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Mpox in persons with advanced HIV infection: a global case series

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ABSTRACT 350

Background. People living with HIV account for 38-50% of those affected in the 2022 multi-country mpox outbreak. Most reported cases had high CD4 counts and similar outcomes to those without HIV. Emerging data suggest worse clinical outcomes and higher mortality in more advanced HIV. We describe the clinical characteristics and outcomes of mpox in a cohort of persons with HIV and low CD4 cell counts (CD4 <350 cells/mm^3).

Methods. A network of clinicians from 19 countries provided data from confirmed mpox cases between May 11 and Dec 24, 2022, in persons with HIV infection and CD4 counts <350 cells/ mm^3. We describe their clinical presentation, complications, and causes of death. Analyses were descriptive.

Findings. We include data of 382 cases: 367 cisgender men, 4 cisgender and 10 transgender women with a median age of 35 years. At mpox diagnosis, 349 (91.4%) were known to be living with HIV; 228/349 (65.3%) adherent to antiretroviral therapy (ART); 32/382 (8.4%) had a concurrent opportunistic illness. The median CD4 count was 211 cells/mm^3 (IQR 117-291); with 85 (22.3%) individuals with CD4 counts <100 cells/mm^3, and 94 (24.6%) 100-200 cells/mm^3. Of those with HIV viral load data available, 193/354 (54.5%) were undetectable. Severe complications were more common in persons with CD4<100 compared to those with >300 cells/mm^3, including necrotising skin lesions (54.1% vs. 6.7%), lung involvement (29.4% vs. 0%) occasionally with nodules, and secondary infections and sepsis (43.5% vs. 9.3%). Overall, 107/382 (28.0%) were hospitalised of whom 27/107 (25.2%) died. All deaths occurred in those with CD4 counts <200 cells/mm^3. Amongst those with CD4 counts <200 cells/mm^3 more deaths occurred in those who also had high a HIV viral load. An immune reconstitution inflammatory syndrome to mpox was suspected in 21/85 (24.7%) persons

initiated or re-initiated on ART of whom 12/21 (57.1%) died. Sixty-two (62/382, 16.2%) received tecovirimat and 7 (2.2%) cidofovir or brincidofovir; three had laboratory confirmation of tecovirimat resistance.

Interpretation. A severe necrotizing form of mpox in the context of advanced immunosuppression appears to behave like an AIDS-defining condition, with a high prevalence of fulminant dermatological and systemic manifestations and death.

Funding. None

RESEARCH IN CONTEXT 635

Evidence before this study

In 2022, mpox, a disease caused by an orthopox virus referred to as monkeypox virus (MPXV) has caused outbreaks in 110 countries. Two distinct clades of MPXV, Clade I and Clade II, have existed in different geographic regions. The subclade IIb, identified in the 2022 outbreak, originates from subclade IIa mpox, which is considered a self-limiting disease. Unlike the previous epidemiological descriptions in West Africa, mpox transmission in this outbreak has been closely associated with the sexual networks of gay-and-bisexual men-who-have-sex-with-men (GBMSM), in which a high proportion of people are living with HIV. Some evidence suggests greater disease severity in people with advanced HIV. This finding warrants careful evaluation of the interplay between HIV, immune status and clinical manifestations of mpox. We searched PubMed for the terms “monkeypox, mpox AND (HIV)” from inception to Dec 31, 2022. Publications were predominantly letters, perspectives, case reports, and public health agency reports. In the multi-country outbreak, scientific publications of case series have described similar clinical outcomes in people living with HIV to those in people without HIV infection. However, most cases series included people with HIV and high CD4 counts (> 500 cells/mm^3) and suppressed HIV viral loads. In contrast, a Nigerian case series in the 2017-18 outbreak reported that more severe outcomes in hospitalized people were observed in persons living with HIV especially those who were viraemic and immunosuppressed. In a Center for Disease Control (CDC) report on 758 mpox cases in persons living with HIV during the multi-country outbreak (median CD4 639 cells/mm^3; 3% < 200/mm^3) 10% (68/758) were hospitalized for a median duration of 2 days (0-7). Worse rectal symptoms were described in those with HIV. A second CDC report identified adverse outcomes in 47 people with HIV and

mpox who had low CD4 counts, 12(26%) died and 5 deaths were attributed to mpox. Based on these data, individuals with HIV and advanced disease have been identified as cases requiring expert clinical advice, close surveillance and prioritised for anti-viral treatments such as tecovirimat, and preventive vaccines (where available).

Added value of this study

This mpox case series is the largest in those with advanced HIV disease. We characterized 382 persons with HIV and CD4 < 350 cells/mm^3. Individuals with lower CD4 counts presented with widespread, large, necrotising, and coalescing skin lesions. Some individuals also developed lung nodules without an alternative confirmed or suspected diagnosis. Severe secondary bacterial infections were common. Frequent and severe oral, ano-genital, and ocular presentations and complications are described. Immune reconstitution inflammatory syndrome (IRIS) was suspected in a quarter of those starting or re-initiating antiretroviral therapy (ART) after mpox diagnosis, 57% of whom died. The greatest disease severity, hospitalisation, and mortality was observed in individuals with both low CD4 count and high HIV viral load. This international case series includes 27 of the 60 persons reported to have died of mpox in the multi-country outbreaks, all 27 are persons with HIV and CD4 < 200 cells/mm^3.

Implications of all the available evidence

Our findings support the consideration of a severe, disseminated, and necrotising form of mpox infection as an AIDS-defining condition in CDC and WHO HIV disease classifications. This is based on the observation of protracted illness with fulminant disseminated necrotising

cutaneous lesions, systemic complications, and mortality in those with CD4 cell counts <200 cells/mm^3. Clinicians should also be aware that starting ART in people with advanced HIV and mpox may contribute to deterioration and possible death, possibly as part of an immune reconstitution syndrome. Our data reinforces the importance of HIV testing in mpox cases. Our findings support the recommendations that all at-risk persons with HIV with a CD4 count <200 cells/mm^3 should be prioritised for preventive mpox vaccination. There should also be consideration for use of potential mpox antivirals where available despite lacking data on their effectiveness and a concerted global effort to ensure access in countries without access to antivirals and vaccines.

BODY TEXT

INTRODUCTION 313

Since May, 2022, around 85,000 human mpox infections have been reported in 110 countries, with transmission predominantly through sexual contact amongst GBMSM.[1] The multi-country outbreak was declared a Public Health Emergency of International Concern (PHEIC) by the World Health Organisation (WHO) in July 2022.[2] People with HIV, accounting for 38-50% of persons diagnosed with mpox,[3] have been disproportionately affected.[3] Most persons living with HIV described in the 2022 case series had HIV viral suppression with median CD4 counts >500 cells/mm^3 and had similar clinical presentations, time to viral clearance, and outcomes to persons without HIV.[4–13]

Data from Nigeria and the USA suggest worse clinical outcomes in those with more HIV-related immunosuppression.[4,14] Two reports from Nigeria during the 2017-2018 outbreak suggested that people with advanced HIV presented with more severe or prolonged mpox. The first described that 4 of 7 deaths in 122 individuals with mpox, occurred in people with untreated advanced HIV.[15] The second report included 9 people with HIV with CD4 cell counts ranging from 20 to 357 cells/mm^3.[16] The authors described confluent rashes, higher rates of secondary bacterial infections and more prolonged illness.[16] More recently, a report from the US-CDC during the 2022 outbreak, confirmed these finding in 47 cases of severe mpox among people with advanced uncontrolled HIV infection.[14] All were hospitalized, had prolonged disease courses, or developed complications, and some had fatal outcomes (i.e., 5 deaths attributed to mpox).[14] Worse rectal disease was described in another CDC series in which 82% of people living with HIV were on ART and 72% were virally suppressed.[4]

Based on the existing data we hypothesized that in the current outbreak, mpox presentations and outcomes in persons living with HIV may differ by CD4 strata and HIV viral load. We leveraged global research networks to describe the characteristics, clinical course and outcomes of mpox in persons with HIV and CD4 count <350 cells/mm^3.

METHODS

Case definition and identification

Participating clinicians were recruited through the international research networks of the London-based Sexual Health and HIV All East Research (SHARE) Collaborative and the Network of the Skin Neglected Tropical Diseases and Sexually Transmitted Infections Unit of the Hospital Germans Trias i Pujol in Spain.[8–10] Researchers in geographic locations with high numbers of mpox diagnoses were approached and invited to contribute mpox cases diagnosed between May 11, 2022, and December 24, 2022. A confirmed case was defined as a polymerase-chain-reaction (PCR)-confirmed MPXV infection in a specimen from any anatomical site. We restricted this series to adults older than 18 years living with HIV and CD4 <350 cells/mm^3 or, in settings where a CD4 count was not always routinely available, HIV infection clinically classified as CDC stage C. We included people living with HIV and CD4 counts <350 cells/mm^3 in line with the widely accepted 2010 consensus statement which defines late presentation of HIV as CD4 <350 cells/mm^3 or an AIDS-defining illness.[17]

CD4 count was categorised as <100, 101-200, 201- 300, and 301-350 cells/mm^3, because CD4 count cut-offs of 100 and 200 are associated with different risk for opportunistic infections (e.g, cryptococcal meningitis is associated with CD4 < 100 cells vs. pneumocystis jirovecci pneumonia (PJP) or toxoplamosis <200 cells).[18] For strata comparison, we grouped the seven individuals with a missing CD4 count with those who had a CD4 count < 100 cells/mm^3. Three of these had an AIDS-defining condition and four had a positive point-of-care qualitative CD4 count test [Visitect CD4 Lateral Flow assay providing a visually interpreted result of above 200 (negative)- or below 200 (positive)]. HIV viral load (VL) was categorised as undetectable (<50 copies/mL), 50-200 (low level viraemia), 200-<log4, ≥log4 log RNA copies/ml. We categorised the presence or absence of clinician reported complications by organ system.

Data collection

Each contributing centre completed a de-identified structured case-report sheet (CRS) adapted from one used in our prior case series to include variables of interest relevant to persons living with HIV and to capture more severe outcomes (Supplementary Figure 1). The CRS used drop down-menus and free-text fields to capture routinely collected data from electronic or paper medical records. The CRS focus on HIV status included CD4 cell count, HIV viral load, concurrent opportunistic infections, and adherence to ART. These data were included with information on mpox presentation, diagnosis, clinical features, complications, and outcome. We also considered four outcomes for management: outpatient, hospitalization, ICU-level care, and death. Duration of hospitalization was the number of days until discharge or until data collection if ongoing by the end of data collection.

Ethical considerations

Participating clinicians identified individuals living with HIV and diagnosed with mpox infection at their site. Informed consent for inclusion was obtained and maintained in accordance with local standards, along with local institutional review board approval as per each site's local requirement. Image-specific consent was obtained from participants (or their families when deceased) for the use of images. De-identified data were securely transferred to the coordinating site.

Statistical analysis

All analyses were descriptive, and no hypothesis testing was conducted. Continuous variables were described as the mean and standard deviation (SD) or median and inter-quartile range (IQR). Categorical variables are described as counts and percentages over the entire sample or the corresponding subgroup. No imputation methods were applied to missing data. Data were analysed using R version 4.2.1. Aggregate or de-identified data are presented to avoid deductive disclosure of the identities of study participants.

Funding

There was no specific funding for this study.

RESULTS

We describe 382 cases of human mpox infection in persons living with HIV with CD4 < 350/mm^3 from sites in 19 countries (10 in Europe, 8 in the Region of the Americas, and 1 in Africa) (Supplementary Figure 2). Most (72.5.2%; 277/382) were originally from the Americas

(Argentina, Brazil, Canada, Chile, Ecuador, Mexico, Peru, USA), 25.9% (99/382) were from the European region (Austria, Belgium, France, Germany, Greece, Italy, Portugal, Spain, Sweden, Switzerland, UK), 1.6% (6/382) from Africa (Nigeria).

The demographic and epidemiological characteristics of the participants are described in Table 1. The median age was 35 years (IQR 30–43). Three hundred and sixty-seven out of 382 (96.1%) identified as cisgender men, 4 cisgender women (1.0%), 10 transgender women (2.6%), and 1 non-binary individual assigned male at birth (0.3%). The ethnicity or race of participants as described by the attending clinician was Black 14.4% (55/382), Latin-American 58.9% (225/382), or White 22.3% (85/382).

Overall, 349/382 (91.4%) were known to be living with HIV prior to mpox diagnosis, and 33/382 (8.6%) were newly diagnosed with HIV infection at the time of the MPXV infection. Of those known to be living with HIV, 84.5% (295/349) were on ART and 65.3% (228/349) were reported as adherent to treatment in the preceding six months. The median CD4 cell count was 211 cells/mm^3 (IQR 117-291). The distribution of CD4 counts was as follows: 85 (22.3%) <100 cells/mm^3, 94(24.6%) 100-200 cells/mm^3, 128(33.5%) 201-300 cells/mm^3, and 75 (19.6%) 301-350 cells/mm^3. CD4 counts were missing in 7 individuals who were assigned to the group with CD4 <100 cells/mm^3as described in the methods and in Table 1,2,3. Overall, 193 individuals (50.5%) were virally suppressed (HIV RNA <50 copies /ml), 26 (6.8%) had low-level HIV viraemia (50-200 copies/ml), 30 (7.9%) had viraemia from 200 to log4 copies/ml, and 105 (27.5%) had viraemia of > log4 copies/ml. HIV RNA values taken within the past 6

months were not available for 28 individuals (7.3%). Overall, 8.4% of patients (32/382) had a concurrent opportunistic infection at the time of the mpox diagnosis.

In terms of clinical presentations (Table 2), 243/382 (63.6%) patients had fever and 364 (95.3%) had a skin rash, which was initially vesiculo-pustular in 297/382 (77.7%) and progressed to ulcerative in 84/382 (22.0%). The median number of skin lesions was 15 (IQR 8-35), and the median duration to resolution was 23 (IQR 18-33) days. Among 36 patients (9.4%) who had 100 or more lesions and 43 patients (11.3%) who had a duration to resolution of forty days or more, the majority had CD4 counts <200 cells/mm^3 and detectable HIV plasma viral loads (Supplementary Figure 3 & 4). Overall, 235 individuals (61.5%) had genital, 203 (53.1%) anal lesions, 144 (37.7%) oral involvement and 20 (5.2%) had ocular involvement. The most common organ complications were dermatological, respiratory, and secondary bacterial infection (Table 2). A total of 94/382 (24.6%) patients developed dermatological complications; 10 (2.6%) of these were ecchymotic or haemorrhagic lesions, and 84 (22.0%) were necrotising lesions, of which 55 (14.4%) were coalescing. The most common presentation was multiple, large (typically greater than 2cm in diameter), rounded ulcers with necrotic centres and a fresh, raised border, located close to the oro-genital regions (Figure 1B. Photographs B1-4) or in distant locations (Figure 1B. B6-8), while verrucous appearance (Figure 1B. B5) was rare. In many instances, erythema and oedema surrounded the ulcer. Lesions involving the mouth, eye, or anus resulted in functional impairment (B1-4). In the anogenital region, some individuals presented with significant tissue damage and phagedenic ulcerations (Figure 1C). Some persons had progression to target-shaped lesions with erythema, swelling and pallor beyond the margins of the ulcer indicating severe necrosis. (Figure 1C) Pseudo Koebner phenomena (i.e., the spread of the skin infection along sites with

skin microtrauma or rubbing) were manifested by ulcers exhibiting a lineal distribution or overlying bony prominences (Supplementary Figure 5). In cases where epithelialization had occurred, tissue destruction resulted in disfiguring scarring (Supplementary Figure 5).

In total, 35/382 (9.2%) people presented with respiratory complications (Table 2). Of these, eleven individuals (2.9%) presented with numerous bilateral diffuse pulmonary nodules; 4/11 diagnosed with an X-ray only, and 7/11 were further characterized on CT scanning. All the radiographic images were reviewed by two specialist radiologists who concurred that these nodular lesions were unusual and characterised by well-defined borders, absence of cavitation and no adjacent areas of ground glass shadowing; most of the nodules were peri-vascular and, generally, ranged in size from of 5 to 20 mm (Supplementary Table 1). In all three patients with nodules in whom BAL or lung biopsy were performed, a positive MPXV PCR result was obtained (with negative microbiological results for *P. jirovecci* and *M. tuberculosis)* (Figure 1A). 8/11 had a CD4 count below 100 cells/mm^3.

12/35 (34.3%) individuals with respiratory complications had dyspnoea of whom - two had normal chest X-rays, and ten had no available radiology report. Additionally, 6/35 (17.1%) individuals presented with pleural effusion (1 with a positive MPXV PCR on BAL), and 3/35 (8.6%) with ground glass changes (2 with suspected opportunistic infections; 1 with a positive MPXV PCR on BAL).

Twelve (3.1%) individuals were reported to have neurological involvement, including one (0.3%) case classified as encephalitis with orbital, frontal and temporal oedema on CT scan,

and with a positive MPXV PCR result, and negative HSV-1 and 2, and VZV results in cerebro-spinal fluid (CSF). Of the nine (2.4%) cases with altered mental status or confusion six had normal CSF and/or radiological findings and three did not undergo imaging or CSF examination. In five cases, confusion was attributed to sepsis, in one to respiratory failure and in one to hepatic encephalopathy. Neurological symptoms were almost exclusively described in persons with HIV with CD4 less than 100 cells/mm^3. (Supplementary Table 2)

In 76/382 (19.9%) individuals, secondary bacterial infections were diagnosed, including cellulitis, abscesses, and sepsis. Among 17 patients with sepsis, 8 had positive blood cultures and the following pathogens were identified: three *Pseudomonas aeruginosa*¸ two ESBL *E. coli*, two polymicrobial, and one *Shigella flexneri.* Additionally, 12 patients had a positive result from an abscess or deep wound sample culture: three *Pseudomonas aeruginosa*¸ two *Klebsiella pneumoniae*, two ESBL *E. coli*, three methicillin-sensitive and two methicillin-resistant *Staphylococcus Aureus*.

All complications were more common in individuals with CD4<100 compared to individuals with CD4>300 cells/mm^3. This included dermatological (57.6% vs. 9.3%), respiratory (29.4% vs. 0%), bacterial infection (43.5% vs. 9.3%), gastrointestinal (27.1% vs. 6.7%), rectal complications (56.5% vs. 28.0%) (Figure 2A).

Overall, 107/382 (28.0%) individuals were hospitalised; of these, 7 (1.8%) survived an admission to intensive care and 27 (7.1%) died (Table 3). Among the 27 people who died, the median CD4 count was 35 cells/mm^3 (IQR 24-100), and the median HIV viral load was 5

346 log copies/ml (IQR 4-5), only one patient was HIV virologically suppressed. Among those
347 who died, severe necrotising or haemorrhagic skin lesions occurred in 25/27 (92.6%),
348 bloodstream or deep tissue bacterial infections (24/27; 88.9%), respiratory symptoms and
349 respiratory failure (23/27; 85.2%), neurological (8/27; 29.6%), rectal (21/27; 77.8%), and
350 oropharyngeal (18/27; 66.7%) involvement were described (Table 3). Ocular disease
351 occurred in (13/27; 48.1%), 8 of whom had peri-orbital cellulitis. The reported cause of
352 death was septic shock and multi-organ failure in 20/27 (74.15%), respiratory failure 4/27
353 (14.8%), disseminated mpox in 2/27 (7.4%) and cardiac arrest in 1/27 (3.7%).
354
355 Rate of hospitalisation and ICU admission increased with declining CD4 counts and rising viral
356 loads (Figure 2). No deaths occurred in individuals with CD4 counts >200cells/mm^3. Mortality
357 was incrementally higher among people in the lowest CD4 strata (CD4<100 27.1% vs. CD4
358 100-200 4.3% vs. CD4>200 0%; Figure 2B) and amongst those with the highest viral loads (HIV
359 VL log≥4 16.2% vs. HIV VL undetectable 0.5%; Figure 2C). In those with CD4 count <100
360 cells/mm^3 (n=85) and available HIV VL, the death rate was 7.1% (1/14) for individuals with VL
361 <50 copies/ml and 29.8% (14/47) for those with HIV VL ≥4 log copies/ml.
362
363 Among 85 persons started or restarted on ART, in 21 (24.7%) the managing clinician
364 suspected IRIS as a cause for clinical deterioration (Supplementary Table 3). Of these, 6
365 (28.6%) were newly diagnosed and 15 (71.4%) were known to be living with HIV but either
366 not receiving or not adherent to ART. All had CD4 count <200 cells/mm^3. The median time
367 from onset of mpox symptoms to the start of ART was 21 days (range 0-73), and from the
368 start of ART to worsening of mpox symptoms was 14 days (range 3-64). Nine of 21 (42.9%)

were treated for IRIS with steroids, and 10 (47.6%) received supportive care. Of those with suspected IRIS, 3/21 (14.3%) were admitted to the ICU, 5 (23.8%) were hospitalised in a general ward, and 12 (57.1%) died.

Forty-three (41.7%) of the 103 hospitalized patients and twenty-one (7.5%) of the 279 outpatients received antivirals to treat mpox. Sixty-two (62/382, 16.2%) individuals received tecovirimat (5 received both oral and IV) and 7 (1.8%) cidofovir or brincidofovir. All patients receiving mpox-specific antiviral therapy were treated in Europe or the USA, except two who received tecovirimat in Brazil. Laboratory confirmation of tecovirimat resistance (presence of FL13L mutations by sequencing) was detected in 3/5 people tested, who had severe immunocompromise, disseminated and progressive mpox infection despite prolonged treatment (>14 days) with tecovirimat and finally died. Sampling for resistance testing was conducted after at least one course of tecovirimat had been completed. Nobody who died had received mpox-vaccination prior to or during 2022.

DISCUSSION

Our large case series describes a severe, disseminated form of mpox infection with 15% mortality in individuals with advanced HIV-related disease characterised by CD4 counts below 200 cells/mm^3. This fulminant form of mpox is characterized by massive necrotising skin, genital and non-genital cutaneous and mucosal lesions, sometimes accompanied by lung involvement with multifocal nodular opacities or respiratory failure, severe cutaneous and bloodstream secondary bacterial infections. The severity of oral and anogenital complications are more marked than previously described.[4–10,19] As described in the CDC classification,

disseminated forms of coccidiodomycosis, histoplamosis and mycobacterium avium complex are considered to be AIDS-defining illnesses.[20] Very similarly, we describe that people with the lowest CD4 counts (<100 cells/mm^3) and highest HIV viral loads (> 4log c/ml) had disseminated forms of mpox strongly suggesting that this severe necrotising form of mpox with systemic involvement is also an AIDS-defining condition (Supplement Table 4).[20] We describe in detail the clinical course of 27 people with CD4 counts < 200 cells/mm^3 who died, representing more than 40% of all mpox deaths reported in 2022. We also wish to raise awareness of the 57% mortality rate in those in whom IRIS was suspected following ART initiation/re-initiation.

This data builds on the observations of the altered natural history and course of mpox that is emerging. To date most information about the intersection of HIV and mpox reports on those with well-controlled HIV infection.[4–11] During the 2022 multi-country outbreak even the largest series include very few people living with HIV and CD4 counts < 350/mm^3 (12%) or <200/mm^3 (3%).[4,21,22] We hypothesized that mpox may have a different clinical presentation in individuals with advanced immunosuppression, as can be the case with some pathogens. Although the self-limiting clinical course in individuals with well-controlled HIV is very similar to that of individuals without HIV, our series provides evidence that the disease is very different in those with advanced HIV. The protracted duration and larger number of skin lesions in these individuals also raises the possibility of a more prolonged period of infectivity, but further studies are needed to investigate this.

Prior work has shown that people living with HIV with high CD4+ T-cell counts (>350 cells/ mm^3) mount a poxvirus-specific T-cell response that is similar to those without HIV infection,[23] but there are no data on immunological responses in those with low CD4 counts (<350 cells/ mm^3). In our series low CD4 cell count especially when < 200/mm^3 was strongly associated with increasing severity of mpox disease relative to those with CD4 200-350/mm^3 and compared to previous reports where CD4 > 500/mm^3. Data from animal model MPXV studies have shown that CD4 depletion before immunisation of non-human primates decreased the development of protective B-cell responses and antibodies, and increased infection severity, which is consistent with our findings.[24] Moreover, in our series, the effect of a low CD4 count on severity or death varied with the HIV plasma viral load, with higher viral loads associated with increased frequency of severe illness in any given CD4 group. Prior work has shown that replicating HIV virions target antigen-specific T cells that are activated to combat other pathogens, resulting in impaired T-cell responses.[25–27] Thus, it is possible that a substantial fraction of MPXV-specific CD4 T cells might die or be impaired due to either complete or abortive HIV infection. Others have shown impaired immune responses to hepatitis B and other vaccines in those with low CD4 and unsuppressed HIV virus replication, providing further evidence that HIV replication may interfere with immune response to other pathogens.[27,28] Based on our findings we believe that a severe necrotising form of mpox with systemic manifestations exists. This form of mpox affected those with CD4 counts <200 cells/mm^3 - the precise CD4 threshold considered to be AIDS-defining in international guidelines (Supplement table 4) . Given the 15% mortality in this group, strong consideration should be given to designating this disseminated form of severe mpox as a new AIDS-defining condition in definitions and guidelines.

Several limitations of our research need to be highlighted. Our data are derived from an observational retrospective convenience case series from countries with high numbers of mpox infections. We were, therefore, unable to assess how well our cohort represents the entire population of people living with HIV and who developed mpox infection. Study sites may have been more likely to include individuals with more severe outcomes which may have biased the relationships we saw between both CD4 counts and HIV viral load and clinical outcomes. Individuals included in this case series had symptoms that led them to seek medical care; therefore, persons who were asymptomatic, had milder symptoms, or lacked access to medical care could have been missed and thus we may have overestimated illness severity.[29] Also outcomes may have been missed if people reattended with severe disease at different sites that were not part of the case series. Due to data collection from multiple sites some characteristics may have been collected in a heterogeneous manner, and laboratory techniques also differed from site to site. Many of the cases had a concomitant opportunistic infection and it may be difficult to ascertain many of the outcomes to mpox relative to the other pathogens. For example, some healthcare settings included did not have access to certain radiological and microbiological investigations so we cannot be certain of the role of mpox as opposed to other opportunistic infections. However, we suggest that the coincident perivascular non-cavitating lung nodular pattern described by two radiologists and seen in eleven patients, without a documented suspicion or microbiological evidence of a co-opportunistic pathogen, may be a manifestation of mpox disease and further research is warranted.

Many of the deaths were associated with multiorgan system failure, and the relative contribution of the mpox to death unclear. We have raised the possibility of IRIS reactions with the initiation of antiretroviral therapy but in the absence of a strict definition and in the absence of details on confounding conditions that may have contributed to adverse outcomes the data are uncertain. Data are currently not available from randomised controlled clinical trials on the impact of MPXV antivirals or preventive vaccines on the course of mpox, and with the limited use in this series their role cannot be evaluated.

Physicians caring for persons with mpox and advanced HIV disease must be made aware of the severe outcomes and high mortality that can occur especially when cutaneous and bloodstream bacterial super-infection set in. Clinical trials tailored to this group are needed to evaluate the impact of antiviral agents and preventive vaccines to modify disease outcomes. In the absence of these data, persons with HIV, low CD4 counts who need to be hospitalised with mpox should be considered for expanded access to these therapies where available. We have raised the risk of deterioration after initiation of antiretroviral therapy that carried a 57% mortality rate. This needs to be considered when caring for persons with HIV and advanced disease with mpox who are not on therapy. Further research into the role of IRIS is necessary to better understand the role of potential interventions, such as early versus delayed initiation of ART, the concomitant use of steroids or other immunomodulatory strategies leading to a reduction in the frequency of IRIS.

Our data also reinforces the recommendation that HIV testing (in addition to other sexual transmitted pathogens) be performed in every case of mpox. Further those with HIV

infection and high risk for mpox infection should be prioritised for preventive vaccine. Two thirds of the deaths we have reported have occurred in Latin America. Our findings are particularly pertinent for countries with low levels of HIV diagnosis and/or without universal free access to ART and intensive care units, where the interaction of uncontrolled HIV infection and mpox is more prevalent. In these countries, a concerted effort to provide urgent access to mpox antivirals and vaccines is of vital importance.

CONTRIBUTORS

OM and CMO conceived and designed the study. CMO, and OM co-ordinated the global collaboration. AA and CGC managed the global data collection. CMO, OM, AA, MM, CGC developed the case report form. MM and OM analysed and interpreted and vouch for the data. All authors except MM, and CMO submitted cases. OM, CMO, AA, CGC and MM drafted the first draft of the manuscript. CGC and JV prepared the image library. SW edited the final draft. All authors reviewed the manuscript and vouch for the accuracy and completeness of the data. All authors were responsible for the final decision to submit for publication and have seen and approved the manuscript. CMO, MM and OM had full access to all data.

DATA SHARING

De-identified participant data collected, including individual participant data, and will be made available from the corresponding author on reasonable request.

DECLARATION OF INTERESTS

We declare no competing interests.

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FIGURE LEGENDS

FIGURE 1. Skin presentation of mpox in advanced HIV disease

Panel A: Disease progression in a patient with CD4 count of 18 cell/mm3 and viral load log5, with pcr- confirmed lung involvement, bowel perforation, IRIS, and death despite having received two courses of IV tecovirimat and one course of IV cidofovir.

Panel B: Photographs of necrotizing lesions in multiple patients. Lesions of the skin and mucous membranes. **B1**: Necrotic ulcers in the peri-labial and nasal areas. Ulcer with tissue destruction on the right upper lip. **B2**: Umbilicated vesiculopustular-like lesions on upper eyelid surrounding an extensive necrotic ulcer. Eyelids and nasal radix with oedema and erythema. **B3**: Mucositis, oedema and erosions of the labial mucosa and tongue. **B4:** Necrotic ulcers with raised edges, some confluent, on the scrotum, dorsum of the fingers, groin, and thighs. **B5:** Numerous verrucous, excrescent, yellowish facial lesions. **B6:** Multiple periumbilical target-like vesiculopustular lesions, with necrotic depressed centre and erythematous halo. **B7**: Large, necrotic, and confluent ulcer on the elbow surrounded by small numerous vesiculopustular lesions. **B8**: Necrotic ulcers, oedema and erythema on the left hand and wrist.

Panel C: Before and after lesions, with progression to severe confluent target-shaped ulcers with dark necrotic centre surrounded by a vesiculopustular halo and peripheral oedema, in the perianal area and back.

Credits: Pictures courtesy of Dr. Judit Villar-García (Figure 1A), Dr Maria Fernanda Peña Vazquez (Figure 1B 1), Dr. Rodríguez Aldama (Figures 1B 3,4,6,7; Figures 1C), Dr Cecilia Agurto Lescano, Dr. Katty Chong Chinchay (Figure1B 5), Dr. Jenny Valverde (Figure 1 B2), Dr. Gonzalez Rodriguez (Figures 2 B8).

FIGURE 2. Complications stratified by CD4 count (A) and outcomes stratified by CD4 count (B) and viral load (C)

627 TABLE 1. BASELINE DEMOGRAPHIC DATA

		TOTAL n (%) N = 382	CD4 <100* N = 85	CD4 100-200 N =94	CD4 201-300 N =128	CD4 >300 N = 75
Age, median (IQR) years		35 (30-43)	35 (32-43)	35 (29 –42)	34(31-42)	36 (30-44)
Gender						
	cisgender women	4 (1.0%)	4 (4.7%)	0	0	0
	transgender women	10 (2.6%)	4 (4.7%)	3 (3.2%)	3 (2.3%)	0
	cisgender men	367(96.1%)	77 (90.6%)	91(96.8%)	125(97.7%)	74(98.7%)
	Non-binary individual**	1 (0.3%)	0	0	0	1 (1.3%)
Region where medical care was provided						
	Africa	6 (1.6%)	3 (3.5%)	1 (1.1%)	2 (1.6%)	0
	Europe	99 (25.9%)	20 (23.5%)	18 (19.1%)	39 (30.5%)	22 (29.3%)
	Latin-America	212 (54.5%)	37 (43.5%)	65 (69.1%9	67 (52.3%)	43 (57.3%)
	North-America	65 (17.0%)	22 (25.9%)	13 (13.8%)	19 (14.8%)	11 (14.7%)
Ethnicity						
	Asian	7 (1.8%)	1 (1.2%)	1 (1.1%)	3 (2.3%)	2 (2.7%)
	Black	55 (14.4%)	26 (30.6%)	10 (10.6%)	14 (10.9%)	5 (6.7%)
	Latin-American	225(58.9%)	44 (51.8%)	63 (67.0%)	76 (59.4%)	42(56.0%)
	Mixed	10 (2.6%)	0	1 (1.1%)	5 (3.9%)	4 (5.3%)
	White	85 (22.3%)	14 (16.5%)	19 (20.2%%)	30 (23.4%)	22 (29.3%)
HIV status						
	Previously known PLWH currently adherent to ARV	228 (59.7)	17(20%)	53 (56.4%)	100 (78.1%)	58(77.3%)
	Previously known PLWH not on ARV or non-adherent	121(31.6%)	53(62.3%)	33 (35.1%)	25(19.6%)	10 (13.3%)
	Newly diagnosed	33(8.6%)	15(17.6%)	8 (8.5%)	3 (2.3%)	7 (9.3%)

	with HIV infection					
CD4 count (cells/mm^3), median (IQR)		211(117-291)	47(27-77)	156 (125-184)	259 (221-280)	326 (316-338)
CD4 count among 27 people who died, (cells/mm^3), median (IQR)		35 (IQR 24-100)				
HIV viral load strata RNA copies/ml)						
	Not available	28(7.3%)	11 (12.9%)	4 (4.3%)	10 (7.8%)	3 (4%)
	<50	193 (50.5%)	14 (16.5%)	50(53.2%)	80 (62.5%)	49 (65.3%)
	50-200	26(6.8%)	3 (3.5%)	6 (6.4%)	8 (6.3%)	9 (12%)
	201-log4	30 (7.9%)	10 (11.8%)	6 (6.4%)	10 (7.8%)	4 (5.3%)
	≥log4	105 (27.5%)	47 (55.3%)	28 (29.8%)	20 (15.6%)	10 (13.3%)
History of mpox vaccination						
	Vaccination before 2022	16(4.2%)	2 (2.4%)	4 (4.3%)	7 (5.7%)	3 (4%)
	Third-generation vaccine for preexposure	21(5.9%)	4 (4.7%)	3 (3.2%)	9 (7.0%)	5 (6.7%)
	Third-generation vaccine postexposure	5 (1.3%)	1 (1.2%)	0 (0%)	3 (2.3%)	1 (1.3%)
Concurrent opportunistic infection						
	Oesophageal candidiasis	4 (1%)	3 (3.5%)	1 (1.1%)	0 (0%)	0 (0%)
	CMV end-organ disease	1 (0.3%)	1 (1.2%)	0 (0%)	0 (0%)	0 (0%)
	Disseminated herpes simplex	1 (0.3%)	1 (1.2%)	0 (0%)	0 (0%)	0 (0%)
	Histoplasmosis	2 (0.5%)	1 (1.2%)	0 (0%)	1 (0.8%)	0 (0%)
	Isosporosis	1 (0.3%)	1 (1.2%)	0 (0%)	0 (0%)	0 (0%)
	Kaposi Sarcoma	4 (1%)	2 (2.4%)	0 (0%)	2 (0.8%)	0 (0%)
	Disseminated Mycobacterium Avium Intracellulare	3 (0.8%)	2 (2.4%)	1 (1.1%)	0 (0%)	0 (0%)

	Pneumocystis jirovecci pneumonia	6 (1.6%)	5 (5.9%)	1 (1.1%)	0 (0%)	0 (0%)
	Toxoplasmosis	2 (0.5%)	1 (1.2%)	0 (0%)	1 (0%)	0 (0%)
	Tuberculosis	8 (2.1%)	5 (5.9%)	1 (1.1%)	2 (0.8%)	0 (0%)

PLWH = People living with HIV; ARV =Antiretroviral therapy; Third generation vaccine= MVA -BVN

**For the purpose of the table, seven individuals were classified as CD4 <100 cells/mm^3 despite not having formal CD4 counts: three individuals from Peru did not have information on CD4 counts due to lack of testing reagents but had CDC Stage C disease on the basis of an opportunistic infection; four patients from Nigeria were tested using a qualitative CD4 count test (Visitect CD4 Lateral Flow Assay, visually interpreted result of above or below 200 CD4 cells/ mm^3) with a result of <200 CD4 cells/mm^3.*

*** This non-binary individual was assigned male at birth.*

636 TABLE 2. CLINICAL DATA

		TOTAL n (%) N = 382	CD4 <100* N = 85	CD4 100-200 N =94	CD4 201-300 N =128	CD4 >300 N = 75
Mpox rash presentation						
Median peak number of skin lesions (IQR)		15 (8-35)	30 (15-100)	20 (12-35)	12 (6-20)	10 (4-15)
Median rash duration in days (IQR)		23 (18-33)	31 (21-45)	26 (19-40)	21 (16-28)	21 (15-30)
Mpox organ complications**						
Dermatological - skin lesions distant to the point of entry						
Overall		94 (24.6%)	49 (57.6%)	20 (21.3%)	18 (14.1%)	7 (9.3%)
	Large necrotizing lesions	84 (22.0%)	46 (54.1%)	19 (20.2%)	14 (10.9%)	5 (6.7%)
	Ecchymosis-haemorrhage	10 (2.6%)	3 (3.5%)	1 (1.1%)	4 (3.1%)	2 (2.7%)
Respiratory						
Overall**		35 (9.2%)	25 (29.4%)	5 (5.3%)	5 (3.9%)	0 (0%)
	Shortness of breath ǂ	12 (3.1%)	7 (8.2%)	2 (2.1%)	3 (2.3%)	0 (0%)
	Ground Glass Changes	3 (0.8%)	2 (2.4%)	1 (1.1%)	0 (0%)	0 (0%)
	Pleural effusion	6 (1.6%)	5 (5.9%)	0 (0%)	1 (0.8%)	0 (0%)
	Consolidation	4 (1.0%)	3 (3.5%)	0 (0%)	1 (0.8%)	0 (0%)
	Lung Nodules	11 (2.9%)	8 (9.4%)	2 (2.1%)	1 (0.8%)	0 (0%)
	Miliary Pattern	1 (0.3%)	1 (1.2%)	0 (0%)	0 (0%)	0 (0%)
CNS						
Overall		12 (3.1%)	9 (10.6%)	1 (1.1%)	0 (0%)	1 (1.3%)
	Encephalitis	1 (0.3%)	0 (0%)	1 (1.1%)	0 (0%)	0 (0%)
	Confusion	9 (2.4%)	9 (10.6%)	0 (0%)	0 (0%)	0 (0%)
	Facial palsy	1 (0.3%)	0 (0.0%)	0 (0%)	0 (0%)	1 (1.3%)
	Other: headache	1 (0.3%)	0 (0%)	1 (1.1%)	0 (0%)	0 (0%)
Bacterial infection						
Overall**		76 (23.2%)	37 (43.5%)	19 (20.2%)	13 (10.2%)	7 (9.3%)
	Non-genital cellulitis	29 (7.6%)	11 (12.9%)	6 (6.4%)	6 (4.7%)	6 (8.0%)
	Genital cellulitis	15 (3.9%)	3 (3.5%)	7 (7.4%)	5 (3.9%)	0 (0%)
	Skin Necrotising cellulitis	9 (2.4%)	6 (7.1%)	2 (2.1%)	1 (0.8%)	0 (0%)

	Pyomyositis or abscess	9 (2.4%)	5 (5.9%)	2 (2.1%)	1 (0.8%)	1 (1.3%)
	Sepsis	17 (4.5%)	15 (17.6%)	2 (2.1%)	0 (0%)	0 (0%)
Ocular						
Overall		20 (5.2%)	13 (15.3%)	6 (6.4%)	0 (0%)	1 (1.3%)
	Conjunctivitis	6 (1.6%)	2 (2.4%)	3 (1.1%)	0 (0%)	1 (1.3%)
	Peri-orbital Oedema	1 (0.3%)	1 (1.2%)	0 (0%)	0 (0%)	0 (0%)
	Keratitis	5 (1.3%)	4 (4.7%)	1 (3.2%)	0 (0%)	0 (0%)
	Periorbital cellulitis	8 (2.1%)	6 (7.1%)	2 (2.1%)	0 (0%)	0 (0%)
Local complications						
Ano-rectal						
Overall		126 (32.9%)	45 (56.5%)	28 (29.8%)	32 (25.0%)	21 (28%)
	Severe pain due to perianal lesions	44 (11.6%)	18 (21.2%)	7 (7.4%)	12 (9.4%)	7 (9.3%)
	Proctitis (anal involvement)	78 (18.4%)	25 (29.4%)	21 (22.3%)	19 (14.8%)	13 (17.3%)
	Rectal wall perforation	3 (1.3%)	2 (2.4%)	0 (0%)	0 (0%)	1 (1.3%)
	Necrotising Rectal Lesions	1 (0.3%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)
Oral						
Overall		85 (22.3%)	29 (34.1%)	23 (24.5%)	15 (11.7%)	18 (24.0%)
	Tonsillar disease affecting swallowing or airways	19 (5.0%)	8 (9.4%)	5 (5.3%)	3 (2.3%)	3 (4%)
	Lymphadenopathy affecting swallowing or airways	12 (3.1%)	5 (5.9%)	4 (4.3%)	2 (1.6%)	1 (1.3%)
	Throat pain without affecting swallowing or airways	54 (14.1%)	16 (18.2%)	14 (14.9%)	10 (7.8%)	14 (18.7%)
Genito-Urinary						
Overall		64 (16.8%)	29 (34.1%)	15 (16.0%)	13 (10.2%)	7 (9.3%)
	Difficulty passing urine or obstruction	12 (3.1%)	6 (7.1%)	4 (4.3%)	1 (0.8%)	1 (1.3%)
	Severe genital pain	7 (1.8%)	3 (3.5%)	1 (1.1%)	0 (0%)	3 (4%)
	Genital oedema	33 (8.6%)	11 (12.9%)	8 (8.5%)	11 (8.5%)	3 (4%)

	Necrotising genital lesions	12 (3.1%)	9 (10.6%)	2 (2.1%)	1 (0.8%)	0 (0%)
Highest Care-level						
	Outpatient	275 (72.0%)	32(37.6%)	69 (73.4%)	111 (86.7%)	63 (84.0%)
	Hospitalization in general ward	73 (19.1%)	26 (30.5%)	19 (20.2%)	16 (12.5%)	12 (16.0%)
	ICU-level#	34 (8.9%)	27 (31.8%)	6 (6.4%)	1 (0.8%)	0 0
Ultimate Outcome						
	Death #	27 (7.1%)	23 (27.1%)	4 (4.3%)	0	0
Organ Support						
Need for ventilation		21(5.5%)	16 (18.8%)	4 (4.3%)	1 (0.8%)	0
Indication for ventilation						
	Respiratory failure	17 (4.5%)	14 (16.5%)	2 (2.1%)	1 (0.8%)	0 (0%)
	Sedation	1 (0.3%)	0 (0%)	1 (1.1%)	0 (0%)	0 (0%)
	Low GCS/Coma	3 (0.8%)	2 (2.4%)	1 (1.1%)	0 (0%)	0 (0%)
Need for Inotropes		16 (4.2%)	13 (15.3%)	3 (3.2%)	0 (0%)	0 (0%)
Antimicrobial treatment						
	Antibiotics	144 (37.7%)	52 (61.2%)	34 (36.2%)	38 (29.7%)	20 (26.7%)
	Tecovirimat (oral)	52(13.6%)	21(24.7%)	11(11.7%)	15 (11.7%)	5 (1.5%)
	Tecovirimat (intravenous)	15 (3.9%)	13 (15.3%)	1 (1.1%)	1 (0.8%)	0 (0%)
	IVIG	6 (1.6%)	6 (7.1%%)	0 (0%)	0 (0%)	0 (0%)
	Cidofovir/Brincidofovir	7 (1.8%)	5 (5.9%)	2 (2.1%)	0 (0%)	0 (0%)
Genotypic resistance to Tecovirimat						
	Samples sequenced	5	4	1	0	0
	Presence of F13L mutations conferring resistance	3	3	0	0	0
Immune restitution inflammatory syndrome (IRIS)						
	Antiretroviral started or restarted	85 (22.3%)	40 (47.1%)	23 (24.5%)	15 (11.70%)	7 (9.3%)
	Deterioration consistent with IRIS	21 (5.5)	15(17.6%)	6 (6.4%)	0	0

	IRIS treatment provided	19 (5.0%) Steroids 9 NSAIDS 1 Supportive care 9	14 (16.5%) Steroids 8 NSAIDS 1 Supportive care 5	5 (5.3%) Steroids 1 NSAIDS 0 Supportive care 4	NA	NA

For the purpose of the table, seven individuals were classified as CD4 <100 cells/mm^3 despite not having formal CD4 counts: three individuals from Peru did not have information on CD4 counts due to lack of testing reagents but had CDC Stage C disease on the basis of an opportunistic infection; four patients from Nigeria were tested using a qualitative CD4 count test (Visitect CD4 Lateral Flow Assay, visually interpreted result of above or below 200 CD4 cells/mm^3) with a result of <200 CD4 cells/mm^3.

***The categories within a group of organ involvements are not mutually exclusive; therefore, an individual may present with multiple manifestations of the group.*

#All individuals who died received ICU-level care.

ǂ Among the 12 patients with dyspnoea, two had a normal chest X-ray, and ten either had no radiology examinations done or the report was unavailable.

Further detail on respiratory and IRIS cases in supplementary tables 1 and 3.

649 **TABLE 3. Detailed information about fatal cases**

650

Patient	Age	Region where medical care was provided	CD4 (cells/mm3)	HIV Viral Load (copies/ml)	HIV and ART Status	Opportunistic Infections	Peak number of lesions	Necrotising skin lesions	Bacterial Infections (Culture result when available)	Respiratory Complications	Ventilatory Support provided *	CNS Complications	Ocular Complications	Rectal Complications	Oropharyngeal Complications	MPX Antiviral Therapy	Started ARV on admission	Suspected IRIS (treatment)	Days from symptom onset to death	Cause of Death
1	35	Americas	32	Log 4	Known HIV but not adherent to ART	Oesophageal candidiasis	300	Yes	Pyomysitis/abscess (skin biopsy: K. Pneumoniae and P. aeruginosa)	None	No	None	None	Pain	Tonsilitis	None - Not available	No	No	51	Shock and Multi-organ failure
2	31	Europe	24	Log5	New diagnosis	None	100	Yes	None	Diffuse perivascular nodules (MPXV positive BAL specimen)	IMV	None	None	None	None	Oral and IV TPOXX, and IVIG	Yes	Yes (nsaids)	196	Shock and Multi-organ failure
3	33	Americas	17	Log 5	Known HIV not on ART	PCP*	100	Yes	Sepsis (blood: ESBL *E. Coli*)	Ground-glass opacification	IMV	None	Periorbital cellulitis	Pain	Lymphadenopathy	Oral and IV TPOXX, Cidofovir, and IVIG	Yes	Yes (steroids)	63	Shock and Multi-organ failure
4	46	Americas	57	Log 4	Known HIV not on ART	None	100	Yes	Sepsis	Ground-glass opacification (MPXV positive BAL specimen)	IMV	Confusion	None	Proctitis	Throat Pain	Oral and IV TPOXX, and IVIG	Yes	Yes (steroids)	87	Shock and Multi-organ failure
5	30	Americas	121	Log 5	New diagnosis	None	250	Yes	Non-genital cellulitis and sepsis	Diffuse perivascular nodules	IMV	None	Periorbital cellulitis	Proctitis	Tonsilitis	None - Not available	Yes	Yes (Supportive care)	47	Shock and Multi-organ failure
6	44	Americas	106	Log 5	Known HIV not on ART	None	100	Yes	Non-genital cellulitis and sepsis	Diffuse perivascular nodules	IMV	Encephalitis	Periorbital cellulitis	Proctitis	Throat Pain	None - Not available	Yes	Yes (Supportive care)	49	Shock and Multi-organ failure
7	37	Americas	25	<50	Known HIV not on ART	Oesophageal candidiasis	150	Yes	Necrotising Cellulitis and sepsis (Swab: *K. pneumoniae, E. faecalis*)	Diffuse perivascular nodules	IMV	Confusion	None	Proctitis	Tonsilitis	None - Not available	Yes	Yes (Supportive care)	38	Respiratory Failure
8	34	Europe	13	Log 5	Known HIV not on ART	None	25	Yes	Perianal and rectal abscesses and sepsis (Blood: ESBL *E. Coli*)	Diffuse perivascular nodules and pleural effusion (MPXV PCR positive in transthoracic lung biopsy)	NIMV	None	Keratitis	Perforation	Lymphadenopathy	Oral and IV TPOXX, and Cidofovir	Yes	Yes (steroids)	117	Shock and Multi-organ failure

9	41	Americas	7	Log 5	Known HIV not on ART	None	200	Yes	Sepsis	Diffuse perivascular nodules	IVM	None	None	None	None	None – Not available	No	No	15	Respiratory Failure
10	41	Americas	171	Log 6	Known HIV not on ART	PCP*	30	Yes	Sepsis	Ground-glass opacification and large lung cavity	No	None	None	Proctitis	Tonsilitis	None – Not available	No	No	18	Shock and Multi-organ failure
11	32	Americas	Unknown	Log 5	Known HIV not on ART	PCP*	20	Haemorrhagic	Sepsis	Consolidation	No	Confusion	Periorbital cellulitis	Proctitis	Lymphadenopathy	None – Not available	No	No	39	Shock and Multi-organ failure
12	23	Americas	Unknown	Unknown	New diagnosis	PCP*	15	Yes	Genital cellulitis	Consolidation	No	None	None	Pain	Throat Pain	None – Not available	No	No	18	Respiratory Failure
13	32	Americas	Unknown	Unknown	Known HIV not on ART	TB*	10	Yes	None	Diffuse perivascular nodules	IMV	None	None	Proctitis	Throat Pain	None – Not available	No	No	32	Shock and Multi-organ failure
14	35	Europe	33	Log 6	New diagnosis	Visceral leishmaniasis	150	Yes	Necrotising Cellulitis (Blood: *P. aeruginosa*)	None	IMV	None	None	Pain	Lymphadenopathy	IV TPOXX	Yes	Yes (steroids)	87	Respiratory Failure
15	46	Americas	6	Log 5	Known HIV but not adherent to ART	Kaposi Sarcoma	50	Yes	Sepsis	Pleural Effusion	IMV	Confusion	None	Proctitis	None	None - Not available	No	No	40	Shock and Multi-organ failure
16	40	Africa	99	Unknown	Known HIV not on ART	TB (pulmonary)*	200	Yes	Sepsis	Consolidation, multilobar	No	None	None	Pain	None	None - Not available	Yes	Unknown	26	Shock and Multi-organ failure
17	47	Americas	32	Log 4	New diagnosis	None	Not known	Yes	Gluteal abscess & Sepsis (Blood: *P. aeruginosa*)	None	No	None	Keratitis	Pain	None	Oral TPOXX, Cidofovir and IVIG	Yes	No	94	Shock and Multi-organ failure
18	41	Americas	10	Log 5	Known HIV not on ART	None	Not known	Yes	Sepsis (Blood: *P. aeruginosa, Clostridum sporogenes*)	Shortness of Breath - Respiratory Failure	IMV	None	Periorbital cellulitis	Pain	Tonsilitis	Oral and IV TPOXX, Cidofovir, and IVIG	Yes	Yes (steroids)	85	Disseminated mpox
19	32	Americas	58	Log 5	Known HIV not on ART	Oesophageal candidiasis	Not known	No	Non-genital cellulitis	Pleural effusion	No	Confusion	Peri-orbital oedema	None	Tonsilitis	Oral and IV TPOXX, and Brincidofovir	Yes	No	78	Cardiac Arrest
20	34	Americas	115	Log5	Known HIV not on ART	None	35	Yes	Sepsis	Shortness of Breath	No	None	None	Pain	None	None - Not available	No	No	26	Shock and Multi-organ failure
21	38	Americas	70	Log5	Known HIV not on ART	None	32	No	Sepsis	Shortness of Breath	IMV	None	Conjunctivitis	Pain	None	None - Not available	Yes	Yes (Supportive care)	71	Shock and Multi-organ failure
22	32	Americas	23	Log5	Known HIV not on ART	CMV retinitis	23	Yes	Sepsis	None	No	None	None	Pain	None	None - Not available	Yes	Unknown	78	Shock and Multi-organ failure
23	48	Africa	90	Unknown	Known HIV but not adherent to ART	TB (disseminated)	1000	Yes	Sepsis (Swab: *K. pneumoniae, P aeruginosa*)	Shortness of breath	NIMV	None	Keratitis	None	Throat Pain	None – Not available	Yes	No	25	Shock and Multi-organ failure
24	45	Africa	110	Unknown	Known HIV not on ART	None	1000	Yes	Sepsis	Shortness of Breath	NIMV	None	Periorbital cellulitis	None	None	None – Not available	No	No	4	Shock and Multi-organ failure

25	28	Africa	99	Unknown	Known HIV not on ART	TB (pulmonary)	1000	Yes	None	Shortness of breath	No	Confusion	Keratitis	None	Throat Pain	None – Not available	No	No	4	Shock and Multi-organ failure
26	29	Americas	35	Log5	New diagnosis	None	50	Yes	Necrotising Cellulitis & sepsis (Blood: Polymicrobial)	Pleural effusion	IMV	Confusion	Periorbital cellulitis	Proctitis	Tonsilitis	Oral and IV TPOXX, and IVIG	Yes	Yes (supportive care)	83	Disseminated mpox
27	33	Americas	35	Log4	Known HIV not on ART	None	50	Yes	Non-genital cellulitis	Pleural effusion & ulcerative lesions on the trachea (MPXV PCR positive on BAL specimen)	IMV	None	None	Proctitis and Bowel obstruction	Throat pain	IV TPOXX	Yes	Yes (steroids)	46	Shock and Multi-organ failure

651

652 Legend: All deceased individuals were cis male, except for patient 16 and 24 that were cis female.

653 None had received smallpox vaccination before 2022 or had been vaccinated as pre-exposure or post-exposure since May 2022. * Since

654 ventilation was often unavailable, answering "no" does not necessarily mean it was not needed.

655 IMV – Invasive Mechanical Ventilation, NIV – Non-Invasive Ventilation

656 *Clinical suspicion, not microbiological confirmation