Optimal Management of Severe Mpox in Patients with Uncontrolled HIV

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Abstract

In May 2022, a cluster of non-travel-related cases of human mpox were reported in the UK. The outbreak has since spread world-wide infecting over 85,000 patients and causing over 100 deaths. Recent data clearly suggest that patients infected with Human Immunodeficiency Virus (HIV) with CD4 counts less than 200 cells per mm ^{3} suffer significantly worse outcomes than immunocompetent patients. The available countermeasures lack robust clinical data and are deployed based on *in vitro* and animal studies as well as extrapolations from use against other poxviruses. In many cases, despite administration of these available treatments, initiation of antiretroviral therapy, and management of Immune Reconstitution Inflammatory Syndrome (IRIS), patients die. This review summarizes available data, identifies knowledge gaps and proposes recommendations on the management of severe mpox in PLWH.

Introduction

Mpox virus (MPXV) is a large double-stranded DNA virus that causes a febrile illness with rash in humans. Until recently, MPXV caused sporadic zoonotic outbreaks primarily in Africa. However, in May 2022, a cluster of non-travel-related cases of human mpox were reported in the United Kingdom. Since those initial infections, the outbreak has spread world-wide infecting over 85,000 patients and causing over 100 deaths. Early outbreak data suggested no significant difference in outcome among people living with Human Immunodeficiency Virus (PLWH, HIV) and those without HIV. However, subsequent data have shown the majority of severe and fatal cases of human mpox infection occur in those with advanced HIV. It is now clear that advanced HIV is a significant risk factor for severe mpox and death, and that Immune Reconstitution Inflammatory Syndrome (IRIS) may play a role in these outcomes.

While the number of new mpox cases has dropped significantly since the outbreak began, recent case clusters suggest ongoing community transmission. This continued circulation poses an ongoing threat to susceptible hosts. Risk factors for progression of disease other than advanced HIV, natural progression of disease, and optimal management remain undefined. While the STOMP Trial and VIRISMAP are actively enrolling patients to address these questions, the decline in cases worldwide (a positive development overall) has stymied hopes of rapid answers. Given the rare occurrence of this infection in the outbreak's current phase, and the absence of clinical trial data to address treatment for the most severe cases, optimal management will require vigilant multidisciplinary collaboration between the specialties involved in the care of these patients. This review summarizes the pathogenesis of mpox, available clinical data, identifies knowledge gaps and proposes recommendations on the management of these most severe cases among patients with advanced HIV with an emphasis on early combination antivirals and longitudinal wound care.

Pathogenesis of mpox

The available data describing the pathogenesis of MPXV infection is limited. Present understanding of MPXV pathogenesis extrapolates from what is known about smallpox virus infection and animal data (Figure

1). MPXV enters the body via infection of mucosal epithelial cells or skin cells. Viral proteins attach to host cells, facilitating membrane fusion and entry. The human proteins to which poxviruses bind include heparans, chondroitin, and laminin which are widely expressed among human cell lines and likely accounts for the virus' ability to infect a wide range of cells. The virus replicates in the cytoplasm of host cells at the site of inoculation and spreads to local lymph nodes. Immunohistochemical evaluations suggest that fibroblasts and dendritic cells are the primary targets of MPXV infection within lymphoid tissue. Infected macrophages then enter the bloodstream producing a cell-associated viremia. From the bloodstream, MPXV disseminates to the skin and other organs. Biopsied lesions from human MPXV infections reveal eosinophilic cytoplasmic inclusions called Guarnieri bodies which are diagnostic of poxvirus infections. In early-stage lesions, keratinocytes exhibit balloon-cell degradation with a mixed inflammatory infiltrate composed of neutrophils and lymphocytes. Advanced lesions reveal full thickness epidermal necrosis with surrounding inflammatory infiltrate composed of lymphocytes, neutrophils and eosinophils.

The interplay between MPXV and the immune system, and specifically T lymphocytes is complex. Early animal data suggest that while MPXV infects and disseminates in macrophages, it did not appear to infect lymphocytes. However, levels of circulating CD4+ T cells, CD8+ T cells, NK cells and B cells all significantly decline in the days following MPXV infection and do not return to normal levels until 10 days after infection. Recent human data also suggest an initial decrease in CD4 lymphocytes in early MPXV infection followed by a clonal expansion. MPXV appears to evade antiviral CD4+ and CD8+T cell responses by directly suppressing T cell activation. Notably, Vaccinia virus appears to preferentially bind antigen presenting cells (APCs) and activated T cells, but not resting T cells. It is unclear if MPXV possesses a similar tropism.

Importantly, CD4+ T cells appear to play a critical role in protection against MPXV. Despite vaccination, SIV-infected macaques with CD4+ T cell counts <300 cells mm-3 were unable to mount an immune response and died when challenged with MPXV. This vulnerability has clearly borne out clinically in the recent 2022 outbreak, with PLWH comprising greater than 80% of the severe cases. Therefore, reconstitution of the immune system appears critical to recovery and clearance of the infection (Figure 2).

Severe mpox in PLWH

Data from mpox cases prior to the 2022 outbreak suggested that patients with HIV complicated by AIDS are at risk for more severe disease. As the 2022 outbreak progressed, the CDC reported that the majority of severe mpox cases occurred in PLWH, particularly in those with low CD4+T Cell counts. This growing body of data suggests PLWH with CD4+ T Cell counts less than 200 cells/mm^3 are at significantly increased risk for fatal outcome (Table 1). Of the most severe cases reported, patients often present with vast necrotizing skin lesions and to develop multiorgan involvement to include the pulmonary, gastrointestinal, musculoskeletal, and central nervous systems. Many develop bacterial superinfection, sepsis and acute respiratory distress syndrome (ARDS). Reports suggest that initiation of ART is often delayed for weeks after presentation. Among the largest cohorts, mortality rates in patients with advanced HIV range from 15 to 40%. Death occurs many weeks to months after the initial presentation. These reports also highlight the phenomenon of IRIS, described as an acute worsening or spreading of a patient's lesions and clinical deterioration approximately 2 weeks after initiation of ART. At this time, it is not clear if these cases represent true IRIS, or simply the natural progression of mpox in severely immunosuppressed patients. Notably, IRIS has been described previously with other poxvirus infections.

Countermeasures

The systemic antiviral treatment options with the most available data against MPXV include tecovirimat (TPOXX®), cidofovir, brincidofovir, and Vaccinia Immune Globulin (VIGIV). Of these options, tecovirimat has recently seen the broadest utilization, given its oral administration and strong safety profile. Tecovirimat targets the MPXV p37 protein, disrupting envelope development and mature virion formation. The CDC has made tecovirmat available through an Expanded Access New Investigational Drug protocol (EA-IND). There is currently no high quality clinical data on tecovirimat's effectiveness against mpox; however, a human clinical trial for effectiveness is ongoing, and the drug has been demonstrated to be safe and well tolerated

in humans. The manufacturer recommends a 14-day treatment course based on the development of humoral immunity, however severe mpox cases in immunosuppressed patients often require much longer courses.

Cidofovir and brincidofovir inhibit viral DNA polymerase. The FDA originally approved cidofovir for the treatment of CMV retinitis, but*in vitro* data suggests it possesses antiviral activity against a wide number of viruses to include O*rthopoxviruses* . Similarly, brincidofovir is an oral prodrug of cidofovir and approved for the treatment of smallpox. It is currently only available through an FDA-authorized emergency use-IND. The clinical effectiveness data for these drugs against human MPXV infection is limited to case reports and cohort studies. Importantly, usage of these drugs may be limited by their toxicities: cidofovir is a known potent nephrotoxin and brincidofovir has been associated with significant hepatotoxicity.

VIGIV is prepared from serum of patients vaccinated against smallpox and is available from the CDC through an expanded access protocol for mpox. Like the other countermeasures, its effectiveness against poxviruses is limited to case reports.

Animal models suggest that delayed administration and host immunosuppression diminish the effectiveness of cidofovir and tecovirimat. Animal data has also shown that tecovirimat has a low barrier to resistance with only a single amino acid substitution of p37 required for reduced antiviral activity to develop. While rare, the current outbreak has seen the rise of resistant MPXV isolates obtained from immunosuppressed hosts on long courses of tecovirimat. Notably, tecovirimat and brincidofovir have been found to have synergistic activity *in vitro* and *in vivo* against poxviruses. While we concede that it is difficult to draw conclusions based these limited data, we support the immediate initiation of combination antiviral therapy with tecovirimat, cidofovir or brincidofovir and VIGIV in addition to rapid initiation of ART to maximally inhibit viral replication in the absence of effective cell-mediate immunity, optimize the potential for antiviral synergy, and shield against the development of resistance.

Wound Care

The most severe cases of mpox evolve over weeks to months. Patients develop multiple necrotic lesions that progress and become secondarily infected until the immune system reconstitutes sufficiently to clear the virus. Therefore, in addition to systemic antiviral therapy and rapid ART, high quality longitudinal wound care provided by a specialist becomes a critical component of management of the severe mpox patient.

In patients with skin and tissue loss resulting in fat, muscle, or bone exposure, advanced wound care principles following the DIME method (Devitalized tissue/Debridement, Infection/Inflammation, Moisture management, Edge). Addressing devitalized tissue or debridement can be done with autolytic, enzymatic (collagenase), ultrasonic or surgical/sharp debridement. The method of debridement that is appropriate is dependent on the patient's pain and ability to tolerate procedures.

Bacterial superinfection is common in these most severe mpox cases. All suspected infections should be cultured, either with biopsy or using the Levine technique, prior to initiation of antibiotic therapy. The ulcers should be cleansed with hypochlorous acid solution, wound cleanser, or mild soap such as baby shampoo. Other chemical cleansers such as sodium hypochlorite solutions, chlorhexadine, alcohol containing solutions, povodine iodine, and hydrogen peroxide should be avoided as they are cytotoxic with a lower therapeutic index than hypochlorous acid.

Moisture management in the ulcers and periwound skin is also essential for healing. The base of the wound requires enough moisture to promote healing without causing maceration of the periwound. A moist wound environment reduces pain, promotes autolytic debridement, collagen formation and epithelialization. Scar formation is also reduced. Moisture can be added to the base of the wound, if needed, by applying hydrogels, hydropolymer, or hydrocolloid dressings. Excess moisture, or heavy exudate, can be managed with alginate, hydrofiber, foam, or superabsorbent dressings.

Despite severe wounds with full thickness necrosis, severe mpox cases can recover complete tissue regeneration with quality wound care (Figure 3).

Optimal Management

The optimal management of these severe cases in PLWH remains unknown. However, based on the available published data summarized above, recommendations from the CDC and our institutional experience, we make the following recommendations on the management of severe mpox in PLWH.

1. Upon identification of severe mpox in PLWH, we recommend consultation with CDC and local health departments, and immediate initiation of tecovirimat in combination with VIGIV and either cidofovir or brincidofivor if these agents are available and not contraindicated. While CDC guidance makes the addition of multiple agents a consideration, we feel strongly that a combination of agents should be employed to maximally inhibit viral replication while the immune system regains the ability to clear the virus. None of the available agents is viricidal, and therefore management should aim for maximal inhibition, effectively 'bridging' the host into a reconstituted state. This strategy also employs the theoretical benefits of protecting against resistance that may result from active viral replication in the presence of a single inhibitor, as well as antiviral synergy. These agents should be continued at least until lesions stop progressing and begin healing, which may take several weeks to months.
2. Eligible patients should be encouraged to enroll the STOMP Trial and VIRISMAP, as combination antivirals against mpox does not exclude patients from these studies.
3. ART should be initiated as soon as feasible, and in accordance with other HIV management guidance. While data are scarce, there appears to be no benefit to delaying ART to attenuate possible IRIS.
4. Patients should be evaluated for alternative etiologies of their disease, as well as concomitant sexually transmitted infections and opportunistic infections as recommended by other HIV management guidance.
5. Providers should perform a thorough history and physical examination to identify all possible organ systems that may be affected but may not be immediately apparent; these include musculoskeletal, ocular, central nervous system, gastrointestinal, pulmonary, and cardiovascular systems.
6. In patients with suspected bacterial infection, providers should obtain appropriate cultures and then provide empiric antibiotics. The duration of empiric antibacterial therapy should be no longer than what would be given for the specific diagnosis that is suspected (ie SSTI or bacteremia) if the suspected diagnosis cannot be ruled out. Antibiotics should not be given indefinitely. While bacterial superinfection of mpox patients is low in the general population, patients with uncontrolled HIV and severe disease have higher incidence of bacterial superinfection. Bacterial infection resulting in sepsis can also be a significant cause of death in these patients, particularly those with anogenital and gastrointestinal lesions.
7. Patients should be closely reassessed longitudinally over the full course of their recovery. As these severe mpox patients progress, they often develop fevers, leukocytosis, progression of lesions and new symptoms over the course of their management. Based on the heterogeneity of published cases, it is not clear if this progression represents the natural course of the disease in severely immunosuppressed hosts, or if there is a true development of IRIS. In the limited data available, there does not appear to be a significant difference in outcome among those who received IRIS treatment and those who did not; nor does there appear to be any benefit to delaying ART initiation.
8. Care should be provided with a multidisciplinary approach to comprehensively and longitudinally address the multiple complex issues that stem from severe MPXV infection as well as any potential barriers to treatment adherence upon discharge. Specialties likely to be involved include: Infectious Disease, Internal Medicine, Pharmacy, Nursing, Wound Care, Pain and Palliative Care, Neurology, General Surgery, Orthopedic Surgery, Urology, Plastic Surgery, Ophthalmology, Dermatology, OBGYN, Psychiatry and Social Work. Quality wound care provided by a specialist is a critical component to this longitudinal care.

Conclusion

The rapid global expansion of mpox cases during the 2022 outbreak demonstrated how a zoonotic infection effectively transformed into a sexually transmitted disease in the modern era. It is now clear that PLWH who

are poorly controlled are at significantly increased risk of severe disease and death. Sporadic case clusters suggest ongoing community transmission, though it remains to be seen if mpox will ultimately become truly endemic. The natural progression of disease in these severe cases, to include possible IRIS and risk factors for progression other than low CD4 T Cell count, must be further clarified, and optimal management remains undefined. While the STOMP trial and VIRISMAP are actively attempting to answer these questions, low case counts have slowed enrollment.

Therefore, until further data are available, we advise that the most severe cases should be treated in consultation with the CDC, with combination antiviral therapy, rapid initiation of ART and followed by a multidisciplinary team to include a wound care specialist over the prolonged course of the recovery. Those at risk should be vaccinated with Jynneos. We also strongly encourage providers to enroll patients into the STOMP trial and VIRISMAP to further define the natural course of this disease and clarify optimal management strategies.

References

Table 1. Select publications providing data on severe MPOX outcomes and management in PLWH.

Author	**Cases with CD4 < 200 (% of total PLWH in study)**	**Severe Manifestations**	**Suspected IRIS (%)**	**Time to initiation of ART (median days)**	**Mortality among PLWH CD4 < 200 (%)**	**Median Days to death after diagnosis**	**Notes**
Mitja et al	179 (85%)	Necrotizing Skin Lesions, lung involvement, CNS involvement, GI involvement, secondary infections, sepsis	21 (25%)	21	27 (15%)	47	57% mortality rate of those with suspected IRIS.
Triana-Gonzalez et al	10 (15.6)	Intestinal obstruction/peritonitis, lung involvement/ARDS,	Not provided	Not provided	4 (40%)	50	Risk factors for mortality: CD4 < 100, absence of ART, >50 lesions at presentation.
Miller et al	40 (93%)	Necrotizing Skin lesions, lung involvement, CNS involvement,	Not provided	Not provided	Not provided	Not provided	Advocates combining anti-MPXV therapies with progression.

Author	Cases with CD4 < 200 (% of total PLWH in study)	Severe Manifestations	Suspected IRIS (%)	Time to initiation of ART (median days)	Mortality among PLWH CD4 < 200 (%)	Median Days to death after diagnosis	Notes
Riser et al	24 (89%)	Necrotizing skin lesions	24 (89%)	15	24 (100%) *Only included deceased	68	23 of the 27 HIV+ patients had CD4 counts < 50
Hermanussen et al	4	Necrotizing skin lesions, deep soft tissue abscess/myositis, GI involvement, CNS involvement	0	Not provided	NA	NA	All patients treated with tecovirimat. Those with CD4 < 200 hospitalized > 2 weeks.
Warner et al	2 (100%)	Necrotizing skin lesions, CNS involvement, septic arthritis, secondary infections, sepsis	2 (100%)	33	1 (50%)	68	Both patients with suspected IRIS.
Pettit et al	2	Necrotizing skin lesions, GI involvement, pulmonary involvement, bacterial superinfection	2 (100%)	Not provided	2 (100%)	35	Both patients with suspected IRIS, treated with steroids and pausing of ART.

Author	Cases with CD4 < 200 (% of total PLWH in study)	Severe Manifestations	Suspected IRIS (%)	Time to initiation of ART (median days)	Mortality among PLWH CD4 < 200 (%)	Median Days to death after diagnosis	Notes
Filippov et al	1	Necrotizing skin lesions, lung involvement, ocular involvement	Never on ART	Never on ART	1	74	Patient declined ART, was treated with cidofovir, tecovirimat and VIGIV.
Stafford et al	1	Necrotizing skin and oral lesions	0	immediate	NA	NA	Patient treated with ART, tecovirimat and cidofovir.
Viguier et al	1	Necrotizing skin lesions	0	47	NA	NA	
Thet et al	1	Necrotizing skin lesions, GI involvement, bacterial superinfection	1	immediate	NA	NA	Patient treated with ART, tecovirimat, and VIGIV. Recovery did not begin until after VIGIV administration
Caria et al	1	Necrotizing skin lesions, GI involvement, lung involvement, CNS involvement	1	46	1 (100%)	107	Patient treated with ART, tecovirimat, and cidofovir.

Author	Cases with CD4 < 200 (% of total PLWH in study)	Severe Manifes-tations	Suspected IRIS (%)	Time to initiation of ART (median days)	Mortality among PLWH CD4 < 200 (%)	Median Days to death after diagnosis	Notes
Martinez et al	0 *Case had CD4 count of 218 cells/mm^3	Necrotizing skin lesions, GI involvement, rectal abscess, bacterial superinfection	1	Not provided	NA	NA	Patient treated with ART, tecovirimat, cidofovir and VIGIV.

Legend: ART – antiretroviral therapy; CD4 – cluster of differentiation 4 T cells; CNS – central nervous system; GI – gastrointestinal system; IRIS – immune reconstitution inflammatory syndrome; PLWH – people living with HIV; VIGIV – Intravenous Vaccinia Immunoglobulin.

Figure 1. Pathogenesis of mpox.

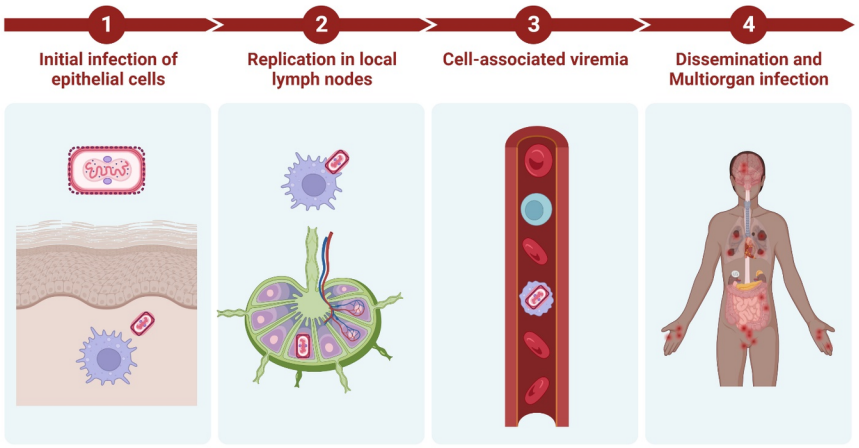

Figure 2. Depiction of the progression of severe mpox in uncontrolled HIV patients and proposed management strategy.

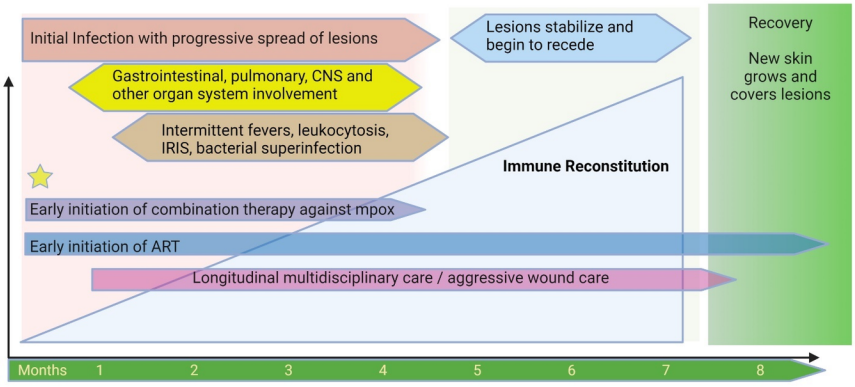

Figure 3. Progression of lesions in a patient with severe mpox. The days refer to days after diagnosis with mpox.