without HIV [21••].

MPXV infection can also trigger an abnormal immune response known as a cytokine storm [22]. Animal studies have shown that this leads to a prominent Th2 response, characterized by elevated levels of pro-inflammatory cytokines [23]. Cytokines promote monocyte migration which may facilitate the spread of cell-associated virus leading to disseminated infection. In NHP models using rhesus macaques, severe infections with variola virus, resulting in lethal outcomes, have been associated with increased serum levels of pro-inflammatory cytokines [24]. The connection between a cytokine storm and the severity of mpox has also been observed in human infections, including those in individuals with weakened immune systems (PWH) [3••, 4]. In addition to host immune factors that contribute to disease pathogenesis, orthopoxviruses possess a multitude of genes encoding proteins that enable them to evade the immune response (reviewed [8]). These immune evasion mechanisms further enhance the ability of MPXV to replicate and cause severe disease in hosts with compromised immune systems.

Clinical Presentation of Mpox in People with HIV

Initial presentations of mpox between those with and without HIV have not been noted to be significantly different [25]. Data from past outbreaks have indicated a wide incubation period of 4–21 days, which favored shorter durations in individuals with direct zoonotic exposure. However, the 2022 multi-national outbreak has shown support for a narrower range of 7–10 days across cases [2]. The viremic phase of the disease, accompanied by systemic symptoms like fever, malaise, myalgias, sore throat, and a generalized rash, was typical of past mpox outbreaks. However, these prodromal symptoms have widely varied in the 2022 outbreak with some reporting this prodrome occurring after the onset of rash. While fever and malaise were consistently reported in most cases, other symptoms like myalgias and generalized lymphadenopathy were not as common as in previous outbreaks. Notably, no clear differences in prodromal presentations have been observed between those living with HIV and those without, across multiple cohorts. Studies of mpox in PWH are summarized in Table 1.

While the initial case series of the current outbreak suggested a similar clinical presentation of mpox among PWH

Table 1 Summary table of clinical studies of mpox in PWH

	Location	Number of PWH with mpox	Median CD4 cell/μL (IQR)	% HIV VL < 50 c/mL	Clinical characteristics	Complications
Thornhill et al. [21••]	Global	218	680 (513–861)	95% (180/190)	24% (75/218) > 10 lesions; 68% (64/95) anogenital lesions; 31% (53/169) STI co-infection	14% (31/218) hospitalized
Hoffmann et al. [26]	Germany	256	691 (IQR NR)	96% (226/236)	17% (40/235) > 10 lesions; 50.4% (127/252) anogenital lesions; 33% (84/252) STI co-infection	2.7% (7/256) hospitalized
Chastain et al. [66]	US	93	587 (IQR NR)	NR	13% (12/93) proctitis; 13% (12/93) STI co-infection	11% (10/93) anal/rectal abscess; 11% (10/93) phimosis
Patel et al. [67]	UK	70	664 (522–894)	96% (55/57) < *200*		
Vivancos-Gallego et al. [68]	Spain	25	630 (481–923)	100% (25/25)	56% (14/25) anal lesions; 24% (6/25) STI co-infection	0% hospitalization
Curran et al. [69]	US	755	639 (452–831)	82% (618/755) < *200*		8% (42/755) hospitalization
Mitjà et al. [3••]	Global	382	211 (117–291)	51% (193/382)	53% (203/382) anal lesions	20% (70/382) secondary bacterial infection; 28% (97/382) hospitalized/ICU; 7% (27/382) death

and those without HIV infection, it is essential to note that PWH in these series were well controlled on anti-retroviral therapy (ART), with almost all of them achieving virological suppression [21••, 26]. As more data has accumulated, specifically from cohorts with advanced HIV and uncontrolled viremia, it has become clear that PWH can present with more extensive and protracted cutaneous manifestations with mucosal involvement. The degree of mpox disease severity in PWH is closely tied to immunologic function and virologic suppression [3••, 27]. Compared to those without HIV, PWH are more likely to present with ano-rectal pain and bleeding, proctitis, peri-rectal abscesses, and phimosis. Similarly, those with advanced HIV are at greater risk of developing multi-organ involvement of mpox including pneumonitis/ARDS, myoperocarditis, colitis, encephalitis, blepharoconjunctivitis, and keratitis [2].

Predictably, PWH, especially those with low CD4 counts or without HIV viral suppression, face a higher risk not only of hospitalization but also of admission to the intensive care unit (ICU) and death. ICU admissions have been primarily due to septic shock, multi-organ system failure, and airway involvement necessitating intubation [3••, 27]. In individuals with advanced HIV and uncontrolled viremia, several cases have shown a progression of mpox disease following the initiation of ART. These reports raise concerns about immune reconstitution inflammatory syndrome (IRIS), and careful consideration should be given to the phenomenon of mpox-IRIS. However, it is crucial for clinicians to acknowledge the absence of well-defined pathologic criteria and the lack of information on confounding conditions in these cases. Data from individuals with advanced HIV support the classification of severe mpox as an opportunistic infection.

Management Considerations of Mpox in PWH

Most PWH and mpox fully recover with or without treatment. However, in 2022 worldwide, a minority of patients have manifested severe clinical symptoms. There are no Food and Drug Administration (FDA)-approved treatments for mpox but medical countermeasures (MCMs) initially formulated for the treatment of smallpox have been repurposed [28]. Patients with HIV may need MCMs for the same reasons as individuals without HIV including severe disease, lesions in concerning locations, or lesions causing secondary complications [28]. PWH with low CD4 + T cell counts or elevated HIV viremia may benefit from treatment due to their immunosuppression; however, no medications have been proven to be effective in randomized controlled trials [3••]. We propose a simple algorithm for mpox treatment

in Fig. 2 and summarize the available treatment modalities in Table 2.

Supportive Care

Supportive care modalities are consistent for all patients with or without HIV and are based primarily on expert opinion. For proctitis, stool softeners can alleviate pain during bowel movements. Topical treatments, such as sitz baths and lidocaine gels, can also provide relief. However, it is important to exercise caution with local immunosuppressants, like topical steroids, due to their potential to enhance virus replication and worsen disease. Over-the-counter analgesics like non-steroidal anti-inflammatory drugs (NSAIDS), provided there is no gastrointestinal bleeding, or acetaminophen can help manage pain. Prescription analgesics such as gabapentin and/or opioids may also be considered where necessary and with a shared decision-making approach specifically as constipation associated with opioid may worsen proctitis symptoms. For patients with painful pharyngeal disease, the

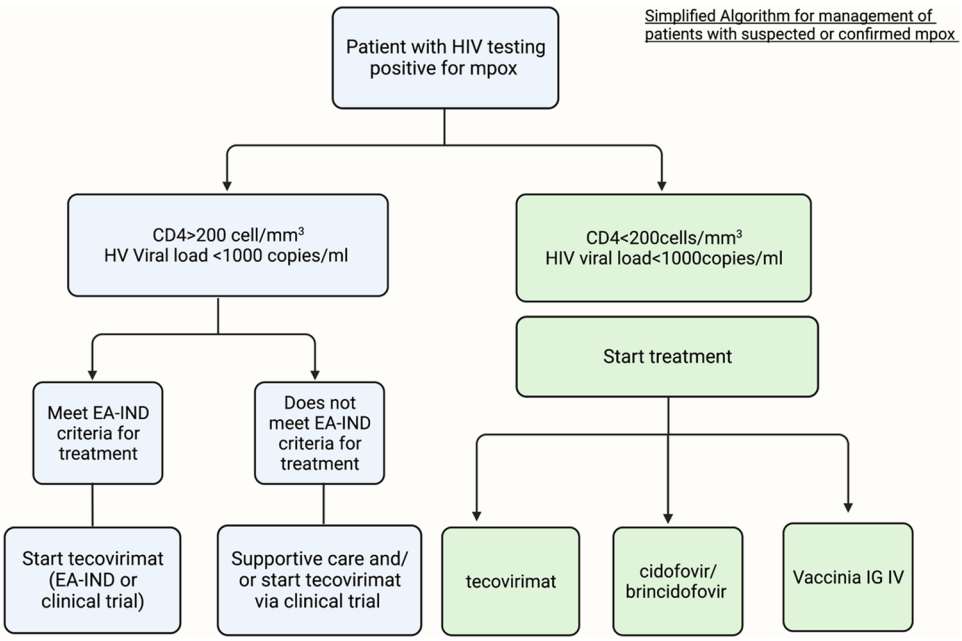

Fig. 2 Simplified algorithm for the management of suspected or confirmed mpox

Table 2 Supportive care and medical countermeasures for treatment of mpox

Symptoms	Supportive care options	Notes
Proctitis	Stool softeners; topical agents: lidocaine gel, sitz baths; oral pain control: non-steroidal anti-inflammatory, gabapentin, opioids	Avoid opioids if possible due to worsening pain with constipation. Avoid topical steroids due to risk of prolonging disease
Oropharyngeal lesions	Topical agents: viscous lidocaine, salt-water gargles; oral pain control: non-steroidal anti-inflammatory, opioids	Monitor for risk of pharyngeal infection
Genital lesions	Keep it clean and dry. Wet to dry dressings for mild debridement. Topical and/or systemic antibiotics for infection	
Medical countermeasures	Dosing	Standard duration**
Tecovirimat*	• 600 mg PO twice daily • 600 mg PO three times daily (> 120 kg) • 200 mg IV twice daily • 300 mg IV twice daily (> 120 kg)	• 14 days
Cidofovir	• 5 mg/kg IV weekly	• 2 weeks (2 doses)
Brincidofovir	• 200 mg PO weekly	• 2 weeks (2 doses)
VIGIV	• 9000 units/kg once	• Once
Trifluridine	• 1 drop into affected eye every 2 h	• < 4 weeks due to corneal injury

**May be extended if indication to prolong

*Pediatric dosing available

application of topical treatments like viscous lidocaine and saltwater gargles, in addition to over-the-counter or prescription pain relief, can be beneficial. Lastly, with secondary bacterial infections being a common complication, the use of topical or systemic antibiotics should be considered when appropriate.

Medical Countermeasures

Tecovirimat

Tecovirimat is an antiviral drug initially developed against variola to treat smallpox infection. It works by inhibiting viral protein, p37, which is highly specific and conserved in orthopoxviruses allowing tecovirimat to have in vitro activity against many orthopoxviruses. Tecovirimat was approved in 2018 via the Food and Drug Administration (FDA) Animal Efficacy Rule or Animal Rule, which allows a pathway for the approval of drugs for severe or life-threatening conditions when it is not ethical or feasible to conduct efficacy trials in humans. Prior to the current outbreak, only human safety studies were available [29]. Tecovirimat has been the first-line therapy during the 2022 outbreak, with over 6800 doses dispensed in the USA through an expanded access investigational new drug (EA-IND) mechanism [30]. While safety data is reassuring, efficacy data from randomized trials are pending [31]. In an observational study of 154 patients treated with tecovirimat, HIV status did not affect patients' clinical presentations or treatment outcomes [32]. However, in a CDC report, all 27 cases of mpox-associated deaths received tecovirimat [33]. Given these limited data available, we would consider that tecovirimat, through a clinical trial or EA-IND, should be administered to patients with advanced HIV or meeting other criteria for treatment.

Cidofovir/Brincidofovir

While animal studies suggest efficacy against orthopoxviruses, there is no data on the effectiveness of cidofovir/brincidofovir to treat mpox [34]. Cidofovir diphosphate acts as a competitive inhibitor to DNA polymerase blocking viral DNA synthesis. Cidofovir is FDA-approved for CMV retinitis and is commercially available. Cidofovir has been used topically, intralesionally, and intravenously for mpox. Case reports demonstrate possible improvement after intravenous cidofovir [35, 36]. However, given the low overall mortality of this disease and the significant risk of renal injury, intravenous cidofovir has primarily been used in individuals who are immunosuppressed and have severe life-threatening mpox disease. Brincidofovir is a pro-drug and has a side chain that gets cleaved releasing cidofovir. While it is less nephrotoxic, it may cause hepatotoxicity [37]. Furthermore, brincidofovir has been associated with the adverse effect of diarrhea which can impair oral absorption of medications including tecovirimat and ART. Brincidofovir is available through the Food and Drug Administration through an EA-IND [38]. Animal models suggest that the combination of tecovirimat and brincidofovir may be synergistic and should be considered for patients with advanced HIV and severe mpox disease [28, 39].

Vaccinia Immunoglobulin (*VIGIV*)

Passive immunoglobulin transfer provides antibodies against vaccinia virus and believed to have cross-protection with MPXV. VIGIV may have benefits in individuals unable to mount an immune response against mpox, notably those with advanced HIV. Case reports demonstrate improvement and VIGIV should be considered in patients with advanced HIV and severe mpox as previously described [28, 40].

Trifluridine Ocular Drops

Trifluridine ocular drops are FDA approved for herpes infection of the eye and are thought to have activity against *Orthopoxvirus*. Its use should be considered in all patients in cases of severe ocular disease preferably in consultation with ophthalmologists [28, 41–44].

ART Initiation

Case reports have suggested that mpox-IRIS is a possibility [45, 46]. Immune reconstitution syndromes have been well described for the *Molluscipoxvirus* infection molluscum contagiosum which is an opportunistic infection in advanced HIV [47]. In a global case series of people with mpox and advanced HIV, 25% of patients who started or re-initiated ART developed suspected IRIS, with a 57% mortality rate in those in whom immune reconstitution inflammatory syndrome was suspected [3••]. However, given the reports of persistent disease in persons with mpox and immunosuppression, the benefits of immune reconstitution likely outweigh the risks. Our expert opinion is for initiating or re-initiating ART as soon as possible to improve the immune response and the chances of MPXV clearance while providing continued supportive care [8] and the mpox-specific MCMs we have discussed. It remains essential to engage all PWH with mpox and adopt a shared decision-making approach to initiating ART.

Corticosteroid Use

The role of corticosteroids in the treatment of mpox is currently unclear. Steroids have been used in case reports to manage suspected IRIS with disappointing results and lethal outcomes [45]. In the global case series, 43% of individuals

with suspected IRIS received steroids; however, their outcomes were not reported [3••]. In the CDC report, 24 of 27 reported deaths received corticosteroids for mpox-related complications or concerns. Given that individuals with persistent disease have lesions with persistently high lesion viral load indicating ongoing MPXV replication, in most cases, the risk of steroids likely outweighs any potential benefits and should be pursued with caution.

Antiviral Resistance

Tecovirimat targets the *Orthopoxvirus* VP37 envelope protein and has a low barrier to selecting for drug resistance. Single-amino acid substitutions in the F13L gene which encodes for VP37 can confer substantial reductions in tecovirimat activity. Previous studies from orthopoxviruses identified more than 20 mutations associated with tecovirimat resistance under drug selection pressure [48]. Epidemiological surveillance in Los Angeles, California, identified six cases of mpox that did not improve on tecovirimat therapy, all of whom were PWH with CD4 < 200, and found a wide-ranging tecovirimat resistance in the virus isolated in vitro when compared to wild-type isolates, suggesting selection for resistance [49]. The CDC has screened 70 isolates from 40 patients and found 50 isolates from 26 patients having resistant phenotypes. Most resistant isolates were associated with immunocompromised patients who had received multiple courses of tecovirimat treatment. Isolates with mutations identified by routine surveillance of patients not treated with tecovirimat remained sensitive [50]. The possibility of resistance to tecovirimat should be considered in patients who fail to respond to therapy or who develop recurrent disease. Combination antiviral therapy should also be considered upfront for immunocompromised individuals with severe and progressive disease.

Prevention of Mpox in People with HIV

Vaccination and Responses in PWH

Vaccines against smallpox offer immune cross-protection against mpox. The US Food and Drug Administration (FDA) has approved a 2nd generation live vaccinia vaccine ACAM2000 and a 3rd generation modified vaccinia Ankara (MVA) vaccine JYNNEOS for pre-exposure prevention of mpox. Live vaccinia vaccines are contraindicated in PWH, pregnancy, and other immunocompromising conditions, but the attenuated MVA-based vaccines are considered safe for these populations. An open-label phase II trial found two doses of MVA vaccine administered subcutaneously and spaced 1 month apart to be equivalently immunogenic in PWH with CD4 + T cell between 200 and 700 cells/mm^3 compared to healthy controls without HIV [51]. A smaller phase II study evaluated the immunogenicity of MVA vaccine in PWH with baseline CD4 + T cell counts < 350 cells/mm^3 who had a history of AIDS and a CD4 + T cell nadir < 200 cells/mm^3 and found the two-dose series of the vaccine to be equally safe and immunogenic compared to healthy controls without apparent added benefit of a third boosting dose [52]. The immune responses to MVA vaccines have not been evaluated in PWH with a current diagnosis of AIDS and CD4 + T cell < 200; however, data from NHP models of SIV-infected macaques suggest that advanced immunosuppression with depleted CD4 + T cells < 300 cells/mm^3 may be associated with insufficient response to vaccines which may impact the level of resulting protection. The role of booster doses or repeat vaccination in PWH with CD4 + T cells < 200 cells/mm^3 is unclear and needs further study.

Considerations for Pre-exposure Prophylaxis Vaccination

Pre-exposure vaccination programs have been integral to the mpox response in North America and Europe. Given that people with HIV (PWH) are over-represented in current mpox cases and that those with advanced HIV are at a higher risk of severe mpox-related hospitalization and death, public health agencies have rightly prioritized these populations for mpox vaccination. This prioritization takes precedence regardless of their sexual history or behaviors, as the focus is on protecting vulnerable individuals and preventing further transmission of the disease.

During the ongoing 2022 outbreak, the real-time effectiveness of MVA-BN against mpox has been extensively studied [53–57]. In one large recent study, complete vaccination with two doses of MVA-BN administered subcutaneously or intradermally 28 days apart was found to have an adjusted vaccine effectiveness of 66% [54] although effectiveness estimate ranges between 66 and 89% across studies [53–57]. Vaccine effectiveness data specifically for PWH are sparse, but one study found that a complete MVA-BN series had a 70.2% adjusted vaccine effectiveness against mpox among people with immunocompromising conditions which included self-report history of HIV [56].

Post-exposure Prophylaxis (PEP)

Individuals with exposure to mpox should be offered mpox vaccine as post-exposure prophylaxis [58]. Vaccination is recommended within 4 days for optimal efficacy, but receipt of vaccine between 4 and 14 days may also confer some degree of protection [59, 60]. Those who do not develop symptomatic infection can complete the full 2-dose vaccine series. Thus far, evidence for this practice is limited to use

of smallpox vaccine in 30 exposed individuals during the 2003 US mpox outbreak, with only 1 subsequent symptomatic infection [61]. While efforts are underway to evaluate this strategy during the 2022 outbreak, public data regarding efficacy is not yet available [62]. Other therapies, including tecovirimat and VIGIV, can be considered for PEP, in cases of significant exposure in patients unlikely to mount an adequate antibody response like those with advanced HIV [25]. There is no efficacy data on these therapies as post-exposure prophylaxis.

Repeat Infections and Post-vaccination Mpox Infections

Recent case series show that past infection and vaccination are not fully protective against mpox [63, 64••, 65]. However, these data suggest such repeat infections or infections after vaccination are rare, characterized by milder disease and relatively reduced pain, fewer instances of bacterial superinfection, and fewer hospitalizations. While clinical characteristics of these repeat or post-vaccination infections appear to be similar among PWH and those without HIV, more information is needed in people with advanced HIV and uncontrolled viremia. Regardless, vaccination remains the most powerful tool available to protect vulnerable populations against mpox. Social determinants which impact marginalized communities from linkage and retention to HIV care are also responsible for gaps in vaccine coverage in these same groups. Harmonizing the response to this syndemic is critical in protecting affected populations and preventing pockets of mpox resurgence.

Future Direction and Outstanding Research Questions

While the acute phase of the global mpox outbreak has mostly subsided, the possibility of a resurgence remains ever-present. Many critical questions remain unanswered, such as the effectiveness of available treatments, vaccines, and the understanding of the immune response to the virus. Additionally, there is a need to investigate the reservoir of the virus and its evolution within the human host (Fig. 3). Urgently addressing these uncertainties necessitates prioritizing funding for research. This proactive approach is a crucial component of the global response to the mpox threat and will enable the world to be better prepared to handle future outbreaks of this disease.

Conclusions

The emergence of mpox on a global scale presents a unique and novel challenge to clinicians who provide care to PWH. Recognizing its potential as an opportunistic infection which can have devastating consequences for people with advanced HIV is crucial. A timely diagnosis and treatment of mpox and the underlying HIV infection are important for improving disease outcomes in PWH. Mpox has garnered widespread international interest and global attention since cases were reported in high-income countries, but the response to the global surge has been marred by inequities in the access to vaccines and therapeutics in low- and middle-income

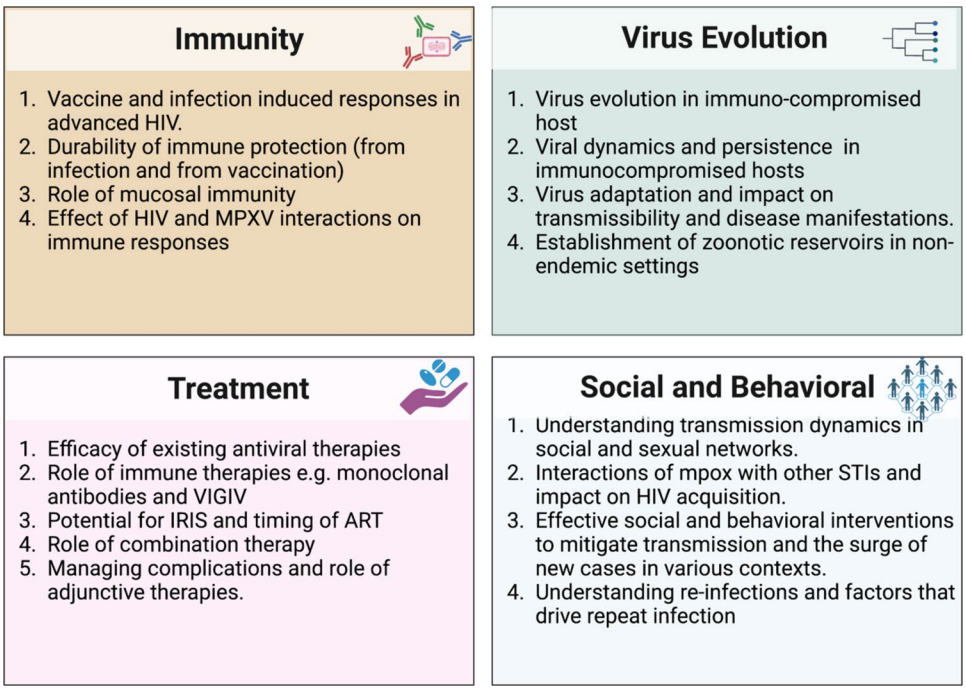

Fig. 3 Future directions and outstanding research questions

countries. Africa for example which has grappled with endemic mpox outbreaks for decades is also home to 70% of PWH. Effectively addressing the collision of these two epidemics requires a response that is centered on equity and justice and prioritizes research and the sharing of resource for treatment and prevention of mpox for all PWH regardless of where they live in the world.

Author contributions BK.Titanji developed the manuscript concept and outline prepared all figures and finalized the references and formatting of the manuscript. BK Titanji, Jason Zucker and Aniruddha Hazra wrote the main manuscript and prepared tables. Jason Zucker and Aniruddha Hazra contributed equally to this work.

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Declarations

Competing interests The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest Dr. Titanji has received honoraria from GSK, Harvard University, and IDSA for talks and conference-related travel not related to the topic of the current manuscript. She is on the advisory board for the non-profit CRITICA, on the advisory board for a Bill and Melinda Gates Foundation funded Project, and the advisory board for the non-profit ICMEC. All these activities are not related to the work presented in this manuscript. Dr. Hazra reports grants from Gilead Sciences, other from Gilead Sciences, and other from ViiV Healthcare, outside the submitted work. Dr. Zucker declares no conflicts of interest.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. CDC. Mpox 2022 Outbreak cases and data 2023 [Available from: https://www.cdc.gov/poxvirus/mpox/response/2022/index.html.
2. Mitjà O, Ogoina D, Titanji BK, Galvan C, Muyembe JJ, Marks M, et al. Monkeypox Lancet. 2023;401(10370):60–74.
3. •• Mitjà O, Alemany A, Marks M, Lezama Mora JI, Rodríguez-Aldama JC, Torres Silva MS, et al. Mpox in people with advanced HIV infection: a global case series. Lancet. 2023;401(10380):939–49. ()
4. Govind A, Lazarte SM, Kitchell E, Chow JY, Estelle CD, Fixsen E, et al. Severe mpox infections in people with uncontrolled human immunodeficiency virus. Clin Infect Dis. 2023;76(10):1843–6.
5. O'Shea J, Daskalakis D, Brooks JT. The emergence of mpox as an HIV-related opportunistic infection. Lancet. 2023;401(10384):1264.
6. Lansiaux E, Jain N, Laivacuma S, Reinis A. The virology of human monkeypox virus (hMPXV): a brief overview. Virus Res. 2022;322:198932.
7. Li H, Huang QZ, Zhang H, Liu ZX, Chen XH, Ye LL, et al. The land-scape of immune response to monkeypox virus. EBioMedicine. 2023;87:104424.
8. Lum FM, Torres-Ruesta A, Tay MZ, Lin RTP, Lye DC, Rénia L, et al. Monkeypox: disease epidemiology, host immunity and clinical interventions. Nat Rev Immunol. 2022;22(10):597–613.
9. Song H, Josleyn N, Janosko K, Skinner J, Reeves RK, Cohen M, et al. Monkeypox virus infection of rhesus macaques induces massive expansion of natural killer cells but suppresses natural killer cell functions. PLoS ONE. 2013;8(10):e77804.
10. Tarín-Vicente EJ, Alemany A, Agud-Dios M, Ubals M, Suñer C, Antón A, et al. Clinical presentation and virological assessment of confirmed human monkeypox virus cases in Spain: a prospective observational cohort study. The Lancet. 2022;400(10353):661–9.
11. Karem KL, Reynolds M, Hughes C, Braden Z, Nigam P, Crotty S, et al. Monkeypox-induced immunity and failure of childhood smallpox vaccination to provide complete protection. Clin Vaccine Immunol. 2007;14(10):1318–27.
12. Nagata N, Saijo M, Kataoka M, Ami Y, Suzaki Y, Sato Y, et al. Pathogenesis of fulminant monkeypox with bacterial sepsis after experimental infection with West African monkeypox virus in a cynomolgus monkey. Int J Clin Exp Pathol. 2014;7(7):4359–70.
13. •• Earl PL, Americo JL, Moss B. Natural killer cells expanded in vivo or ex vivo with IL-15 overcomes the inherent susceptibility of CAST mice to lethal infection with orthopoxviruses. PLoS Pathog. 2020;16(4):1008505. ()
14. Mikulak J, Oriolo F, Zaghi E, Di Vito C, Mavilio D. Natural killer cells in HIV-1 infection and therapy. AIDS. 2017;31(17):2317–30.
15. Strassburg MA. The global eradication of smallpox. Am J Infect Control. 1982;10(2):53–9.
16. McIntosh K, Cherry JD, Benenson AS, Connor JD, Alling DW, Rolfe UT, et al. Clinical and serologic study of four smallpox vaccines comparing variations of dose and route of administration. Standard percutaneous revaccination of children who receive primary percutaneous vaccination. J Infect Dis. 1977;135(1):155–66.
17. Kempe CH, Bowles C, Meiklejohn G, Berge TO, St Vincent L, Babu BV, et al. The use of vaccinia hyperimmune gamma-globulin in the prophylaxis of smallpox. Bull World Health Organ. 1961;25(1):41–8.
18. Moir S, Fauci AS. B-cell responses to HIV infection. Immunol Rev. 2017;275(1):33–48.
19. Swain SL, McKinstry KK, Strutt TM. Expanding roles for CD4+ T cells in immunity to viruses. Nat Rev Immunol. 2012;12(2):136–48.
20. •• Edghill-Smith Y, Golding H, Manischewitz J, King LR, Scott D, Bray M, et al. Smallpox vaccine-induced antibodies are necessary and sufficient for protection against monkeypox virus. Nat Med. 2005;11(7):740–7. ()
21. •• Thornhill JP, Barkati S, Walmsley S, Rockstroh J, Antinori A, Harrison LB, et al. Monkeypox virus infection in humans across 16 countries — April–June 2022. New England J Med. 2022;387(8):679–91. ()
22. Fajgenbaum DC, June CH. Cytokine Storm. N Engl J Med. 2020;383(23):2255–73.
23. Johnston SC, Johnson JC, Stonier SW, Lin KL, Kisalu NK, Hensley LE, et al. Cytokine modulation correlates with severity of monkeypox disease in humans. J Clin Virol. 2015;63:42–5.
24. Johnson RF, Dyall J, Ragland DR, Huzella L, Byrum R, Jett C, et al. Comparative analysis of monkeypox virus infection

of cynomolgus macaques by the intravenous or intrabronchial inoculation route. J Virol. 2011;85(5):2112–25.
25. O'Shea J, Filardo TD, Morris SB, Weiser J, Petersen B, Brooks JT. Interim guidance for prevention and treatment of monkeypox in persons with HIV infection - United States, August 2022. MMWR Morb Mortal Wkly Rep. 2022;71(32):1023–8.
26. Hoffmann C, Jessen H, Wyen C, Grunwald S, Noe S, Teichmann J, et al. Clinical characteristics of monkeypox virus infections among men with and without HIV: a large outbreak cohort in Germany. HIV Med. 2023;24(4):389–97.
27. Miller MJ, Cash-Goldwasser S, Marx GE, Schrodt CA, Kimball A, Padgett K, et al. Severe monkeypox in hospitalized patients - United States, August 10-October 10, 2022. MMWR Morb Mortal Wkly Rep. 2022;71(44):1412–7.
28. Rao AK, Schrodt CA, Minhaj FS, Waltenburg MA, Cash-Goldwasser S, Yu Y, et al. Interim clinical treatment considerations for severe manifestations of mpox - United States, February 2023. MMWR Morb Mortal Wkly Rep. 2023;72(9):232–43.
29. Grosenbach DW, Honeychurch K, Rose EA, Chinsangaram J, Frimm A, Maiti B, et al. Oral tecovirimat for the treatment of smallpox. N Engl J Med. 2018;379(1):44–53.
30. CDC. Demographics of patients receiving TPOXX for treatment of mpox 2023 [Available from: https://www.cdc.gov/poxvirus/mpox/response/2022/demographics-TPOXX.html. Accessed 1 Sept 2023
31. O'Laughlin K, Tobolowsky FA, Elmor R, Overton R, O'Connor SM, Damon IK, et al. Clinical use of tecovirimat (Tpoxx) for treatment of monkeypox under an investigational new drug protocol - United States, May-August 2022. MMWR Morb Mortal Wkly Rep. 2022;71(37):1190–5.
32. McLean J, Stoeckle K, Huang S, Berardi J, Gray B, Glesby MJ, et al. Tecovirimat treatment of people with HIV during the 2022 mpox outbreak : a retrospective cohort study. Ann Intern Med. 2023;176(5):642–8.
33. Riser AP, Hanley A, Cima M, Lewis L, Saadeh K, Alarcón J, et al. Epidemiologic and clinical features of mpox-associated deaths - United States, May 10, 2022-March 7, 2023. MMWR Morb Mortal Wkly Rep. 2023;72(15):404–10.
34. Andrei G, Snoeck R. Cidofovir activity against poxvirus infections. Viruses. 2010;2(12):2803–30.
35. Stafford A, Rimmer S, Gilchrist M, Sun K, Davies EP, Waddington CS, et al. Use of cidofovir in a patient with severe mpox and uncontrolled HIV infection. Lancet Infect Dis. 2023;23(6):e218–26.
36. Raccagni AR, Candela C, Bruzzesi E, Mileto D, Canetti D, Rizzo A, et al. Real-life use of cidofovir for the treatment of severe monkeypox cases. J Med Virol. 2023;95(1):e28218.
37. Adler H, Gould S, Hine P, Snell LB, Wong W, Houlihan CF, et al. Clinical features and management of human monkeypox: a retrospective observational study in the UK. Lancet Infect Dis. 2022;22(8):1153–62.
38. CDC. Mpox: treatment information for healthcare professionals 2023 [Available from: https://www.cdc.gov/poxvirus/mpox/clinicians/treatment.html. Accessed 1 Sept 2023
39. Quenelle DC, Prichard MN, Keith KA, Hruby DE, Jordan R, Painter GR, et al. Synergistic efficacy of the combination of ST-246 with CMX001 against orthopoxviruses. Antimicrob Agents Chemother. 2007;51(11):4118–24.
40 Thet AK, Kelly PJ, Kasule SN, Shah AK, Chawala A, Latif A, et al. The use of vaccinia immune globulin in the treatment of severe mpox. Virus infection in human immunodeficiency virus/AIDS. Clin Infect Dis. 2023;76(9):1671–3.
41. Hyndiuk RA, Seideman S, Leibsohn JM. Treatment of vaccinial keratitis with trifluorothymidine. Arch Ophthalmol. 1976;94(10):1785–6.
42. Pepose JS, Margolis TP, LaRussa P, Pavan-Langston D. Ocular complications of smallpox vaccination. Am J Ophthalmol. 2003;136(2):343–52.
43. Cash-Goldwasser S, Labuda SM, McCormick DW, Rao AK, McCollum AM, Petersen BW, et al. Ocular monkeypox - United States, July-September 2022. MMWR Morb Mortal Wkly Rep. 2022;71(42):1343–7.
44. Perzia B, Theotoka D, Li K, Moss E, Matesva M, Gill M, et al. Treatment of ocular-involving monkeypox virus with topical trifluridine and oral tecovirimat in the 2022 monkeypox virus outbreak. Am J Ophthalmol Case Rep. 2023;29:101779.
45. Warner NC, Shishido A, Fulco PP, Sastry S. Immune reconstitution inflammatory syndrome due to monkeypox in two patients with AIDS. AIDS. 2023;37(7):1187–8.
46. Martinez AE, Frattaroli P, Vu CA, Paniagua L, Mintz J, Bravo-Gonzalez A, Zamudio P, Barco A, Rampersad A, Lichtenberger P, Gonzales-Zamora JA. Successful outcome after treatment with cidofovir, vaccinia, and extended course of tecovirimat in a newly-diagnosed HIV Patient with severe mpox: A case report. Vaccines (Basel). 2023;11(3):650. https://doi.org/10.3390/vaccines11030650.
47 Yang HS, Li CW, Hsieh FN, Liu CH, Lee JYY, Yang CC. Molluscum contagiosum-associated immune reconstitution inflammatory syndrome in human immunodeficiency virus infection. Dermatologica Sinica. 2016;34(4):196–9.
48. Duraffour S, Lorenzo MM, Zöller G, Topalis D, Grosenbach D, Hruby DE, et al. ST-246 is a key antiviral to inhibit the viral F13L phospholipase, one of the essential proteins for Orthopoxvirus wrapping. J Antimicrob Chemother. 2015;70(5):1367–80.
49. Garrigues JM, Hemarajata P, Karan A, Shah NK, Alarcón J, Marutani AN, et al. Identification of tecovirimat resistance-associated mutations in human monkeypox virus - Los Angeles county. Antimicrob Agents Chemother. 2023;67(7):e0056823.
50. Smith TG, Gigante CM, Wynn NT, Matheny A, Davidson W, Yang Y, Condori RE, O'Connell K, Kovar L, Williams TL, Yu YC, Petersen BW, Baird N, Lowe D, Li Y, Satheshkumar PS, Hutson CL. Tecovirimat Resistance in Mpox Patients, United States, 2022-2023. Emerg Infect Dis. 2023;29(12). https://doi.org/10.3201/eid2912.231146.
51. Overton ET, Stapleton J, Frank I, Hassler S, Goepfert PA, Barker D, et al. Safety and immunogenicity of modified vaccinia Ankara-Bavarian Nordic smallpox vaccine in vaccinia-naive and experienced human immunodeficiency virus-infected individuals: an open-label, controlled clinical phase II trial. Open Forum Infect Dis. 2015;2(2):ofv040.
52. Overton ET, Lawrence SJ, Stapleton JT, Weidenthaler H, Schmidt D, Koenen B, et al. A randomized phase II trial to compare safety and immunogenicity of the MVA-BN smallpox vaccine at various doses in adults with a history of AIDS. Vaccine. 2020;38(11):2600–7.
53. Hazra A, Rusie L, Hedberg T, Schneider JA. Human monkeypox virus infection in the immediate period after receiving modified vaccinia Ankara vaccine. JAMA. 2022;328(20):2064–7.
54. Deputy NP, Deckert J, Chard AN, Sandberg N, Moulia DL, Barkley E, et al. Vaccine Effectiveness of JYNNEOS against mpox disease in the United States. N Engl J Med. 2023;388(26):2434–43.
55. Rosenberg ES, Dorabawila V, Hart-Malloy R, Anderson BJ, Miranda W, O'Donnell T, et al. Effectiveness of JYNNEOS vaccine against diagnosed mpox infection - New York, 2022. MMWR Morb Mortal Wkly Rep. 2023;72(20):559–63.
56. Dalton AF, Diallo AO, Chard AN, Moulia DL, Deputy NP, Fothergill A, et al. Estimated effectiveness of JYNNEOS vaccine in preventing mpox: a multijurisdictional case-control study - United States, August 19, 2022-March 31, 2023. MMWR Morb Mortal Wkly Rep. 2023;72(20):553–8.

57. Owens LE, Currie DW, Kramarow EA, Siddique S, Swanson M, Carter RJ, et al. JYNNEOS vaccination coverage among persons at risk for mpox - United States, May 22, 2022-January 31, 2023. MMWR Morb Mortal Wkly Rep. 2023;72(13):342–7.
58. CDC. Mpox interim consideration - vaccines overview 2023 [Available from: Treatment Information for Healthcare Professionals. https://www.cdc.gov/poxvirus/mpox/clinicians/treatment.html. Accessed on 28 Sept 2023
59 Keckler MS, Salzer JS, Patel N, Townsend MB, Nakazawa YJ, Doty JB, et al. IMVAMUNE(®) and ACAM2000(®) provide different protection against disease when administered postexposure in an intranasal monkeypox challenge prairie dog model. Vaccines. 2020;8(3):396.
60. Massoudi MS, Barker L, Schwartz B. Effectiveness of postexposure vaccination for the prevention of smallpox: results of a Delphi analysis. J Infect Dis. 2003;188(7):973–6.
61. CDC. Update: multistate outbreak of monkeypox--Illinois, Indiana, Kansas, Missouri, Ohio, and Wisconsin, 2003. MMWR Morb Mortal Wkly Rep. 2003;52(27):642–6.
62. Luong Nguyen LB, Ghosn J, Durier C, Tachot C, Tartour E, Touati A, et al. A prospective national cohort evaluating ring MVA vaccination as post-exposure prophylaxis for monkeypox. Nat Med. 2022;28(10):1983–4.
63. Faherty EAG, Holly T, Ogale YP, Crisler G, Becht A, Kern D, et al. Notes from the field: emergence of an mpox cluster primarily affecting persons previously vaccinated against mpox - Chicago, Illinois, March 18-June 12, 2023. MMWR Morb Mortal Wkly Rep. 2023;72(25):696–8.
64. Jamard S, Handala L, Faussat C, Vincent N, Stefic K, Gaudy-Graffin C, et al. Resurgence of symptomatic mpox among vaccinated patients: first clues from a new-onset local cluster. Infect Dis Now. 2023;53(4):104714.
65. Hazra A, Zucker, J, Bell,, E Flores,J, Gordon L, . Mpox in people with past infection or complete vaccination course: a global case series. 2023. This work describes a global series ofmpox infection in previously vaccinated individuals and individuals with previous mpox infection.
66. Chastain DB, Motoa G, Ortiz-Martínez Y, Gharamti A, Henao-Martínez AF. Characteristics and clinical manifestations of monkeypox among people with and without HIV in the United States: a retrospective cohort. AIDS. 2023;37(4):611–6.
67. Patel A, Bilinska J, Tam JCH, Da Silva FD, Mason CY, Daunt A, et al. Clinical features and novel presentations of human monkeypox in a central London centre during the 2022 outbreak: descriptive case series. BMJ. 2022;378:e072410.
68. Vivancos-Gallego MJ, Sánchez-Conde M, Rodríguez-Domínguez M, Fernandez-Gonzalez P, Martínez-García L, Garcia-Mouronte E, et al. Human monkeypox in people with HIV: transmission, clinical features, and outcome. Open Forum Infect Dis. 2022;9(11):ofac557.
69. Curran KG, Eberly K, Russell OO, Snyder RE, Phillips EK, Tang EC, et al. HIV and sexually transmitted infections among persons with monkeypox - eight U.S. Jurisdictions, May 17-July 22, 2022. MMWR Morb Mortal Wkly Rep. 2022;71(36):1141–7.