

1 **ARTICLE TYPE**

2 Original research

3

4 **TITLE:**

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

6

7 **AUTHORS**

8 Oriol Mitjà, PhD*¹ Andrea Alemany, MD*¹ Michael Marks, PhD*^{2,3,4} Jezer I. Lezama Mora, MD⁵ Juan
9 Carlos Rodríguez-Aldama, MD⁶ Mayara Secco Torres Silva, MD⁷ Ever Arturo Corral Herrera, MD⁸ Prof
10 Brenda Crabtree-Ramirez, MD⁸ Prof José Luis Blanco, PhD^{9,10,11} Nicolo Girometti, MD¹² Valentina
11 Mazzotta, MD¹³ Aniruddha Hazra, MD¹⁴ Macarena Silva, MD¹⁵ Juan José Montenegro-Idrogo, MD^{16,17}
12 Prof Kelly Gebo, PhD¹⁸ Prof Jade Ghosn, PhD^{19,20} María Fernanda Peña Vázquez, MD²¹ Eduardo Matos
13 Prado, PhD²² Uche Unigwe, MD²³ Judit Villar-García, PhD²⁴ Noah Wald-Dickler, MD^{25,26} Jason Zucker,
14 PhD²⁷ Roger Paredes, PhD²⁸ Prof Alexandra Calmy, PhD²⁹ Laura Waters, PhD³⁰ Cristina Galvan-Casas,
15 MD^{1, 31} Prof Sharon Walmsley, MD MSc³² Prof Chloe M Orkin, MD MSc³³ on behalf of SHARE-NET
16 writing group

17

18 *These authors equally contributed to this work.

19 **AFFILIATIONS**

20 ¹Skin Neglected Tropical diseases and Sexually Transmitted Infections section, Fight Infectious
21 Diseases Foundation, University Hospital Germans Trias i Pujol, Badalona, Spain

22 ²Clinical Research Department, London School of Hygiene & Tropical Medicine, London, UK

23 ³ Hospital for Tropical Diseases, University College London Hospitals. London, UK

24 ⁴ Division of Infection and Immunity, University College London, London, UK

25 ⁵Clinica Especializada Condesa Cuauhtémoc, Mexico City, Mexico

26 ⁶Clinica Especializada Condesa Iztapalapa, Mexico City, Mexico

27 ⁷Instituto Nacional de Infectología Evandro Chagas, Fundação Oswaldo Cruz (INI-Fiocruz), Rio de
28 Janeiro, Brazil

29 ⁸Departamento de Infectología, Instituto Nacional de Ciencias Médicas y Nutrición, Salvador Zubirán,
30 México City, México

31 ⁹Infectious Diseases Department, Hospital Clínic de Barcelona, Barcelona University, Barcelona, Spain

32 ¹⁰Centro de Investigación Biomédica en Red de Enfermedades Infecciosas (CIBERINFEC), Instituto de
33 Salud Carlos III, Madrid, Spain

34 ¹¹Institut d'Investigacions Mèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

35 ¹²Chelsea and Westminster Hospital NHS Foundation Trust – Department of HIV and Genitourinary
36 Medicine, UK

37 ¹³National Institute for Infectious Disease, Lazzaro Spallanzani, Rome, Italy

38 ¹⁴Section of Infectious Diseases and Global Health, University of Chicago Medicine, Chicago, IL, USA

39 ¹⁵Hospital San Borja Arriarán, Santiago de Chile, Chile

40 ¹⁶Hospital Nacional Dos de Mayo, Lima, Perú

41 ¹⁷Centro de Investigaciones Tecnológicas Biomédicas y Medioambientales (CITBM), Lima, Perú

42 ¹⁸Johns Hopkins University School of Medicine, Baltimore, MD, USA

43 ¹⁹Assistance Publique – Hôpitaux de Paris Nord, Department of Infectious Diseases, Bichat University
44 Hospital, Paris, France

45 ²⁰Université Paris Cité, INSERM UMR 1137 IAME, Paris, France

46 ²¹Hospital Enrique Garcés del Sur, Quito, Ecuador

47 ²²Hospital Nacional Arzobispo Loayza, Lima, Perú

48 ²³Infectious Disease Unit Department of Medicine, University of Nigeria Teaching Hospital, Enugu,
49 Nigeria

50 ²⁴Infectious Disease Unit, Hospital del Mar. Department of Medicine and Life Sciences, Universitat
51 Pompeu Fabra. IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain.

52 ²⁵ Los Angeles County + University of Southern California Medical Center, Los Angeles, California

53 ²⁶Keck School of Medicine of the University of Southern California, Los Angeles, California

54 ²⁷Division of Infectious Diseases, Columbia University Irving Medical Center, New York, NY 10032, USA

55 ²⁸Infectious Disease Department, Fight Infectious Diseases Foundation, University Hospital Germans
56 Trias i Pujol, Badalona, Spain

57 ²⁹HIV/AIDS Unit, Division of Infectious Diseases – Geneva University Hospitals, Geneva, Switzerland

58 ³⁰Central & North West London NHS Trust, London, UK

59 ³¹Hospital Universitario de Móstoles, Madrid, Spain

60 ³²University Health Network, University of Toronto, Toronto, Canada

61 ³³Blizard Institute and SHARE Collaborative, Queen Mary University of London, Department of
62 Infection and Immunity, Barts Health NHS Trust, London, UK

63

64

65 **CORRESPONDING AUTHOR**

66 Professor Chloe Orkin

67 Department of Immunobiology, The Blizard Building, 4 Newark Street,
68 E1 2AT, London, UK

69 c.m.orkin@qmul.ac.uk

70

71 **WORD COUNT**

72 Abstract: 328

73 Research in context: 607

74 Body text: 3520

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/mm³).

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/ mm³. 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/mm³ (IQR 117-291);
92 with 85 (22.3%) individuals with CD4 counts <100 cells/mm³, and 94 (24.6%) 100-200
93 cells/mm³. 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/mm³, 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/mm³. Amongst those with CD4 counts <200
99 cells/mm³ 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/mm³) 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/mm³; 3% < 200/mm³) 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/mm³. 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/mm³.

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/mm³. 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/mm³ 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.¹ The multi-
168 country outbreak was declared a Public Health Emergency of International Concern (PHEIC)
169 by the World Health Organisation (WHO) in July 2022.² People with HIV, accounting for 38-
170 50% of persons diagnosed with mpox,³ have been disproportionately affected.³ Most persons
171 living with HIV described in the 2022 case series had HIV viral suppression with median CD4
172 counts >500 cells/mm³ and had similar clinical presentations, time to viral clearance, and
173 outcomes to persons without HIV.⁴⁻¹³

174

175 Data from Nigeria and the USA suggest worse clinical outcomes in those with more HIV-
176 related immunosuppression.^{4,14,15} 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.¹⁴ The second report included 9 people with HIV with CD4 cell counts
180 ranging from 20 to 357 cells/mm³.¹⁵ The authors described confluent rashes, higher rates of
181 secondary bacterial infections and more prolonged illness.¹⁵ 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.¹⁶ All were hospitalized, had prolonged
184 disease courses, or developed complications, and some had fatal outcomes (i.e., 5 deaths
185 attributed to mpox).¹⁶ 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.⁴

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/mm³.

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.⁸⁻¹⁰ 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/mm³ 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/mm³ in line with the widely accepted 2010 consensus statement which
206 defines late presentation of HIV as CD4 <350 cells/mm³ or an AIDS-defining illness.¹⁷

207

208 CD4 count was categorised as <100, 101-200, 201- 300, and 301-350 cells/mm³, 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).¹⁸ For strata comparison, we grouped the seven
212 individuals with a missing CD4 count with those who had a CD4 count < 100 cells/mm³. 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-<log₄, ≥log₄ 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/mm³ 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/mm³ (IQR 117-291). The distribution of CD4 counts was as follows: 85 (22.3%)
270 <100 cells/mm³, 94(24.6%) 100-200 cells/mm³, 128(33.5%) 201-300 cells/mm³, and 75
271 (19.6%) 301-350 cells/mm³. CD4 counts were missing in 7 individuals who were assigned to
272 the group with CD4 <100 cells/mm³ 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 log₄ copies/ml,
275 and 105 (27.5%) had viraemia of > log₄ 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/mm³ 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/mm³.

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/mm³.

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/mm³. 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/mm³ (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/mm³. 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 log₁₀≥4 16.2% vs. HIV VL undetectable 0.5%; Figure 2C). In those with CD4 count <100
363 cells/mm³ (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/mm³. 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/mm³. 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.^{4-10,19} As described in the CDC classification,
395 disseminated forms of coccidioidomycosis, histoplasmosis and mycobacterium avium complex
396 are considered to be AIDS-defining illnesses.²⁰ Very similarly, we describe that people with
397 the lowest CD4 counts (<100 cells/mm³) 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).²⁰ We
400 describe in detail the clinical course of 27 people with CD4 counts < 200 cells/mm³ 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.⁴⁻¹¹ During the 2022 multi-country outbreak even the
408 largest series include very few people living with HIV and CD4 counts < 350/mm³ (12%) or
409 <200/mm³ (3%).^{4,21,22} 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 mm³) mount a poxvirus-specific T-cell response that is similar to those without HIV infection,²³
419 but there are no data on immunological responses in those with low CD4 counts (<350 cells/
420 mm³). In our series low CD4 cell count especially when < 200/mm³ was strongly associated
421 with increasing severity of mpox disease relative to those with CD4 200-350/mm³ and
422 compared to previous reports where CD4 > 500/mm³. 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.²⁴ 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.²⁵⁻
430 ²⁷ 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.^{27,28} 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/mm³ - 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.²⁹ 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

509 **ACKNOWLEDGMENTS**

510 We thank Roser Escrig for her assistance in administering data sharing agreements, and

511 Gerard Carot-Sans for providing comments to the manuscript. We would like to thank the

512 Swiss HIV Cohort Study network, who made possible and facilitated data collection. We wish

513 to acknowledge Dr Maria Beiras-Garcia, Department of imaging and Radiology, Complejo

514 Hospitalario de Pontevedra, Pontevedra, Spain for reviewing and commenting on the

515 radiological images. Thank you to the individuals with mpox and families of deceased

516 individuals who graciously consented to contribute data to further knowledge of this disease.

517 **REFERENCES**

- 518 1 Centers for Disease Control and Prevention (CDC). 2022 Mpox Outbreak Global Map.
519 2022. <https://www.cdc.gov/poxvirus/monkeypox/response/2022/world-map.html>
520 (accessed Jan 15, 2023).
- 521 2 Wenham C, Eccleston-Turner M. Monkeypox as a PHEIC: implications for global
522 health governance. *Lancet* 2022; **400**: 2169–71.
- 523 3 Mitjà O, Ogoina D, Titanji BK, *et al.* Monkeypox. *Lancet* 2022; **401**: 60–74.
- 524 4 Curran KG. HIV and sexually transmitted infections among persons with monkeypox—
525 eight US jurisdictions, May 17–July 22, 2022. *MMWR Morb Mortal Wkly Rep* 2022; **71**.
- 526 5 Girometti N, Byrne R, Bracchi M, *et al.* Demographic and clinical characteristics of
527 confirmed human monkeypox virus cases in individuals attending a sexual health
528 centre in London, UK: an observational analysis. *Lancet Infect Dis* 2022; **22**: 1321–8.
- 529 6 Mailhe M, Beaumont A-L, Thy M, *et al.* Clinical characteristics of ambulatory and
530 hospitalized patients with monkeypox virus infection: an observational cohort study.
531 *Clin Microbiol Infect* 2022; : doi.org/10.1016/j.cmi.2022.08.012.
- 532 7 Patel A, Bilinska J, Tam JCH, *et al.* Clinical features and novel presentations of human
533 monkeypox in a central London centre during the 2022 outbreak: descriptive case
534 series. *Br Med J* 2022; **378**.
- 535 8 Tarín-Vicente EJ, Alemany A, Agud-Dios M, *et al.* Clinical presentation and virological
536 assessment of confirmed human monkeypox virus cases in Spain: a prospective
537 observational cohort study. *Lancet* 2022; **400**: 661–9.
- 538 9 Thornhill JP, Barkati S, Walmsley S, *et al.* Monkeypox virus infection in humans across
539 16 countries—April–June 2022. *N Engl J Med* 2022; **387**: 679–91.

- 540 10 Thornhill JP, Palich R, Ghosn J, *et al.* Human monkeypox virus infection in women and
541 non-binary individuals during the 2022 outbreaks : a global case series. *Lancet* 2022;
542 **400**: 1953–65.
- 543 11 Suñer C, Ubals M, Tarín-Vicente EJ, *et al.* Viral dynamics in patients with monkeypox
544 infection: a prospective cohort study in Spain. *Lancet Infect Dis* 2022; **400**: 661–9.
- 545 12 Núñez I, García-Grimshaw M, Ceballos-Liceaga SE, *et al.* Epidemiological and clinical
546 characteristics of patients with human monkeypox infection in Mexico: A nationwide
547 observational study. *Lancet Reg Heal* 2022; : 100392.
- 548 13 Silva MST, Coutinho C, Torres TS, *et al.* Ambulatory and hospitalized patients with
549 suspected and confirmed mpox: An observational cohort study from Brazil. *Lancet*
550 *Reg Heal* 2022; : 100406.
- 551 14 Yinka-Ogunleye A, Aruna O, Dalhat M, *et al.* Outbreak of human monkeypox in
552 Nigeria in 2017–18: a clinical and epidemiological report. *Lancet Infect Dis* 2019; **19**:
553 872–9.
- 554 15 Ogoina D, Iroezindu M, James HI, *et al.* Clinical Course and Outcome of Human
555 Monkeypox in Nigeria. *Clin Infect Dis* 2020; **71**: E210–4.
- 556 16 Miller MJ, Cash-Goldwasser S, Marx GE, *et al.* Severe Monkeypox in Hospitalized
557 Patients — United States, August 10–October 10, 2022. *MMWR Morb Mortal Wkly*
558 *Rep.* 2022; : 71:1412–1417.
- 559 17 Antinori A, Coenen T, Costagiola D, *et al.* Late presentation of HIV infection: a
560 consensus definition. *HIV Med* 2011; **12**: 61–4.
- 561 18 Croxford S, Stengaard AR, Brännström J, *et al.* Late diagnosis of HIV: An updated
562 consensus definition. *HIV Med* 2022; **23**: 1202–8.

- 563 19 Hoffmann C, Jessen H, Wyen C, *et al.* Clinical characteristics of monkeypox virus
564 infections among men with and without HIV: A large outbreak cohort in Germany.
565 *HIV Med* 2022; : Online ahead of print. doi: 10.1111/hiv.13378.
- 566 20 CDC C for DC and P. 1993 Revised Classification System for HIV Infection and
567 Expanded Surveillance Case Definition for AIDS Among Adolescents and Adults. 1993.
568 <https://www.cdc.gov/mmwr/preview/mmwrhtml/00018871.htm> (accessed Jan 26,
569 2023).
- 570 21 Vaughan AM, Cenciarelli O, Colombe S, *et al.* A large multi-country outbreak of
571 monkeypox across 41 countries in the WHO European Region, 7 March to 23 August
572 2022. *Eurosurveillance* 2022; **27**: 2200620.
- 573 22 Philpott D, Hughes CM, Alroy KA, *et al.* Epidemiologic and clinical characteristics of
574 monkeypox cases—United States, May 17–July 22, 2022. *MMWR. Morb. Mortal.*
575 *Wkly. Rep.* 2022; **71**. <http://dx.doi.org/10.15585/mmwr.mm7132e3>.
- 576 23 Karem KL, Reynolds M, Hughes C, *et al.* Monkeypox-induced immunity and failure of
577 childhood smallpox vaccination to provide complete protection. *Clin Vaccine Immunol*
578 2007; **14**: 1318–27.
- 579 24 Edghill-Smith Y, Bray M, Whitehouse CA, *et al.* Smallpox vaccine does not protect
580 macaques with AIDS from a lethal monkeypox virus challenge. *J Infect Dis* 2005; **191**:
581 372–81.
- 582 25 Saharia KK, Koup RA. T cell susceptibility to HIV influences outcome of opportunistic
583 infections. *Cell* 2013; **155**: 505–14.
- 584 26 Klatt NR, Chomont N, Douek DC, Deeks SG. Immune activation and HIV persistence:
585 implications for curative approaches to HIV infection. *Immunol Rev* 2013; **254**: 326–

586 42.

587 27 Geldmacher C, Koup RA. Pathogen-specific T cell depletion and reactivation of
588 opportunistic pathogens in HIV infection. *Trends Immunol* 2012; **33**: 207–14.

589 28 Tian Y, Hua W, Wu Y, *et al.* Immune response to hepatitis b virus vaccine among
590 people living with hiv: A meta-analysis. *Front Immunol* 2021; : 5538.

591 29 Ferré VM, Bachelard A, Zaidi M, *et al.* Detection of Monkeypox Virus in Anorectal
592 Swabs From Asymptomatic Men Who Have Sex With Men in a Sexually Transmitted
593 Infection Screening Program in Paris, France. *Ann Intern Med* 2022; **175**: 1491–2.

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/mm³ and viral load log₅,
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
622 Lescano, Dr. Katty Chong Chinchay (Figure1B 5), Dr. Jenny Valverde (Figure 1 B2), Dr. Gonzalez
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 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-log ₄	30 (7.9%)	10 (11.8%)	6 (6.4%)	10 (7.8%)	4 (5.3%)
	≥log ₄	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/mm³ 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/ mm³) with a result of <200 CD4 cells/mm³.*

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/mm³ 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/mm³) with a result of <200 CD4 cells/mm³.

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