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3

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

6

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75

76 **KEY WORDS**

77 Monkeypox; Monkeypox virus; MPXV; HIV; immunosuppression; mpox; AIDS, CD4, IRIS

78 **ABSTRACT 350**

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

84 **Methods.** A network of clinicians from 19 countries provided data from confirmed mpox  
85 cases between May 11 and Jan 18 , 2023, in persons with HIV infection and CD4 counts <350  
86 cells/ mm<sup>3</sup>. We describe their clinical presentation, complications, and causes of death.  
87 Analyses were descriptive.

88 **Findings.** We include data of 382 cases: 367 cisgender men, 4 cisgender and 10 transgender  
89 women with a median age of 35 years. At mpox diagnosis, 349 (91.4%) were known to be  
90 living with HIV; 228/349 (65.3%) adherent to antiretroviral therapy (ART); 32/382 (8.4%) had  
91 a concurrent opportunistic illness. The median CD4 count was 211 cells/mm<sup>3</sup> (IQR 117-291);  
92 with 85 (22.3%) individuals with CD4 counts <100 cells/mm<sup>3</sup>, and 94 (24.6%) 100-200  
93 cells/mm<sup>3</sup>. Of those with HIV viral load data available, 193/354 (54.5%) were undetectable.  
94 Severe complications were more common in persons with CD4<100 compared to those with  
95 >300 cells/mm<sup>3</sup>, including necrotising skin lesions (54.1% vs. 6.7%), lung involvement (29.4%  
96 vs. 0%) occasionally with nodules, and secondary infections and sepsis (43.5% vs. 9.3%).  
97 Overall, 107/382 (28.0%) were hospitalised of whom 27/107 (25.2%) died. All deaths  
98 occurred in those with CD4 counts <200 cells/mm<sup>3</sup>. Amongst those with CD4 counts <200  
99 cells/mm<sup>3</sup> more deaths occurred in those who also had high a HIV viral load. An immune  
100 reconstitution inflammatory syndrome to mpox was suspected in 21/85 (24.7%) persons

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

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

107 **Funding.** None

108

109 **RESEARCH IN CONTEXT 635**

110 *Evidence before this study*

111 In 2022, mpox, a disease caused by an orthopox virus referred to as monkeypox virus (MPXV)  
112 has caused outbreaks in 110 countries. Two distinct clades of MPXV, Clade I and Clade II, have  
113 existed in different geographic regions. The subclade IIb, identified in the 2022 outbreak,  
114 originates from subclade IIa mpox, which is considered a self-limiting disease. Unlike the  
115 previous epidemiological descriptions in West Africa, mpox transmission in this outbreak has  
116 been closely associated with the sexual networks of gay-and-bisexual men-who-have-sex-  
117 with-men (GBMSM), in which a high proportion of people are living with HIV. Some evidence  
118 suggests greater disease severity in people with advanced HIV. This finding warrants careful  
119 evaluation of the interplay between HIV, immune status and clinical manifestations of mpox.  
120 We searched PubMed for the terms “monkeypox, mpox AND (HIV)” from inception to Dec 31,  
121 2022. Publications were predominantly letters, perspectives, case reports, and public health  
122 agency reports. In the multi-country outbreak, scientific publications of case series have  
123 described similar clinical outcomes in people living with HIV to those in people without HIV  
124 infection. However, most cases series included people with HIV and high CD4 counts (> 500  
125 cells/mm<sup>3</sup>) and suppressed HIV viral loads. In contrast, a Nigerian case series in the 2017-18  
126 outbreak reported that more severe outcomes in hospitalized people were observed in  
127 persons living with HIV especially those who were viraemic and immunosuppressed. In a  
128 Center for Disease Control (CDC) report on 758 mpox cases in persons living with HIV during  
129 the multi-country outbreak (median CD4 639 cells/mm<sup>3</sup>; 3% < 200/mm<sup>3</sup>) 10% (68/758) were  
130 hospitalized for a median duration of 2 days (0-7). Worse rectal symptoms were described in  
131 those with HIV. A second CDC report identified adverse outcomes in 47 people with HIV and

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

136

#### 137 *Added value of this study*

138 This mpox case series is the largest in those with advanced HIV disease. We characterized  
139 382 persons with HIV and CD4 < 350 cells/mm<sup>3</sup>. Individuals with lower CD4 counts  
140 presented with widespread, large, necrotising, and coalescing skin lesions. Some individuals  
141 also developed lung nodules without an alternative confirmed or suspected diagnosis.  
142 Severe secondary bacterial infections were common. Frequent and severe oral, ano-genital,  
143 and ocular presentations and complications are described. Immune reconstitution  
144 inflammatory syndrome (IRIS) was suspected in a quarter of those starting or re-initiating  
145 antiretroviral therapy (ART) after mpox diagnosis, 57% of whom died. The greatest disease  
146 severity, hospitalisation, and mortality was observed in individuals with both low CD4 count  
147 and high HIV viral load. This international case series includes 27 of the 60 persons reported  
148 to have died of mpox in the multi-country outbreaks, all 27 are persons with HIV and CD4 <  
149 200 cells/mm<sup>3</sup>.

150

#### 151 *Implications of all the available evidence*

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



155 cutaneous lesions, systemic complications, and mortality in those with CD4 cell counts <200  
156 cells/mm<sup>3</sup>. Clinicians should also be aware that starting ART in people with advanced HIV and  
157 mpox may contribute to deterioration and possible death, possibly as part of an immune  
158 reconstitution syndrome. Our data reinforces the importance of HIV testing in mpox cases.  
159 Our findings support the recommendations that all at-risk persons with HIV with a CD4 count  
160 <200 cells/mm<sup>3</sup> should be prioritised for preventive mpox vaccination. There should also be  
161 consideration for use of potential mpox antivirals where available despite lacking data on  
162 their effectiveness and a concerted global effort to ensure access in countries without access  
163 to antivirals and vaccines.

164 **BODY TEXT**

165 **INTRODUCTION 313**

166 Since May, 2022, around 85,000 human mpox infections have been reported in 110 countries,  
167 with transmission predominantly through sexual contact amongst GBMSM.<sup>1</sup> The multi-  
168 country outbreak was declared a Public Health Emergency of International Concern (PHEIC)  
169 by the World Health Organisation (WHO) in July 2022.<sup>2</sup> People with HIV, accounting for 38-  
170 50% of persons diagnosed with mpox,<sup>3</sup> have been disproportionately affected.<sup>3</sup> Most persons  
171 living with HIV described in the 2022 case series had HIV viral suppression with median CD4  
172 counts >500 cells/mm<sup>3</sup> and had similar clinical presentations, time to viral clearance, and  
173 outcomes to persons without HIV.<sup>4-13</sup>

174

175 Data from Nigeria and the USA suggest worse clinical outcomes in those with more HIV-  
176 related immunosuppression.<sup>4,14,15</sup> Two reports from Nigeria during the 2017-2018 outbreak  
177 suggested that people with advanced HIV presented with more severe or prolonged mpox.  
178 The first described that 4 of 7 deaths in 122 individuals with mpox, occurred in people with  
179 untreated advanced HIV.<sup>14</sup> The second report included 9 people with HIV with CD4 cell counts  
180 ranging from 20 to 357 cells/mm<sup>3</sup>.<sup>15</sup> The authors described confluent rashes, higher rates of  
181 secondary bacterial infections and more prolonged illness.<sup>15</sup> More recently, a report from the  
182 US-CDC during the 2022 outbreak, confirmed these finding in 47 cases of severe mpox among  
183 people with advanced uncontrolled HIV infection.<sup>16</sup> All were hospitalized, had prolonged  
184 disease courses, or developed complications, and some had fatal outcomes (i.e., 5 deaths  
185 attributed to mpox).<sup>16</sup> Worse rectal disease was described in another CDC series in which  
186 82% of people living with HIV were on ART and 72% were virally suppressed.<sup>4</sup>

187

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

192

## 193 **METHODS**

### 194 *Case definition and identification*

195 Participating clinicians were recruited through the international research networks of the  
196 London-based Sexual Health and HIV All East Research (SHARE) Collaborative and the  
197 Network of the Skin Neglected Tropical Diseases and Sexually Transmitted Infections Unit of  
198 the Hospital Germans Trias i Pujol in Spain.<sup>8-10</sup> Researchers in geographic locations with  
199 high numbers of mpox diagnoses were approached and invited to contribute mpox cases  
200 diagnosed between May 11, 2022, and January 18, 2023. A confirmed case was defined as a  
201 polymerase-chain-reaction (PCR)-confirmed MPXV infection in a specimen from any  
202 anatomical site. We restricted this series to adults older than 18 years living with HIV and  
203 CD4 <350 cells/mm<sup>3</sup> or, in settings where a CD4 count was not always routinely available,  
204 HIV infection clinically classified as CDC stage C. We included people living with HIV and CD4  
205 counts <350 cells/mm<sup>3</sup> in line with the widely accepted 2010 consensus statement which  
206 defines late presentation of HIV as CD4 <350 cells/mm<sup>3</sup> or an AIDS-defining illness.<sup>17</sup>

207

208 CD4 count was categorised as <100, 101-200, 201- 300, and 301-350 cells/mm<sup>3</sup>, because CD4  
209 count cut-offs of 100 and 200 are associated with different risk for opportunistic infections  
210 (e.g, cryptococcal meningitis is associated with CD4 < 100 cells vs. *Pneumocystis jirovecci*  
211 pneumonia (PJP) or toxoplasmosis <200 cells).<sup>18</sup> For strata comparison, we grouped the seven  
212 individuals with a missing CD4 count with those who had a CD4 count < 100 cells/mm<sup>3</sup>. Three  
213 of these had an AIDS-defining condition and four had a positive point-of-care qualitative CD4  
214 count test [Visitect CD4 Lateral Flow assay providing a visually interpreted result of above 200  
215 (negative)- or below 200 (positive)]. HIV viral load (VL) was categorised as undetectable (<50  
216 copies/mL), 50-200 (low level viraemia), 200-<log<sub>4</sub>, ≥log<sub>4</sub> log RNA copies/ml. We categorised  
217 the presence or absence of clinician reported complications by organ system.

218

#### 219 *Data collection*

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

230

231 *Ethical considerations*

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

238

239 *Statistical analysis*

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

246

247 *Funding*

248 There was no specific funding for this study.

249

250 **RESULTS**

251 We describe 382 cases of human mpox infection in persons living with HIV with CD4 <  
252 350/mm<sup>3</sup> from sites in 19 countries (10 in Europe, 8 in the Region of the Americas, and 1 in  
253 Africa) (**Supplementary Figure 2**). Most (72.5%; 277/382) were originally from the Americas

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

257

258 The demographic and epidemiological characteristics of the participants are described  
259 in **Table 1**. The median age was 35 years (IQR 30–43). Three hundred and sixty-seven out of  
260 382 (96.1%) identified as cisgender men, 4 cisgender women (1.0%), 10 transgender women  
261 (2.6%), and 1 non-binary individual assigned male at birth (0.3%). The ethnicity or race of  
262 participants as described by the attending clinician was Black 14.4% (55/382), Latin-American  
263 58.9% (225/382), or White 22.3% (85/382).

264

265 Overall, 349/382 (91.4%) were known to be living with HIV prior to mpox diagnosis, and  
266 33/382 (8.6%) were newly diagnosed with HIV infection at the time of the MPXV infection. Of  
267 those known to be living with HIV, 84.5% (295/349) were on ART and 65.3% (228/349) were  
268 reported as adherent to treatment in the preceding six months. The median CD4 cell count  
269 was 211 cells/mm<sup>3</sup> (IQR 117-291). The distribution of CD4 counts was as follows: 85 (22.3%)  
270 <100 cells/mm<sup>3</sup>, 94(24.6%) 100-200 cells/mm<sup>3</sup>, 128(33.5%) 201-300 cells/mm<sup>3</sup>, and 75  
271 (19.6%) 301-350 cells/mm<sup>3</sup>. CD4 counts were missing in 7 individuals who were assigned to  
272 the group with CD4 <100 cells/mm<sup>3</sup> as described in the methods and in **Table 1,2,3**. Overall,  
273 193 individuals (50.5%) were virally suppressed (HIV RNA <50 copies /ml), 26 (6.8%) had low-  
274 level HIV viraemia (50-200 copies/ml), 30 (7.9%) had viraemia from 200 to log<sub>4</sub> copies/ml,  
275 and 105 (27.5%) had viraemia of > log<sub>4</sub> copies/ml. HIV RNA values taken within the past 6

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

278  
279 In terms of clinical presentations (Table 2), 243/382 (63.6%) patients had fever and 364  
280 (95.3%) had a skin rash, which was initially vesiculo-pustular in 297/382 (77.7%) and  
281 progressed to ulcerative in 84/382 (22.0%). The median number of skin lesions was 15 (IQR  
282 8-35), and the median duration to resolution was 23 (IQR 18-33) days. Among 36 patients  
283 (9.4%) who had 100 or more lesions and 43 patients (11.3%) who had a duration to resolution  
284 of forty days or more, the majority had CD4 counts <200 cells/mm<sup>3</sup> and detectable HIV plasma  
285 viral loads (Supplementary Figure 3 & 4). Overall, 235 individuals (61.5%) had genital, 203  
286 (53.1%) anal lesions, 144 (37.7%) oral involvement and 20 (5.2%) had ocular involvement. The  
287 most common organ complications were dermatological, respiratory, and secondary bacterial  
288 infection (Table 2). A total of 94/382 (24.6%) patients developed dermatological  
289 complications; 10 (2.6%) of these were ecchymotic or haemorrhagic lesions, and 84 (22.0%)  
290 were necrotising lesions, of which 55 (14.4%) were coalescing. The most common  
291 presentation was multiple, large (typically greater than 2cm in diameter), rounded ulcers with  
292 necrotic centres and a fresh, raised border, located close to the oro-genital regions (Figure  
293 1B. Photographs B1-4) or in distant locations (Figure 1B. B6-8), while verrucous appearance  
294 (Figure 1B. B5) was rare. In many instances, erythema and oedema surrounded the ulcer.  
295 Lesions involving the mouth, eye, or anus resulted in functional impairment (B1-4). In the  
296 anogenital region, some individuals presented with significant tissue damage and phagedenic  
297 ulcerations (Figure 1C). Some persons had progression to target-shaped lesions with  
298 erythema, swelling and pallor beyond the margins of the ulcer indicating severe necrosis.  
299 (Figure 1C) Pseudo Koebner phenomena (i.e., the spread of the skin infection along sites with

300 skin microtrauma or rubbing) were manifested by ulcers exhibiting a lineal distribution or  
301 overlying bony prominences . In cases where epithelialization had occurred, tissue  
302 destruction resulted in disfiguring scarring ([Supplementary Figure 5 &6, and Dermatology](#)  
303 [Atlas](#)).

304

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

315

316 12/35 (34.3%) individuals with respiratory complications had dyspnoea of whom - two had  
317 normal chest X-rays, and ten had no available radiology report. Additionally, 6/35 (17.1%)  
318 individuals presented with pleural effusion (1 with a positive MPXV PCR on BAL), and 3/35  
319 (8.6%) with ground glass changes (2 with suspected opportunistic infections; 1 with a positive  
320 MPXV PCR on BAL).

321



322 Twelve (3.1%) individuals were reported to have neurological involvement (Supplementary  
323 Table 2), including one (0.3%) case classified as encephalitis with orbital, frontal and temporal  
324 oedema on CT scan, and with a positive MPXV PCR result, and negative HSV-1 and 2, and VZV  
325 results in cerebro-spinal fluid (CSF). Of the nine (2.4%) cases with altered mental status or  
326 confusion six had normal CSF and/or radiological findings and three did not undergo imaging  
327 or CSF examination. In five cases confusion was attributed to sepsis, in one to respiratory  
328 failure in one to hepatic encephalopathy, and the cause was undetermined in two cases.  
329 Neurological symptoms were almost exclusively described in persons with HIV with CD4 less  
330 than 100 cells/mm<sup>3</sup>.

331

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

339

340 All complications were more common in individuals with CD4<100 compared to individuals  
341 with CD4>300 cells/mm<sup>3</sup>. This included dermatological (57.6% vs. 9.3%), respiratory (29.4%  
342 vs. 0%), CNS (10.6% vs. 1.3%), bacterial infection (43.5% vs. 9.3%), ocular (15.3% vs. 1.3%),  
343 gastrointestinal (27.1% vs. 6.7%), rectal complications (56.5% vs. 28.0%), oropharyngeal  
344 (34.1% vs. 24.0%), and genito-urinary 34.1% vs. 9.3%) (Figure 2A).

345

346 Overall, 107/382 (28.0%) individuals were hospitalised; of these, 7 (1.8%) survived an  
347 admission to intensive care and 27 (7.1%) died (Table 3). Among the 27 people who died,  
348 the median CD4 count was 35 cells/mm<sup>3</sup> (IQR 24-100), and the median HIV viral load was 5  
349 log copies/ml (IQR 4-5), only one patient was HIV virologically suppressed. Among those  
350 who died, severe necrotising or haemorrhagic skin lesions occurred in 25/27 (92.6%),  
351 bloodstream or deep tissue bacterial infections (24/27; 88.9%), respiratory symptoms and  
352 respiratory failure (23/27; 85.2%), neurological (8/27; 29.6%), rectal (21/27; 77.8%), and  
353 oropharyngeal (18/27; 66.7%) involvement were described (Table 3). Ocular disease  
354 occurred in (13/27; 48.1%), 8 of whom had peri-orbital cellulitis. The reported cause of  
355 death was septic shock and multi-organ failure in 20/27 (74.15%), respiratory failure 4/27  
356 (14.8%), disseminated mpox in 2/27 (7.4%) and cardiac arrest in 1/27 (3.7%).

357

358 Rate of hospitalisation and ICU admission increased with declining CD4 counts and rising viral  
359 loads (Figure 2). No deaths occurred in individuals with CD4 counts >200cells/mm<sup>3</sup>. Mortality  
360 was incrementally higher among people in the lowest CD4 strata (CD4<100 27.1% vs. CD4  
361 100-200 4.3% vs. CD4>200 0%; Figure 2B) and amongst those with the highest viral loads (HIV  
362 VL log<sub>10</sub>≥4 16.2% vs. HIV VL undetectable 0.5%; Figure 2C). In those with CD4 count <100  
363 cells/mm<sup>3</sup> (n=85) and available HIV VL, the death rate was 7.1% (1/14) for individuals with VL  
364 <50 copies/ml and 29.8% (14/47) for those with HIV VL ≥4 log copies/ml.

365

366 Among 85 persons started or restarted on ART, in 21 (24.7%) the managing clinician  
367 suspected IRIS as a cause for clinical deterioration (Supplementary Table 3). Of these, 6

368 (28.6%) were newly diagnosed and 15 (71.4%) were known to be living with HIV but either  
369 not receiving or not adherent to ART. All had CD4 count <200 cells/mm<sup>3</sup>. The median time  
370 from onset of mpox symptoms to the start of ART was 21 days (range 0-73), and from the  
371 start of ART to worsening of mpox symptoms was 14 days (range 3-64). Nine of 21 (42.9%)  
372 were treated for IRIS with steroids, and 10 (47.6%) received supportive care. Of those with  
373 suspected IRIS, 3/21 (14.3%) were admitted to the ICU, 5 (23.8%) were hospitalised in a  
374 general ward, and 12 (57.1%) died.

375

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

386

## 387 **DISCUSSION**

388 Our large case series describes a severe, disseminated form of mpox infection with 15%  
389 mortality in individuals with advanced HIV-related disease characterised by CD4 counts below  
390 200 cells/mm<sup>3</sup>. This fulminant form of mpox is characterized by massive necrotising skin,

391 genital and non-genital cutaneous and mucosal lesions, sometimes accompanied by lung  
392 involvement with multifocal nodular opacities or respiratory failure, severe cutaneous and  
393 bloodstream secondary bacterial infections. The severity of oral and anogenital complications  
394 are more marked than previously described.<sup>4-10,19</sup> As described in the CDC classification,  
395 disseminated forms of coccidioidomycosis, histoplasmosis and mycobacterium avium complex  
396 are considered to be AIDS-defining illnesses.<sup>20</sup> Very similarly, we describe that people with  
397 the lowest CD4 counts (<100 cells/mm<sup>3</sup>) and highest HIV viral loads (> 4log c/ml) had  
398 disseminated forms of mpox strongly suggesting that this severe necrotising form of mpox  
399 with systemic involvement is also an AIDS-defining condition (Supplement Table 4).<sup>20</sup> We  
400 describe in detail the clinical course of 27 people with CD4 counts < 200 cells/mm<sup>3</sup> who died,  
401 representing more than 40% of all mpox deaths reported in 2022. We also wish to raise  
402 awareness of the 57% mortality rate in those in whom IRIS was suspected following ART  
403 initiation/re-initiation.

404

405 This data builds on the observations of the altered natural history and course of mpox that is  
406 emerging. To date most information about the intersection of HIV and mpox reports on those  
407 with well-controlled HIV infection.<sup>4-11</sup> During the 2022 multi-country outbreak even the  
408 largest series include very few people living with HIV and CD4 counts < 350/mm<sup>3</sup> (12%) or  
409 <200/mm<sup>3</sup> (3%).<sup>4,21,22</sup> We hypothesized that mpox may have a different clinical presentation  
410 in individuals with advanced immunosuppression, as can be the case with some pathogens.  
411 Although the self-limiting clinical course in individuals with well-controlled HIV is very similar  
412 to that of individuals without HIV, our series provides evidence that the disease is very  
413 different in those with advanced HIV. The protracted duration and larger number of skin

414 lesions in these individuals also raises the possibility of a more prolonged period of infectivity,  
415 but further studies are needed to investigate this.

416

417 Prior work has shown that people living with HIV with high CD4+ T-cell counts (>350 cells/  
418 mm<sup>3</sup>) mount a poxvirus-specific T-cell response that is similar to those without HIV infection,<sup>23</sup>  
419 but there are no data on immunological responses in those with low CD4 counts (<350 cells/  
420 mm<sup>3</sup>). In our series low CD4 cell count especially when < 200/mm<sup>3</sup> was strongly associated  
421 with increasing severity of mpox disease relative to those with CD4 200-350/mm<sup>3</sup> and  
422 compared to previous reports where CD4 > 500/mm<sup>3</sup>. Data from animal model MPXV studies  
423 have shown that CD4 depletion before immunisation of non-human primates decreased the  
424 development of protective B-cell responses and antibodies, and increased infection  
425 severity after monkeypox virus challenge, which is consistent with our findings.<sup>24</sup> Moreover,  
426 in our series, the effect of a low CD4 count on severity or death varied with the HIV plasma  
427 viral load, with higher viral loads associated with increased frequency of severe illness in any  
428 given CD4 group. Prior work has shown that replicating HIV virions target antigen-specific T  
429 cells that are activated to combat other pathogens, resulting in impaired T-cell responses.<sup>25-</sup>  
430 <sup>27</sup> Thus, it is possible that a substantial fraction of MPXV-specific CD4 T cells might die or be  
431 impaired due to either complete or abortive HIV infection. Others have shown impaired  
432 immune responses to hepatitis B and other vaccines in those with low CD4 and unsuppressed  
433 HIV virus replication, providing further evidence that HIV replication may interfere with  
434 immune response to other pathogens.<sup>27,28</sup> Based on our findings we believe that a severe  
435 necrotising form of mpox with systemic manifestations exists. This form of mpox affected  
436 those with CD4 counts <200 cells/mm<sup>3</sup> - the precise CD4 threshold considered to be AIDS-

437 defining in international guidelines (Supplement table 4). Given the 15% mortality in this  
438 group, strong consideration should be given to designating this disseminated form of severe  
439 mpox as a new AIDS-defining condition in definitions and guidelines.

440

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

460 opportunistic pathogen, may be a manifestation of mpox disease and further research is  
461 warranted.

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

469

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

482

483 Our data also reinforces the recommendation that HIV testing (in addition to other sexual  
484 transmitted pathogens) be performed in every case of mpox. Further those with HIV  
485 infection and high risk for mpox infection should be prioritised for preventive vaccine. Two  
486 thirds of the deaths we have reported have occurred in Latin America. Our findings are  
487 particularly pertinent for countries with low levels of HIV diagnosis and/or without universal  
488 free access to ART and intensive care units, where the interaction of uncontrolled HIV  
489 infection and mpox is more prevalent. In these countries, a concerted effort to provide  
490 urgent access to mpox antivirals and vaccines is of vital importance.

491

#### 492 **CONTRIBUTORS**

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

501

#### 502 **DATA SHARING**

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

505



506 **DECLARATION OF INTERESTS**

507 We declare no competing interests.

508

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594

595

596 **FIGURE LEGENDS**

597

598 **FIGURE 1. Skin presentation of mpox in advanced HIV disease**

599

600 **Panel A:** Disease progression in a patient with CD4 count of 18 cell/mm<sup>3</sup> and viral load log<sub>5</sub>,  
601 with pcr- confirmed lung involvement, bowel perforation, IRIS, and death despite having  
602 received two courses of IV tecovirimat and one course of IV cidofovir.

603

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

615

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

619

620 Credits: Pictures courtesy of Dr. Judit Villar-García (Figure 1A), Dr Maria Fernanda Peña  
621 Vazquez (Figure 1B 1), Dr. Rodríguez Aldama (Figures 1B 3,4,6,7; Figures 1C), Dr Cecilia Agurto  
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623 Rodriguez (Figures 2 B8).

624

625

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

628

629

630 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%)	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 <sup>3</sup> ), 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 <sup>3</sup> ), 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-log <sub>4</sub>	30 (7.9%)	10 (11.8%)	6 (6.4%)	10 (7.8%)	4 (5.3%)
	≥log <sub>4</sub>	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%)



	<i>Pneumocystis jirovecii pneumonia</i>	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%)

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

632 *\*For the purpose of the table, seven individuals were classified as CD4 <100 cells/mm<sup>3</sup> despite not having formal*  
633 *CD4 counts: three individuals from Peru did not have information on CD4 counts due to lack of testing reagents*  
634 *but had CDC Stage C disease on the basis of an opportunistic infection; four patients from Nigeria were tested*  
635 *using a qualitative CD4 count test (Visitect CD4 Lateral Flow Assay, visually interpreted result of above or below*  
636 *200 CD4 cells/ mm<sup>3</sup>) with a result of <200 CD4 cells/mm<sup>3</sup>.*

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

638

639 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
Gastrointestinal						
Overall		55 (14.4%)	23 (27.1%)	14 (14.9%)	13 (6.4%)	5 (6.7%)
	Diarrhoea	38 (9.9%)	15 (17.6%)	9 (9.6%)	10 (7.8%)	4 (5.3%)
	Gastrointestinal Bleeding	20 (5.2%)	6 (7.1%)	7 (7.4%)	4 (3.1%)	3 (4%)
	Obstruction	6 (1.6%)	1 (1.2%)	2 (2.1%)	2 (1.6%)	1 (1.3%)
	Oesophagitis	11 (2.9%)	7 (8.2%)	3 (3.2%)	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	3	3	0	0	0

	conferring resistance					
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

640 \*For the purpose of the table, seven individuals were classified as CD4 <100 cells/mm<sup>3</sup> despite not having formal  
641 CD4 counts: three individuals from Peru did not have information on CD4 counts due to lack of testing reagents  
642 but had CDC Stage C disease on the basis of an opportunistic infection; four patients from Nigeria were tested  
643 using a qualitative CD4 count test (Visitect CD4 Lateral Flow Assay, visually interpreted result of above or below  
644 200 CD4 cells/mm<sup>3</sup>) with a result of <200 CD4 cells/mm<sup>3</sup>.

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

647 #All individuals who died received ICU-level care.

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

650

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

652 TABLE 3. Detailed information about fatal cases

653

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	Pyomyositis/abscesses (skin biopsy: <i>K. Pneumoniae</i> and <i>P. aeruginosa</i> )	None	No	None	None	Pain	Tonsillitis	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	PJP*	100	Yes	Sepsis (blood: ESBL <i>E. Coli</i> )	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	Tonsillitis	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: <i>K. pneumoniae</i> , <i>E. faecalis</i> )	Diffuse perivascular nodules	IMV	Confusion	None	Proctitis	Tonsillitis	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 <i>E. Coli</i> )	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	PJP*	30	Yes	Sepsis	Ground-glass opacification and large lung cavity	No	None	None	Proctitis	Tonsillitis	None – Not available	No	No	18	Shock and Multi-organ failure
11	32	Americas	Unknown	Log 5	Known HIV not on ART	PJP*	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	PJP*	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: <i>P. aeruginosa</i> )	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: <i>P. aeruginosa</i> )	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: <i>P. aeruginosa</i> , <i>Clostridium sporogenes</i> )	Shortness of Breath	IMV	None	Periorbital cellulitis	Pain	Tonsillitis	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	Periorbital oedema	None	Tonsillitis	Oral and IV TPOXX, and Brincidofovir	Yes	No	78	Cardiac Arrest
20	34	Americas	115	Log 5	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	Log 5	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	Log 5	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: <i>K. pneumoniae</i> , <i>P. aeruginosa</i> )	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	Tonsillitis	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

654

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

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

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

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

659 \*Clinical suspicion, not microbiological confirmation