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CROI 2023: Epidemiology, Diagnosis, and Management of MPox

Jason Zucker, MD
Columbia University Vagelos College of Physicians and Surgeons, New York, New York

Abstract: *The 2023 Conference on Retroviruses and Opportunistic Infections (CROI) emphasized emerging infectious diseases such as COVID-19 and mpox. Despite emerging from countries in which it was endemic only 9 months before the conference, mpox was well covered, with more than 60 presentations addressing various topics. There was a focus on the rapid development and implementation of tests to reduce the time to diagnosis, as well as multiplex panels to increase the accuracy of differential diagnosis. Presenters also highlighted the ability to diagnose mpox from multiple compartments, such as with rectal and pharyngeal swabs, and provided crucial information on the duration of positivity that may impact isolation requirements. Clinical experiences were described, including risk factors for severe disease and syndemic management. High rates of concomitant sexually transmitted infection (STI) were reported. Finally, prevention was a key topic, with presenters pointing to the contributions of individual behavioral changes and vaccine efficacy to reducing new cases.*

Keywords: mpox, testing, vaccination, prevention, modified vaccinia Ankara, monkeypox virus, MVA, tecovirimat

Author Correspondence: Send correspondence to Jason Zucker, MD, 622 W 168th St, PH876-A, New York, NY 10032, or email Jz2700@cumc.columbia.edu.

In 2022, mpox, formerly a disease endemic to West and Central Africa, quickly spread to more than 100 countries worldwide, resulting in more than 85,000 cases. At the 2023 Conference on Retroviruses and Opportunistic Infections (CROI), Brooks from the Centers for Disease Control and Prevention opened a special session on the mpox outbreak by providing an overview of the current understanding of the disease (Abstract 39). He emphasized the strong evidence suggesting sexual transmission among gay, bisexual, and other men who have sex with men (gbMSM) and cited recent literature indicating transmission up to 4 days before symptom onset. Brooks also noted the rapid and significant decline in mpox cases, due partly to behavioral changes, and early data on vaccine effectiveness.

Brooks closed his presentation by emphasizing that there is still much to learn about mpox; mpox remains a public health threat worldwide and it is crucial to continue monitoring the situation closely for a possible resurgence. Finally, better understanding and management of this emerging infectious disease will require the completion of randomized clinical trials of possible treatments, increased vaccination among individuals with a higher likelihood of disease acquisition, and establishment of the durability of immunity from vaccination and natural infection.

Mpox Epidemiology

Epidemiology plays a vital role in managing emerging infectious diseases by providing insights into strategies for diagnosing, managing, controlling, and preventing disease. Stored samples can provide clues to when outbreaks start and how disease spreads. For example, the Netherlands reported its first mpox case on May 10, 2022; however, the impact of undiagnosed prior infection was unknown. Hoornenborg and colleagues presented data from analysis of stored anorectal samples positive for gonorrhea or chlamydia from 2 large sexual health centers in the Netherlands (Abstract 897). They retrospectively tested samples from February 14 to May 18, 2022; among 401 samples, only 2 samples from the first week of May were positive for monkeypox virus (MPXV) This timing coincides with the appearance of the first cases across Europe, suggesting that the outbreak expanded quickly and highlighting how quickly disease can spread within sexual networks.

The 2022 mpox outbreak primarily affected adult gbMSM, with a small number of cases occurring in women and children. During the session on epidemiology and prevention of mpox and SARS-CoV-2 infection, Sachdev and colleagues presented work on determining the rate of transmission of mpox to pediatric household contacts (children aged <16 years) in California using contact tracing data (Abstract 209). They identified 79 index cases with 129 total contacts, of whom 18 developed symptoms and 6 were confirmed or presumed positive. Among the 6 pediatric patients, the overall secondary attack rate was 4.7%, but all of the pediatric patients were under age 10 years, and the secondary attack rate of children under age 10 years was 7.1%. Only 14% of contacts received postexposure prophylaxis. Among those who

received it, there were no infections. Factors associated with household transmission included delayed diagnosis of the index cases and lack of prevention precautions at home. Crucially, no tertiary transmission was identified among children attending day care while symptomatic. These data, which are consistent with the results of previous African studies, provide crucial details about the risk of household exposure and the potential benefit of postexposure prophylaxis.[1] This information can also constitute the foundation of an evidence base for day care centers and schools developing exposure protocols.

The spread of mpox was characterized by rapid expansion and then a rapid decline in cases. At CROI, the underlying factors contributing to this decline were explored in several sessions. Panovska-Griffiths and colleagues identified the time elapsed between symptom onset and diagnosis as a crucial variable in modeling the rapid decline of mpox (Abstract 925). Using data from the United Kingdom to model the mpox outbreak, they quantified the impact of delayed diagnosis on disease transmission dynamics. Their analysis revealed a significant decrease in the average delay from symptom onset to presentation for health care, from 22 days in May 2022 to 7 days by August 2022. Further, they demonstrated that the rapid decline in cases might be partly attributable to improved diagnostic practices, highlighting the importance of timely and accurate diagnosis in public health emergencies.

Ghosn presented data on MPXV sequence diversity in Paris (Abstract 236). They sequenced samples from 148 individuals with mpox and compared the epidemic isolates with reference strains (preepidemic strains). They found 32 mutational patterns, including epidemic strain–specific mutational patterns. One profile closely resembled the clade III preepidemic viruses in a patient returning from Asia, suggesting the ongoing introduction of nonepidemic mpox and highlighting the need to continue considering mpox in the differential diagnosis outside of the current outbreak.

Mpox Diagnosis

Diagnostic Developments

Timely and accurate diagnosis is essential in disease outbreaks to enable public health officials to track the spread of the disease and implement appropriate control measures. However, one of the earliest challenges in the mpox outbreak was the limited availability of diagnostic testing. To address these challenges, sites developed local diagnostics with unique and improved performance characteristics.

Kagan and colleagues reported on the development of a single test that can simultaneously detect orthopoxvirus (OPXV) and MPXV in lesion specimens (Abstract 955). The test had excellent performance, with 100% detection and 100% specificity among unrelated pathogens, and could detect MPXV at levels as low as 100 copies/mL. However, in 9 cases samples were OPXV positive and MPXV negative, and subsequent sequencing revealed a *crmB* gene deletion that removed the MPXV probe

target region.[2] By including 2 targets in a single well, their test improved throughput by avoiding tiered testing, thus increasing capacity, and simultaneously preventing missed diagnoses caused by genomic deletions.

Obermeier and colleagues described the rapid development of a multiplex polymerase chain reaction (PCR) assay targeting both OPXV and MPXV (Abstract 954). This locally created assay was developed by the end of May 2022, early in the outbreak. It could detect MPXV in skin lesions and from genital, rectal, and oropharyngeal swabs. The assay demonstrated excellent performance, and despite the receipt of more than 2000 samples, 95% were tested within 24 hours. The development of rapid diagnostic tools is critical for clinicians asking patients to isolate while awaiting results and facilitates the implementation of public health interventions to prevent the propagation of outbreaks.

Diagnostic Dilemmas

The US Food and Drug Administration has approved only tests using samples from lesional swabs. However, several case reports have indicated that patients may have positive mucosal swabs (rectum and pharynx) without skin lesions and sometimes without any symptoms.[3-5] Matic and colleagues showed that viral loads were highest in skin lesions, particularly genital lesions, and rectal swabs, using cycle threshold (Ct) values (Abstract 953). Urine, throat, whole blood, and nasopharyngeal swabs frequently had detectable virus, but with higher Ct values (lower estimated viral loads) than with skin lesion swabs, although Ct values were still consistent with possible infectivity.[6] Hoornenberg presented data from the Amsterdam Centre for Sexual Health showing lower Ct values from lesion and rectal swabs than from throat swabs (Abstract 911). However, in the experience of Matic and colleagues, submitting multiple specimen types did not improve diagnostic yield when skin lesions were present (Abstract 953). These findings suggest that nonlesion swabs may provide important diagnostic information for patients without skin lesions. Furthermore, the elevated viral loads on genital lesion and rectal swabs support the hypothesis that sexual transmission was a significant driver of the recent outbreak.

Diagnostic Testing and Duration of Infection

Testing for mpox is critical for monitoring viral shedding, which can provide valuable information about the duration of infection. In a cohort of 21 patients tested longitudinally, Tan and colleagues investigated the weekly shedding of MPXV (Abstract 292). They found that 95% of rectal swabs and 76% of semen samples were PCR positive at the final sampling time point (median, 34.5 days). In an observational study, Lescure and colleagues found that some patients had PCR-positive samples after day 14, including in 30% of rectal samples, even when symptoms and active lesions had already resolved (Abstract 737). Although further analysis is needed to correlate detectable DNA with infectivity, these findings suggest that infectivity could

persist even after skin lesions have completely healed. Larger samples, viral cultures, and contact tracing studies are necessary to better define the duration of infectivity, which can guie public health recommendations and help clinicians counsel patients on when it is safe to resume sexual activity.

Mpox Clinical Presentations and Management

Missed Opportunities

Diagnostic testing is beneficial only if patients and practitioners recognize the need for testing during a patient encounter. Ogale and colleagues analyzed a cross-sectional online survey called the American Men's Internet Survey (AMIS), focusing on gbMSM (Abstract 950). Of the 842 individuals surveyed in the mpox supplement released in August 2022, 47 of 52 gbMSM with recent rash and HIV and sexually transmitted infection (STI) testing did not undergo mpox testing. This worrisome finding was common in older participants (>40 years of age), individuals living in the South, non-Hispanic White individuals, those without HIV, those with more than 2 sex partners, and those engaging in condomless anal sex. Atkins and colleagues identified barriers to testing in the same AMIS survey, including low self-testing efficacy, lack of knowledge of testing sites, inconvenient hours, and high testing costs (Abstract 951). Most individuals seeking care with symptoms consistent with mpox did not undergo testing, indicating the urgent need for increased awareness and access to mpox testing. These studies highlight the need to integrate mpox testing with HIV and STI testing. Disparities in mpox testing mirror those of other epidemics, emphasizing the need for targeted efforts and mpox-neutral approaches.

An mpox-neutral approach can be facilitated by use of a multiplex panel to routinely test for infection when screening individuals for ulcerative diseases. Titanji presented a promising solution involving a novel multiplex PCR assay that can detect MPXV, herpes simplex virus, and varicella zoster virus in clinical specimens (Abstract 952). Use of this panel can help identify coinfections during mpox outbreaks and detect cases early, when the infection is not initially considered. The assay is easy to use, rapid, and reliable and may improve the overall diagnosis and management of vesicular and ulcerative lesions.

Mpox Clinical Presentations

Orkin presented a highly discussed global case series that sheds light on the impact of mpox on individuals with HIV and CD4+ counts less than 350 cells/µL (Abstract 173). The study gathered data from 19 countries using a standardized case report form and included 382 participants. The results revealed a 30% mortality rate among individuals with a CD4+ count less than 100 cells/µL and a viral load greater than 10,000 copies/mL (4 $\log_{10}$ copies/mL). Additionally, participants with a CD4+ count less than 200 cells/µL experienced more complications, including severe necrotizing lesions, disseminated

infection (including pulmonary nodules), and secondary bacterial infections. The findings suggest that mpox in people with HIV who have low CD4+ counts and elevated viral loads can be a severe, disfiguring, and life-threatening opportunistic infection that should be considered an AIDS-defining illness. These results underscore the importance of making vaccination available to those at greatest risk of severe complications and developing studies of specific antiviral agents in this population. This work was published in *the Lancet* concurrently with the presentation.[7]

The results of several studies also supported and expanded on the finding that individuals with untreated or uncontrolled HIV are at a higher risk of complications and severe or fatal mpox. Garcia and colleagues described and provided graphic images for a case series from New York City of 11 patients with HIV with low CD4+ counts (median, 30 cells/µL; range, 3-153 cells/µL) who presented with severe manifestations including burnlike lesions, globe collapse, airway edema, and gastrointestinal ulcers and bleeding (Abstract 735). Although time to antiviral therapy was not reported, most of these patients received several antiviral therapies and despite those efforts, had a median hospitalization length of 57 days, with a 45% mortality rate.

Cholli and colleagues found that CD4+ count less than 200 cells/µL was the most common risk factor for severe or fatal mpox in the US (Abstract 912). Silva and colleagues demonstrated a similar finding in Brazil (Abstract 905). All patients with severe complications had HIV, and all patients with a CD4+ count less than 200 cells/µL required hospitalization. Similarly, Garneau and colleagues demonstrated that in Baltimore, individuals with a CD4+ count less than 350 cells/µL had higher odds of hospitalization (odds ratio, 29; 95% CI, 3.95-213) and reported that patients hospitalized with mpox often required surgical evaluation and had an increased mortality rate (Abstract 907). These findings were consistent with the work of Philpott and colleagues, which showed individuals with a CD4+ count less than 350 cells/µL (relative risk, 3.2; 95% CI, 2.1-5.1) and those not actively engaged in care to have higher rates of hospitalization (relative risk, 2.4; 95% CI, 1.3-4.2) (Abstract 903).

Vaidya and colleagues found that in California, individuals with unsuppressed viral loads and low CD4+ counts were more likely to be hospitalized for mpox if they lived in areas with limited access to a healthy lifestyle based on the Healthy Places Index (Abstract 902). Similarly, Corma-Gomez and colleagues found that patients with uncontrolled HIV, as indicated by a viral load greater than 1000 copies/mL, had higher rates of severe mpox using a composite outcome of severe disease (Abstract 904). Aldred and colleagues also showed that individuals with a viral load greater than 200 copies/µL had a higher rate of hospitalization and more frequent complications in Atlanta (Abstract 906). Taken together, these findings highlight the importance of s public health strategies designed to improve the HIV care continuum and help more patients with HIV access services, treatment, and vaccination.

The studies reported above used various outcomes and composite outcomes to describe the “severity” of mpox infection without a

standardized clinical severity score. Standardized clinical severity scores facilitate quantitative comparison of disease severity between groups of patients to illuminate factors associated with severe illness and facilitate evaluation of interventions and treatment efficacy. Zucker and colleagues presented their development and pilot testing of an mpox severity scoring system (MPOX-SSS) (Abstract 738). An iteratively developed 7-element score could be calculated retrospectively for 172 of 200 patients. They found higher scores in patients treated with tecovirimat, those with a CD4+ count less than 200 cells/mL, and those who presented more than 3 days after symptom onset. The score showed change over time in a subset of patients. The tool has potential usefulness for evaluating treatment options but requires further validation in more extensive observational and randomized clinical trials.

Mpox and Coinfections

At the onset of the outbreak, mpox was observed to have high rates of coinfection with STIs. Management of these overlapping outbreaks, known as syndemic management, can improve overall health outcomes.

Polk and colleagues described the implementation of a protocol for coinfection testing in a large integrated health care system that included HIV testing at the time of mpox testing in 17 emergency departments and 44 urgent care centers (Abstract 944). This protocol increased HIV testing (from 2.3 to 3.8 tests per 1000 visits; $P = .01$) and new diagnoses (from 1.4 to 3.9 new HIV diagnoses per month; $P = .02$), and 27 of 41 patients newly diagnosed with HIV during this period had concurrent mpox testing. These results highlight the potential benefits of decision support interventions that can increase testing for HIV in an outbreak setting.

In Texas, Monterosso and colleagues used mpox reporting to identify individuals with undiagnosed HIV or lost-to-follow-up from HIV care, allowing them to confirm their status and receive expedited care services (Abstract 895). Their work demonstrates the potential synergy between HIV services and mpox testing and treatment and the importance of innovative data-to-care initiatives in ending the HIV epidemic.

In London, Girometti and colleagues reported that concurrent STI rates were 31% among individuals with HIV and mpox attending a sexual health clinic (Abstract 736). In Denver, in a case-control study of patients tested for OPXV, Carlson and colleagues found that patients who tested positive were more likely to have had an STI in the preceding year or 6 months or to have one concurrently at the time of diagnosis (Abstract 1033). Niehaus and colleagues reported that at the Duke University Health System, most patients who were tested for mpox did not receive comprehensive STI testing but that rates of STI positivity were high when it was performed (Abstract 1035). They emphasized the need for improved STI screening in individuals being screened for mpox and suggested that an electronic medical record order set may be one strategy to improve comprehensive STI testing. These abstracts further support the need for syndemic management,

ensuring that facilities offer and perform concurrent HIV, STI, and mpox testing.

Mpox Treatment

During the special session on mpox, Issacs discussed molecular pathogenesis and therapeutic targets (Abstract 40). He described the unique replication cycle of MPXV, which replicates entirely in the cytoplasm of the cell, unlike most DNA viruses, which replicate in the nucleus. He discussed the relationship between the current outbreak strain and the strain in Nigeria in 2017, highlighting missed opportunities to get ahead of this outbreak. He described mutational differences that may explain the virulence differences between the clade I and clade II viruses. He also reviewed the limited data on mpox therapeutics, including vaccinia immunoglobulin, DNA polymerase inhibitors cidofovir and brincidofovir, and tecovirimat, a novel viral protein inhibitor. Issacs emphasized that tecovirimat, which results in an attenuated virus that spreads poorly, still requires the immune system to clear the virus. Furthermore, tecovirimat has a low barrier to resistance, with a single nucleotide change leading to resistance. Combined, these 2 factors may explain why we continue to see such severe disease in immunocompromised patients despite treatment.

Regarding antiviral treatment, human data on the efficacy of tecovirimat are limited. Yazdanpanah presented an observational study of 122 patients, 21 of whom received tecovirimat (Abstract 737). They found that patients receiving tecovirimat were less likely to have lesion resolution by day 14, and that one-third of the patients treated with tecovirimat still had active lesions or complications on day 28. However, this finding was confounded by the fact that tecovirimat was more likely to be administered to patients who presented with complications or more severe disease and those who were admitted to the hospital, consistent with guidelines.

Mpox Treatment Equity

One challenge to achieving equity in mpox treatment is the use of investigational drugs that require considerable administrative burden. To improve mpox treatment equity, it is essential to ensure that services are available in safety-net clinics and that all eligible patients are offered treatment. Karmarkar and colleagues reviewed 465 cases of mpox in a safety-net sexual health clinic in King County, Washington (Abstract 913). Of the 404 patients with treatment data, 77% received tecovirimat, with no significant differences observed among race and ethnicity categories. However, the proportion of patients who received tecovirimat varied depending on the diagnosis site, with clinics with fewer resources being less likely to prescribe tecovirimat.

Another strategy to improve equity in the treatment of mpox is using telehealth services to provide access to tecovirimat. Mgbako and colleagues demonstrated the effectiveness of a telehealth model in providing tecovirimat access to patients when prescriber capacity was limited (Abstract 1102). As of August 2022, the telehealth model had

provided tecovirimat to 69 patients, who constituted 83% of all patients treated at their site. However, although the telehealth model improved access for some patients, telehealth was not available to patients without a smart device. Furthermore, despite the high prevalence of STI (and HIV) coinfection in individuals with mpox, as previously highlighted, 40% of patients did not receive any STI testing in this telehealth model.

Mpox Immunology

Benet and colleagues studied outpatients diagnosed with mpox during the 2022 outbreak in Barcelona, Spain (Abstract 378). The aim of the study was to evaluate the time from symptom onset to viral DNA clearance and disease severity by analyzing antibody responses. Samples were collected at diagnosis and weekly for 1 month, and then at 91 and 180 days. The authors found that 90% of participants had detectable levels of IgG, and the breadth of IgG titers between people with and without HIV was similar. A rapid and strong polyclonal response was associated with milder presentations and a shorter time to viral clearance. However, individuals with HIV had lower and less durable IgG responses at 21 and 91 days after mpox diagnosis, with many patients losing their IgG response. This loss of IgG after infection may put individuals with HIV at increased likelihood of reinfection, highlighting the need to reconsider vaccination policies for people with HIV after infection.

Mpox Prevention

The rapid rise and fall of the mpox outbreak has sparked discussion of how the outbreak was successfully contained and the lessons learned for managing future emerging infectious diseases. Research on the strategies implemented, such as individual behavioral change, vaccination, and immunity, was presented at CROI 2023. By studying the trajectory of the mpox outbreak, we can better prepare for and respond to future outbreaks of mpox as well as other emerging infectious diseases.

Behavioral Changes

During the special session on mpox, Brooks highlighted the AMIS, which reported that gbMSM were taking proactive measures to protect themselves and their partners from mpox (Abstract 39). These measures included a 48% reduction in sexual partners, a 50% reduction in one-time sexual encounters, and a 49% reduction in sex with partners met on mobile apps or in sex venues. Phillips and colleagues corroborated these findings in their study of individuals living in Illinois (n = 469) that drew on the Keeping it LITE trial, which examined factors associated with HIV infection in young adults (Abstract 898). Notably, a greater proportion of participants (68%) reduced their number of sexual partners than in the AMIS. Additionally, individuals used 2 unique strategies to protect themselves: reducing sexual activity and

using protection methods such as having sex with their clothes on. These findings underscore the importance of harm reduction methods over abstinence-only messaging in promoting safer sexual behavior during outbreaks. Although similar findings were reported in the United States, Rossotti and colleagues conducted a study comparing the sexual behaviors of 435 users of preexposure prophylaxis before and during the mpox outbreak in Italy (Abstract 899). Surprisingly, most participants did not alter the frequency of their sexual activity, the number of sexual partners, or the use of condoms, and only a minority of participants (26%) received 2 doses of vaccine. Nevertheless, the outbreak decreased dramatically in Italy, leading the authors to hypothesize that factors such as the saturation of priority groups or hesitance to get tested and face mandatory quarantine measures may have played a role in the rapid decline of cases.

Vaccination

As widespread mpox vaccination is relatively new, it is essential to measure the effectiveness and durability of vaccination. Moreover, with the US Food and Drug Administration's Emergency Use Authorization for administering pediatric vaccination and intradermal doses for adults, knowing the vaccine's short- and long-term efficacy and safety is of utmost importance. Although studies are ongoing, early data presented at CROI show promise for the role of vaccination in preventing or stopping future mpox outbreaks.

During the special session on the mpox virus outbreak, Frey discussed the history of vaccination from smallpox to mpox, including the development of modified vaccinia Ankara (MVA) (Abstract 41). She explained the differences between smallpox and mpox and the risks associated with replicating vaccines, such as accidental spread and serious complications. She highlighted the benefits of the MVA vaccine, which does not replicate and produce infectious virus. These benefits include safety and 100% seroconversion after the second dose with neutralizing antibodies that are noninferior to those of live attenuated replicating virus. Frey also discussed the potential of intradermal injection, showing that the lower intradermal dose was immunologically noninferior to the subcutaneous dose, though associated with more erythema and induration. Finally, she reviewed the early data suggesting that mpox incidence estimates were higher among the unvaccinated than among those who received the vaccine. For those receiving 2 doses of the vaccine, the incidence rate ratio was 9.6 (95% CI, 6.9-13.2), with no difference between subcutaneous and intradermal administration.[8]

Although data are now accruing, the rapid onset of the mpox outbreak led policymakers to make decisions based on limited data. One of the earliest decisions was to pursue dose-sparing strategies for MVA vaccination without evidence of vaccine efficacy. As vaccine efficacy data were limited, modeling became a critical tool with which to evaluate potential efficacy and scenarios using dose-sparing strategies. Dimitrov and colleagues simulated high and low vaccine efficacy of fractional dose vaccine effectiveness (Abstract 1002). They found that in the context of a limited vaccine supply, as long as

the fractional dose vaccination retains moderate effectiveness, there is a net benefit to providing smaller intradermal doses to more people over full subcutaneous doses to fewer people. These findings support the decision made in many countries and jurisdictions.

Vaccine Effectiveness

During the session on epidemiology and prevention of mpox and SARS-CoV-2 infection, Titanji and colleagues offered valuable insights into vaccine effectiveness (Abstract 207). Currently the evidence on vaccine effectiveness is limited to a World Health Organization survey in 1988 that estimated first-generation vaccine efficacy at 85% and a recent UK Health Security Agency study that suggested an efficacy of 78% after the first dose; a Centers for Disease Control and Prevention study indicated that unvaccinated individuals had a 10-fold greater likelihood of mpox infection. Titanji conducted a retrospective, test-negative case-control study among US military personnel (2003-2017) to investigate the effectiveness of the mpox vaccine. Among 1007 military personnel tested for nonvariola orthopox virus, 21% had prior smallpox vaccination with a median time from vaccination of 13 years, and 30% (298) tested positive. They estimated a vaccine effectiveness of 66% for first-generation smallpox vaccines and 72% for second-generation smallpox vaccines. Although the study population was unique, with a reliable data source, it relied on prior and older vaccinia vaccinations.

During the same session, Ghosn shared data from the DOXYVAC (Combined Prevention of Sexually Transmitted Infections in Men Who Have Sex With Men and Using Oral Tenofovir Disoproxil Fumarate/ Emtricitabine for HIV Pre-Exposure Prophylaxis) trial, which was conducted to evaluate the impact of doxycycline for postexposure prophylaxis and meningitis B vaccine for gonorrhea prevention in individuals at increased likelihood of STIs (Abstract 208). Among the 472 study participants, there were 77 cases of mpox. Mpox was more likely to occur in younger participants, those with more sexual partners, those engaging in condomless anal intercourse, and those who did not receive vaccination for smallpox during childhood. After vaccination was recommended, the incidence rate of mpox decreased significantly, with an incidence rate ratio of 0.010. However, multivariate analysis showed that although the number of individuals having more than 10 sexual partners in the preceding 3 months decreased after the outbreak, this change in sexual behavior had a limited impact on mpox incidence in this population.

Vaccine Immunology

At the onset of the mpox outbreak, the availability of the MVA vaccine was severely restricted, and several countries opted for a dose-sparing approach, employing intradermal dosing to increase the number of doses available. Before this outbreak, there was limited information on the efficacy of the dose-sparing approach. Although a National Institutes of Health–funded study on this strategy is

ongoing, several researchers presented preliminary findings at CROI 2023.

Mazzotta and colleagues evaluated the immune response to MVA vaccination, reporting on the first dose response to subcutaneous versus intradermal dosing (Abstract 375). In a population in which most people (81%) received intradermal dosing, intradermal dosing was associated with a higher rate of systemic and local self-reported adverse events; however, intradermal dosing was also associated with an elevated immunologic response, including elevated levels of IgG and neutralizing antibodies. Although humoral immunity is essential to vaccine effectiveness, T cell responses are also important. Mazzotta and colleagues also examined humoral and T cell responses after MVA vaccination, comparing responses among individuals with and without HIV and those with and without prior smallpox vaccination (Abstract 374). The first dose of MVA vaccination elicited a humoral response that was more robust in those individuals who had previously been vaccinated for smallpox and greater in those who did not have HIV. In fact, among people with HIV, less than half seroconverted after the first shot. On the other hand, the T cell responses were diminished in those with prior smallpox vaccination. These findings strongly suggest that all patients, regardless of prior vaccination or HIV status, would benefit from at least a 2-shot vaccination series. Although this study describes only responses up to 4 weeks after the last dose, longer follow-up is needed to understand the long-term durability of humoral and cellular immune responses to vaccination.

To better understand the impact of hybrid routes of immunization, it is important to investigate the effects of switching to intradermal dosing after initial subcutaneous administration of MVA. Moschese and colleagues evaluated the neutralization titers induced by a hybrid vaccination schedule (first dose subcutaneous, second dose intradermal) in 35 patients with available samples at 3 time points: baseline, week 4, and week 12 (Abstract 377). Although all patients had neutralizing antibodies, 29% experienced a decline in titer from 4 weeks after subcutaneous vaccination to 8 weeks after intradermal vaccination. Further research is needed to determine whether this finding is unique to the hybrid vaccination schedule and whether it has any clinical implications.

Oom described the rapid development of an observational mpox vaccine study that started enrolling before the end of July 2022 and has enrolled more than 100 patients to date (Abstract 1001). Among the enrolled individuals, 58% had received a hybrid vaccination strategy, 24% had received intradermal dosing for both doses, and 20% had a history of prior smallpox vaccination. Although this study is planned to span 3 years and is still early in its course, results of initial analysis are consistent with those reported in other studies presented at CROI, including the finding that individuals with HIV and preserved CD4+ counts respond well to the vaccine and that participants with a history of smallpox immunization have higher antibody titers. The researchers aim to follow the enrolled individuals for up to 3 years, providing insights into the vaccine's immunologic effects over time.

Mpox Serologic Testing

Although serology has limited utility in acute infections, it can be valuable in epidemiologic research. Kurpitz and colleagues developed a novel immunoassay that measures vaccine response and distinguishes between MPXV infection and previous vaccination (Abstract 379). This development has important implications for future epidemiologic studies, which can employ this test to establish the prevalence of MPXV infection and detect asymptomatic community transmission, particularly in settings where many vulnerable individuals are vaccinated.

Mpox Vaccination Equity

Since the beginning of the mpox vaccination planning, concerns have been raised regarding the inequitable distribution of vaccines, which may result in wider disparities in mpox infection and outcomes. Knowledge and attitudes toward vaccination may influence vaccination rates. In a survey conducted by Castel and colleagues involving 249 people with HIV receiving care at 14 sites in Washington, DC, 90% had heard of mpox (Abstract 1004). Of the 201 people with HIV who had heard of mpox and answered vaccination questions, 21% were vaccinated, 39% planned to be vaccinated, and 39% did not plan to be vaccinated. Notably, young MSM were more likely to be vaccinated than non-MSM and females with HIV. Given the potential for more severe disease in individuals with HIV, this finding suggests that offering education and vaccination to all people with HIV may help avoid inequitable vaccine distribution.

Woodhouse and colleagues reported significant vaccination disparities at a southeastern clinic, where White and privately insured patients were more likely to receive the vaccine than Black and non–privately insured patients, respectively; only one-third of individuals with a recent STI received the vaccine (Abstract 1003). The authors suggested that early flags such as current prior STI status could have alerted practitioners to the need for vaccination. Similarly, Mara and colleagues in San Francisco found that among people without mpox, only 42% of those with HIV and 65% of those using preexposure prophylaxis were vaccinated (Abstract 1000). Additionally, Black individuals, transgender women, and people experiencing homelessness were less likely to be vaccinated, highlighting the need for targeted outreach to reduce disparities and ensure equitable vaccine distribution.

Mpox and the Future Research Agenda

In the special session on the mpox outbreak, all of the speakers highlighted the need for future investment in MPXV research, including more genetic sequencing to determine whether any mutations have enhanced human transmission or pathogenesis. There is much to be learned about transmission, including presymptomatic transmission and duration of infectivity from different compartments. Treatment including evidence-based supportive care options, the effectiveness of

tecovirimat during this outbreak, and the roles of vaccinia immunoglobulin, cidofovir, and brincidofovir all require further study. Finally, further research on the MVA vaccine used in this outbreak is needed to better understand vaccine efficacy, durability, and effectiveness.

To help answer the question of effectiveness, tecovirimat prescribers should consider referring patients to a clinical trial for treatment. In the US, clinicians can refer patients to the STOMP (Study of Tecovirimat for Human Monkeypox Virus) clinical trial,[9] in the United Kingdom clinicians can refer patients to the PLATINUM (Placebo-Controlled Randomised Trial of Tecovirimat in Non-hospitalised Monkeypox Patients) trial,[10] and in Brazil clinicians can refer patients to the UNITY (Assessment of the Efficacy and Safety of Tecovirimat in Patients With Monkeypox Virus Disease) trial.[11]

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