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

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Summary

Background People living with HIV have accounted for 38–50% of those affected in the 2022 multicountry mpox outbreak. Most reported cases were in people who had high CD4 cell counts and similar outcomes to those without HIV. Emerging data suggest worse clinical outcomes and higher mortality in people with more advanced HIV. We describe the clinical characteristics and outcomes of mpox in a cohort of people with HIV and low CD4 cell counts (CD4 <350 cells per mm³).

Methods A network of clinicians from 19 countries provided data of confirmed mpox cases between May 11, 2022, and Jan 18, 2023, in people with HIV infection. Contributing centres completed deidentified structured case report sheets to include variables of interest relevant to people living with HIV and to capture more severe outcomes. We restricted this series to include only adults older than 18 years living with HIV and with a CD4 cell count of less than 350 cells per mm³ or, in settings where a CD4 count was not always routinely available, an HIV infection clinically classified as US Centers for Disease Control and Prevention stage C. We describe their clinical presentation, complications, and causes of death. Analyses were descriptive.

Findings We included data of 382 cases: 367 cisgender men, four cisgender women, and ten transgender women. The median age of individuals included was 35 (IQR 30–43) years. At mpox diagnosis, 349 (91%) individuals were known to be living with HIV; 228 (65%) of 349 adherent to antiretroviral therapy (ART); 32 (8%) of 382 had a concurrent opportunistic illness. The median CD4 cell count was 211 (IQR 117–291) cells per mm³, with 85 (22%) individuals with CD4 cell counts of less than 100 cells per mm³ and 94 (25%) with 100–200 cells per mm³. Overall, 193 (51%) of 382 had undetectable viral load. Severe complications were more common in people with a CD4 cell count of less than 100 cells per mm³ than in those with more than 300 cells per mm³, including necrotising skin lesions (54% *vs* 7%), lung involvement (29% *vs* 0%) occasionally with nodules, and secondary infections and sepsis (44% *vs* 9%). Overall, 107 (28%) of 382 were hospitalised, of whom 27 (25%) died. All deaths occurred in people with CD4 counts of less than 200 cells per mm³. Among people with CD4 counts of less than 200 cells per mm³, more deaths occurred in those with high HIV viral load. An immune reconstitution inflammatory syndrome to mpox was suspected in 21 (25%) of 85 people initiated or re-initiated on ART, of whom 12 (57%) of 21 died. 62 (16%) of 382 received tecovirimat and seven (2%) received cidofovir or brincidofovir. Three individuals had laboratory confirmation of tecovirimat resistance.

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

Funding None.

Lancet 2023; 401: 939–49

Published **Online** February 21, 2023 https://doi.org/10.1016/S0140-6736(23)00273-8

This online publication has been corrected. The corrected version first appeared at thelancet.com on April 6, 2023

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Introduction

Since May, 2022, around 85 000 human mpox (formerly known as monkeypox) infections have been reported in 110 countries, with transmission predominantly through sexual contact among men who have sex with men.[1] The multicountry outbreak was declared a public health emergency of international concern by WHO in July, 2022.[2] People with HIV have been disproportionately affected, accounting for 38–50% of people diagnosed with mpox.[3] Most people living with HIV described in the 2022 case series had HIV viral suppression with median CD4 counts of more than 500 cells per mm³ and had similar clinical presentations, time to monkeypox viral clearance, and outcomes to people without HIV.[4–13]

Data from Nigeria and the USA suggest worse clinical outcomes in people with more HIV-related immunosuppression.[4,14–16] Two reports from Nigeria during the 2017–18 outbreak suggested that people with advanced

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Research in context

Evidence before this study

In 2022, mpox, a disease caused by an orthopox virus referred to as monkeypox virus has caused outbreaks in 110 countries. Two distinct clades of monkeypox virus, clade I and clade II, have existed in different geographical regions. The subclade IIb, identified in the 2022 outbreak, originates from subclade IIa mpox, which is considered a self-limiting disease. Unlike the previous epidemiological descriptions in west Africa, monkeypox virus transmission in this outbreak has been closely associated with the sexual networks of gay and bisexual men who have sex with men, in which a high proportion of people are living with HIV. Some evidence suggests greater disease severity in people with advanced HIV. These findings warrant careful evaluation of the interplay between HIV, immune status, and clinical manifestations of mpox. We searched PubMed for the terms "monkeypox, mpox AND (HIV)" from database inception to Dec 31, 2022. Publications were predominantly letters, perspectives, case reports, and public health agency reports. In the multicountry outbreak, scientific publications of case series have described similar clinical outcomes in people living with HIV to those in people without HIV infection. However, most cases series included people with HIV and high CD4 cell counts (>500 cells per mm^3) and suppressed HIV viral loads. In contrast, a Nigerian case series in the 2017–18 outbreak reported that people living with HIV had more severe outcomes when hospitalised, especially those who were viraemic and immunosuppressed. In a US Centers for Disease Control and Prevention (CDC) report on 758 mpox cases in people living with HIV during the multicountry outbreak (median CD4 639 [IQR 452–831] cells per mm^3; 12% had <350 cells per mm^3 and 3% had <200 cells per mm^3). 68 (10%) of 758 were hospitalised for a median duration of 2 (IQR 0–7) days. Worse rectal symptoms were described in those with HIV. A second CDC report identified adverse outcomes in 47 people with HIV and mpox who had low CD4 counts; 12 (26%) died and five deaths were attributed to mpox. On the basis of these data, individuals with HIV and advanced disease have been identified as requiring expert clinical advice, close surveillance, and prioritisation for antiviral treatments, such as tecovirimat, and preventive vaccines (where available).

Added value of this study

This mpox case series is the largest to investigate people with advanced HIV disease. We characterised 382 people with HIV and CD4 less than 350 cells per mm^3. Individuals with lower CD4 counts presented with widespread, large, necrotising, and coalescing skin lesions. Some individuals also developed lung nodules without an alternative confirmed or suspected diagnosis. Severe secondary bacterial infections were common. Frequent and severe oral, anogenital, and ocular presentations and complications were described. Immune reconstitution inflammatory syndrome was suspected in a quarter of those starting or reinitiating antiretroviral therapy after mpox diagnosis, 57% of whom died. The greatest disease severity, hospitalisation, and mortality was observed in individuals with both low CD4 count and high HIV viral load. This international case series includes 27 of the 60 people reported to have died of mpox in the multicountry outbreaks; all 27 were people with HIV and a CD4 cell count of less than 200 cells per mm^3.

Implications of all the available evidence

Our findings support the consideration of a severe, disseminated, and necrotising form of mpox as an AIDS-defining condition in CDC and WHO HIV disease classifications. This finding is based on the observation of protracted illness with fulminant disseminated necrotising cutaneous lesions, systemic complications, and mortality in those with CD4 cell counts of less than 200 cells per mm^3. Clinicians should also be aware that starting antiretroviral therapy in people with advanced HIV and mpox could contribute to deterioration and possible death, possibly as part of an immune reconstitution syndrome. Our data reinforces the importance of HIV and CD4 testing in mpox cases. Our findings support the recommendations that all people at risk of mpox with HIV and a CD4 cell count of less than 200 cells per mm^3 should be prioritised for preventive mpox vaccination. There should also be consideration for use of potential mpox antivirals where available, despite lacking data on their effectiveness, and a concerted global effort to ensure access in countries without access to antivirals and vaccines.

HIV presented with more severe or prolonged mpox. The first report[15] described that four of seven deaths in 122 individuals with mpox occurred in people with untreated advanced HIV. The second report included nine (of 40) people with HIV with CD4 cell counts of 20–357 cells per mm^3.[16] The authors described these nine people had more confluent rashes, higher rates of secondary bacterial infections and more prolonged illness than people without HIV.[16] More recently, a report from the US Centers for Disease Control and Prevention (CDC) during the 2022 outbreak confirmed these findings with 47 cases of severe mpox among people with advanced uncontrolled HIV infection.[14] All 47 people were hospitalised, had prolonged disease courses, or developed complications, and five deaths were attributed to mpox.[14] Worse rectal disease has also been described in another CDC series, in which 82% of people living with HIV were on antiretroviral therapy (ART) and 72% were virally suppressed.[4]

On the basis of the existing data, we hypothesised that, in the current outbreak, mpox presentations and outcomes in people living with HIV might differ by CD4 strata and HIV viral load. We used global research networks to describe the characteristics, clinical course, and outcomes of mpox in people with HIV and CD4 count less than 350 cells per mm^3.

Methods

Case definition and identification

Participating clinicians were recruited through the international research networks of the London-based Sexual Health and HIV All East Research (SHARE) Collaborative (London, UK) and the Network of the Skin Neglected Tropical Diseases and Sexually Transmitted Infections Unit of the Hospital Germans Trias i Pujol (Barcelona, Spain).[8–11] Researchers globally in locations with high numbers of mpox diagnoses were approached and invited to contribute mpox cases diagnosed between May 11, 2022, and Jan 18, 2023. A confirmed case was defined as a PCR-confirmed monkeypox virus infection in a specimen from any anatomical site. We restricted this series to include only adults older than 18 years living with HIV and with a CD4 cell count of less than 350 cells per mm³ or, in settings where a CD4 count was not always routinely available, an HIV infection clinically classified as CDC stage C. We included people living with HIV who had CD4 cell counts of less than 350 cells per mm³ in line with the widely accepted 2010 consensus statement,[17] which defines late presentation of HIV as a CD4 cell count of less than 350 cells per mm³ or an AIDS-defining illness.

CD4 cell count was categorised as less than 100, 101–200, 201–300, and 301–350 cells per mm³, because CD4 cell count cutoffs of 100 cells per mm³ and 200 cells per mm³ are associated with different risks of opportunistic infections (eg, cryptococcal meningitis is associated with CD4 cell count of <100 cells and *Pneumocystis jirovecci* pneumonia or toxoplasmosis is associated with a count of <200 cells).[18] For strata comparison, we grouped the seven individuals with a missing CD4 cell count measurement with those who had a CD4 count of less than 100 cells per mm³. Three of these individuals had an AIDS-defining condition and four had a positive point-of-care qualitative CD4 cell count test (Visitect CD4 Lateral Flow assay providing a visually interpreted result of >200 cells per mm³ [negative] or <200 cells per mm³ [positive]). HIV viral load was categorised as undetectable (<50 RNA copies per mL), 50–200 RNA copies per mL (low-level viraemia), 201 copies per mL to log4 copies per mL, and log4 RNA copies per mL or more. We categorised the presence or absence of clinician-reported complications by organ system.

Data collection

Each contributing centre completed a deidentified structured case report sheet (CRS) adapted from one used in our previous case series[10] to include variables of interest relevant to people living with HIV and to capture more severe outcomes (appendix p 8). The CRS used drop-down menus and free-text fields to capture routinely collected data from electronic or paper medical records. The CRS focus on HIV status included CD4 cell count, HIV viral load, concurrent opportunistic infections, and adherence to ART. These data were included with information on mpox presentation, diagnosis, clinical features, complications, and outcome. We also considered four outcomes for management: outpatient, hospitalisation, intensive care unit-level care, and death. Duration of

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	Total (n=382)	CD4 <100 cells per mm³* (n=85)	CD4 100–200 cells per mm³ (n=94)	CD4 201–300 cells per mm³ (n=128)	CD4 >300 cells per mm³ (n=75)
Median age, years	35 (30–43)	35 (32–43)	35 (29–42)	34 (31–42)	36 (30–44)
Gender					
Cisgender women	4 (1%)	4 (5%)	0	0	0
Transgender women	10 (3%)	4 (5%)	3 (3%)	3 (2%)	0
Cisgender men	367 (96%)	77 (91%)	91 (97%)	125 (98%)	74 (99%)
Non-binary individual†	1 (0%)	0	0	0	1 (1%)
Region where medical care was provided					
Africa	6 (2%)	3 (4%)	1 (1%)	2 (2%)	0
Europe	99 (26%)	20 (24%)	18 (19%)	39 (30%)	22 (29%)
Latin America	212 (55%)	37 (44%)	65 (69%)	67 (52%)	43 (57%)
North America	65 (17%)	22 (26%)	13 (14%)	19 (15%)	11 (15%)
Ethnicity					
Asian	7 (2%)	1 (1%)	1 (1%)	3 (2%)	2 (3%)
Black	55 (14%)	26 (31%)	10 (11%)	14 (11%)	5 (7%)
Latin American	225 (59%)	44 (52%)	63 (67%)	76 (59%)	42 (56%)
Mixed	10 (3%)	0	1 (1%)	5 (4%)	4 (5%)
White	85 (22%)	14 (16%)	19 (20%)	30 (23%)	22 (29%)
HIV status					
Previously known PLWH currently adherent to ART	228 (60%)	17 (20%)	53 (56%)	100 (78%)	58 (77%)
Previously known PLWH not on ART or non-adherent	121 (32%)	53 (62%)	33 (35%)	25 (20%)	10 (13%)
Newly diagnosed with HIV infection	33 (9%)	15 (18%)	8 (9%)	3 (2%)	7 (9%)
CD4 cell count (cells per mm³)	211 (117–291)	47 (27–77)	156 (125–184)	259 (221–280)	326 (316–338)
CD4 count among 27 people who died, (cells per mm³)	35 (IQR 24–100)	32 (20–64)	118 (112–134)	..	..
HIV viral load strata RNA copies per mL					
Not available	28 (7%)	11 (13%)	4 (4%)	10 (8%)	3 (4%)
<50	193 (51%)	14 (16%)	50 (53%)	80 (63%)	49 (65%)
50–200	26 (7%)	3 (4%)	6 (6%)	8 (6%)	9 (12%)
201–log4	30 (8%)	10 (12%)	6 (6%)	10 (8%)	4 (5%)
≥log4	105 (27%)	47 (55%)	28 (30%)	20 (16%)	10 (13%)
History of mpox vaccination					
Vaccination before 2022	16 (4%)	2 (2%)	4 (4%)	7 (5%)	3 (4%)
Third-generation vaccine for pre-exposure	21 (5%)	4 (5%)	3 (3%)	9 (7%)	5 (7%)
Third-generation vaccine postexposure	5 (1%)	1 (1%)	0	3 (2%)	1 (1%)

(Table 1 continues on next page)

	Total (n=382)	CD4 <100 cells per mm³* (n=85)	CD4 100–200 cells per mm³ (n=94)	CD4 201–300 cells per mm³ (n=128)	CD4 >300 cells per mm³ (n=75)
(Continued from previous page)					
Concurrent opportunistic infection					
Overall	32 (8%)	22 (26%)	4 (4%)	6 (5%)	0
Oesophageal candidiasis	4 (1%)	3 (4%)	1 (1%)	0	0
Cytomegalovirus end-organ disease	1 (0%)	1 (1%)	0	0	0
Disseminated herpes simplex	1 (0%)	1 (1%)	0	0	0
Histoplasmosis	2 (1%)	1 (1%)	0	1 (1%)	0
Isosporosis	1 (0%)	1 (1%)	0	0	0
Kaposi Sarcoma	4 (1%)	2 (2%)	0	2 (1%)	0
Disseminated *Mycobacterium avium* intracellulare	3 (1%)	2 (2%)	1 (1%)	0	0
Pneumocystis jirovecci pneumonia	6 (2%)	5 (6%)	1 (1%)	0	0
Toxoplasmosis	2 (1%)	1 (1%)	0	1 (1%)	0
Tuberculosis	8 (2%)	5 (6%)	1 (1%)	2 (2%)	0

Data are in median (IQR) or n (%), unless specified otherwise. Third generation vaccine was modified vaccinia Ankara-Bavarian Nordic. ART=antiretroviral therapy. PLWH=people living with HIV. *For the purpose of the table, seven individuals were classified as having a CD4 cell count of less than 100 cells per mm³ despite not having formal CD4 counts: three individuals from Peru did not have information on CD4 cell counts due to absence of testing reagents but had US Centers for Disease Control and Prevention stage C disease on the basis of an opportunistic infection; four patients from Nigeria were tested using a qualitative CD4 cell count test (Visitect CD4 Lateral Flow Assay, visually interpreted result of above or below 200 CD4 cells per mm³) with a result of less than 200 cells per mm³. †This non-binary individual was assigned male at birth.

Table 1: **Baseline demographic data**

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hospitalisation was the number of days until discharge or until data collection if ongoing by the end of data collection.

Ethical considerations

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

Statistical analysis

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

Role of the funding source

There was no funding source for this study.

Results

We describe 382 cases of human mpox infection in people living with HIV with a CD4 cell count of less than 350 cells per mm³ from sites in 19 countries (appendix p 14). Most individuals (277 [73%] of 382) were originally from the Americas (Argentina, Brazil, Canada, Chile, Ecuador, Mexico, Peru, and USA), 99 (26%) of 382 were from the Europe (Austria, Belgium, France, Germany, Greece, Italy, Portugal, Spain, Sweden, Switzerland, and UK), and six (2%) of 382 from Africa (Nigeria). The demographic and epidemiological characteristics of the participants are described in table 1.

In terms of clinical presentations (table 2), 243 (64%) of 382 individuals had fever and 364 (95%) had a skin rash, which was initially vesiculopustular in 297 (78%) of 382 and progressed to ulcerative in 84 (22%). The median number of skin lesions was 15 (IQR 8–35), and the median duration to resolution was 23 (IQR 18–33) days. Among 36 (9%) individuals who had 100 or more lesions and 43 (11%) people who had a duration to resolution of 40 days or more, the majority had CD4 cell counts of less than 200 cells per mm³ and detectable HIV plasma viral loads (appendix pp 15–16). Overall, 235 (62%) individuals had genital lesions, 203 (53%) anal lesions, 144 (38%) had oral involvement, and 20 (5%) had ocular involvement. The most common organ complications were dermatological, respiratory, and secondary bacterial infection (table 2). A total of 94 (25%) of 382 people developed dermatological complications. Ten (3%) of these individuals developed ecchymotic or haemorrhagic lesions and 84 (22%) developed necrotising lesions, of which 55 (14%) were coalescing. The most common presentation was multiple, large (typically greater than 2 cm in diameter), rounded ulcers with necrotic centres and a fresh, raised border, located close to the orogenital regions (figure 1B–D) or in distant locations (figure 1E, F), whereas verrucous appearance (figure 1E) was rare (appendix pp 30–49). In many instances, erythema and oedema surrounded the ulcer. Lesions involving the mouth, eye, or anus resulted in functional impairment (figure 1B, C, F). In the anogenital region, some individuals presented with substantial tissue damage and phagedenic ulcerations (figure 1F). Some people had progression to target-shaped lesions with erythema, swelling, and pallor beyond the margins of the ulcer indicating severe necrosis (figure 1F). Pseudo-Koebner phenomena (ie, the spread of the skin infection along sites with skin microtrauma or rubbing) were manifested by ulcers with a lineal distribution or overlying bony prominences (appendix p 17). In cases where epithelialisation had occurred, tissue destruction resulted in disfiguring scarring (appendix p 18).

In total, 35 (9%) of 382 individuals presented with respiratory complications (appendix p 19). Of these,

11 (3%) presented with numerous bilateral diffuse pulmonary nodules: four of these 11 diagnosed were with an x-ray only and seven were further characterised on CT scanning (figure 1A). All the radiographic images were reviewed by two specialist radiologists who concurred that these nodular lesions were unusual and characterised by well-defined borders, absence of cavitation, and no adjacent areas of ground-glass shadowing. Most of the nodules were perivascular (suggesting haematogenous spread) and, generally, ranged in size from 5 mm to 20 mm (appendix p 19, 51–52). In all three individuals with nodules in whom bronchoalveolar lavage or lung biopsy were done, a positive monkeypox virus PCR result was obtained (with negative microbiological results for *Pneumocystis jirovecii* and *Mycobacterium tuberculosis*; figure 1A). Eight of 11 had a CD4 cell count below 100 cells per mm³.

12 (34%) of 35 individuals with respiratory complications were reported as dyspnoea with no specific pathological findings, of whom, two had normal chest x-rays and ten had no available radiology report. Additionally, six (17%) of 35 individuals presented with pleural effusion (one with a positive monkeypox virus PCR on bronchoalveolar lavage) and three (9%) of 35 presented with ground-glass changes (two with suspected opportunistic infections and one with a positive monkeypox virus PCR on bronchoalveolar lavage).

A total of 12 (3%) individuals were reported to have neurological involvement (appendix p 22), including one case classified as encephalitis with orbital, frontal, and temporal oedema on CT scan, a positive monkeypox virus PCR result, and negative herpes simplex virus (HSV)-1 and HSV-2, and varicella zoster virus results in cerebrospinal fluid. Of the nine (2%) individuals with altered mental status or confusion, six had normal cerebrospinal fluid or radiological findings and three did not undergo imaging or cerebrospinal fluid examination. Confusion was attributed to sepsis in five individuals, respiratory failure in one, and hepatic encephalopathy in one, and the cause was undetermined in two cases. Neurological symptoms were almost exclusively described in people with a CD4 count of less than 100 cells per mm³.

In 76 (20%) of 382 individuals, secondary bacterial infections were diagnosed, including cellulitis, abscesses, and sepsis. Among 17 people with sepsis, eight had positive blood cultures: three with *Pseudomonas aeruginosa*, two with extended spectrum β-lactamase *Escherichia coli*, two with polymicrobial infection, and one with *Shigella flexneri*. Additionally, 12 individuals had a positive result from an abscess or deep wound sample culture: three with *Pseudomonas aeruginosa*, two with *Klebsiella pneumoniae*, two with extended spectrum β-lactamase *E coli*, three with methicillin-sensitive *Staphylococcus aureus*, and two methicillin-resistant *S aureus*.

All complications were more common in people with a CD4 cell count of less than 100 cells per mm³ compared with individuals with more than 300 cells per mm³. Complications included dermatological (49 [58%] of 85 *vs* 7 [9%] of 75), respiratory (25 [29%] of 85 *vs* 0 of 75), and bacterial infection (37 [44%] of 85 *vs* 7 [9%] of 75; figure 2A).

Overall, 107 (28%) of 382 individuals were hospitalised; of these, seven (2%) survived an admission to intensive care, and 27 (7%) died (appendix p 23). Among the

See Online for appendix

	Total (n=382)	CD4 <100 cells per mm³* (n=85)	CD4 100–200 cells per mm³ (n=94)	CD4 201–300 cells per mm³ (n=128)	CD4 >300 cells per mm³ (n=75)
Mpox rash presentation					
Peak number of skin lesions	15 (8–35)	30 (15–100)	20 (12–35)	12 (6–20)	10 (4–15)
Rash duration in days	23 (18–33)	31 (21–45)	26 (19–40)	21 (16–28)	21 (15–30)
Mpox organ complications†					
Dermatological skin lesions distant from the point of entry					
Overall	94 (25%)	49 (58%)	20 (21%)	18 (14%)	7 (9%)
Large necrotising lesions	84 (22%)	46 (54%)	19 (20%)	14 (11%)	5 (7%)
Ecchymosis haemorrhage	10 (3%)	3 (4%)	1 (1%)	4 (3%)	2 (3%)
Respiratory					
Overall	35 (9%)	25 (29%)	5 (5%)	5 (4%)	0
Shortness of breath‡	12 (3%)	7 (8%)	2 (2%)	3 (2%)	0
Ground glass changes	3 (1%)	2 (2%)	1 (1%)	0	0
Pleural effusion	6 (2%)	5 (6%)	0	1 (1%)	0
Consolidation	4 (1%)	3 (4%)	0	1 (1%)	0
Lung nodules	11 (3%)	8 (9%)	2 (2%)	1 (1%)	0
Miliary pattern	1 (0%)	1 (1%)	0	0	0
CNS					
Overall	12 (3%)	9 (11%)	1 (1%)	0	1 (1%)
Encephalitis	1 (0%)	0	1 (1%)	0	0
Confusion	9 (2%)	9 (11%)	0	0	0
Facial palsy	1 (0%)	0	0	0	1 (1%)
Other: headache	1 (0%)	0	1 (1%)	0	0
Bacterial infection					
Overall	76 (20%)	37 (44%)	19 (20%)	13 (10%)	7 (9%)
Non-genital cellulitis	29 (8%)	11 (13%)	6 (6%)	6 (5%)	6 (8%)
Genital cellulitis	15 (4%)	3 (4%)	7 (7%)	5 (4%)	0
Skin necrotising cellulitis	9 (2%)	6 (7%)	2 (2%)	1 (1%)	0
Pyomyositis or abscess	9 (2%)	5 (6%)	2 (2%)	1 (1%)	1 (1%)
Sepsis	17 (4%)	15 (18%)	2 (2%)	0	0
Ocular					
Overall	20 (5%)	13 (15%)	6 (6%)	0	1 (1%)
Conjunctivitis	6 (2%)	2 (2%)	3 (3%)	0	1 (1%)
Periorbital oedema	1 (0%)	1 (1%)	0	0	0
Keratitis	5 (1%)	4 (5%)	1 (1%)	0	0
Periorbital cellulitis	8 (2%)	6 (7%)	2 (2%)	0	0

(Table 2 continues on next page)

27 individuals who died, the median CD4 cell count was 35 (IQR 24–100) cells per mm³ and the median HIV viral load was log5 (IQR 4–5) RNA copies per mL, and only one patient was HIV virologically suppressed. Among those who died, severe necrotising or haemorrhagic skin lesions were described in 25 (93%) of 27, bloodstream or deep tissue bacterial infections in 24 (89%), respiratory symptoms and respiratory failure in 23 (85%), neurological involvement in eight (30%), rectal involvement in 21 (78%), and oropharyngeal involvement in 18 (67%). Ocular disease occurred in 13 (48%) of 27, eight of whom had periorbital cellulitis. The reported cause of death was septic shock and multiorgan failure in 20 (74%) of 27, respiratory failure in four (15%), disseminated mpox in two (7%), and cardiac arrest in one (4%).

The rate of hospitalisation and intensive care unit admission increased with declining CD4 cell counts (figure 2B) and rising viral loads (figure 2C). No deaths occurred in individuals with CD4 counts of more than 200 cells per mm³. Death was incrementally more likely among people in the lowest CD4 strata (CD4 <100 cells per mm³ 27% *vs* CD4 100–200 cells per mm³ 4% *vs* CD4 >200 cells per mm³ 0%; figure 2B) and among those with the highest viral loads (HIV viral load ≥log4 16% *vs* HIV viral load undetectable 1%; figure 2C). In people with a CD4 cell count of less than 100 cells per mm³ (n=85) and available HIV viral load, one (7%) of 14 individuals with a viral load of less than 50 copies per mL died and 14 (30%) of 47 individuals with HIV viral load of log4 copies per mL or more died.

Among 85 people who started or restarted on ART, 21 (25%) had suspected immune reconstitution inflammatory syndrome as a cause for clinical deterioration (appendix p 27). Of these, six (29%) were newly diagnosed and 15 (71%) were known to be living with HIV but were not receiving or not adherent to ART. All 21 people had a CD4 cell count of less than 200 cells per mm³. The median time from onset of mpox symptoms to the start of ART was 21 (range 0–73) days, and from the start of ART to worsening of mpox symptoms was 14 (range 3–64) days. Nine (43%) of 21 were treated for immune reconstitution inflammatory syndrome with steroids, and ten (48%) received supportive care. Of those with suspected immune reconstitution inflammatory syndrome, three (14%) of 21 were admitted to an intensive care unit, five (24%) were hospitalised in a general ward, and 12 (57%) died.

43 (42%) of the 103 individuals who had been hospitalised (including ten of the 27 people who died) and 21 (8%) of the 279 outpatients received antivirals to treat mpox. 62 (16%) of 382 individuals received tecovirimat (five received both oral and intravenous doses) and seven (2%) received cidofovir or brincidofovir. All people receiving mpox-specific antiviral therapy were treated in Europe or the USA, except two who received tecovirimat in Brazil. Laboratory confirmation of tecovirimat resistance (presence of *FL13L* mutations by sequencing) was detected in three of five people tested, who had severe immunocompromise, disseminated, and progressive mpox infection despite prolonged treatment (>14 days) with tecovirimat and finally died. Sampling for

	Total (n=382)	CD4 <100 cells per mm³* (n=85)	CD4 100–200 cells per mm³ (n=94)	CD4 201–300 cells per mm³ (n=128)	CD4 >300 cells per mm³ (n=75)
(Continued from previous page)					
Local complications					
Anorectal					
Overall	126 (33%)	45 (53%)	28 (30%)	32 (25%)	21 (28%)
Severe pain due to perianal lesions	44 (12%)	18 (21%)	7 (7%)	12 (9%)	7 (9%)
Proctitis (anal involvement)	78 (20%)	25 (29%)	21 (22%)	19 (15%)	13 (17%)
Rectal wall perforation	3 (1%)	2 (2%)	0	0	1 (1%)
Necrotising rectal lesions	1 (0%)	0	0	1 (1%)	0
Oropharyngeal					
Overall	85 (22%)	29 (34%)	23 (24%)	15 (12%)	18 (24%)
Tonsillar disease affecting swallowing or airways	19 (5%)	8 (9%)	5 (5%)	3 (2%)	3 (4%)
Lymphadenopathy affecting swallowing or airways	12 (3%)	5 (6%)	4 (4%)	2 (2%)	1 (1%)
Throat pain without affecting swallowing or airways	54 (14%)	16 (19%)	14 (15%)	10 (8%)	14 (19%)
Genitourinary					
Overall	64 (17%)	29 (34%)	15 (16%)	13 (10%)	7 (9%)
Difficulty passing urine or obstruction	12 (3%)	6 (7%)	4 (4%)	1 (1%)	1 (1%)
Severe genital pain	7 (2%)	3 (4%)	1 (1%)	0	3 (4%)
Genital oedema	33 (9%)	11 (13%)	8 (9%)	11 (9%)	3 (4%)
Necrotising genital lesions	12 (3%)	9 (11%)	2 (2%)	1 (1%)	0
Highest care level					
Outpatient	275 (72%)	32 (38%)	69 (73%)	111 (87%)	63 (84%)
Hospitalisation in general ward	73 (19%)	26 (31%)	19 (20%)	16 (13%)	12 (16%)
Intensive care unit§	34 (9%)	27 (32%)	6 (6%)	1 (1%)	0
Ultimate Outcome					
Death§	27 (7%)	23 (27%)	4 (4%)	0	0
Organ support					
Need for ventilation	21 (5%)	16 (19%)	4 (4%)	1 (1%)	0
Need for inotropes	16 (4%)	13 (15%)	3 (3%)	0	0
Indication for ventilation					
Respiratory failure	17 (4%)	14 (16%)	2 (2%)	1 (1%)	0
Sedation	1 (0%)	0	1 (1%)	0	0
Low Glasgow Coma Score or coma	3 (1%)	2 (2%)	1 (1%)	0	0

(Table 2 continues on next page)

resistance testing was done after at least one course of tecovirimat had been completed. Nobody who died had received mpox vaccination before or during 2022.

Discussion

Our large case series describes a severe, disseminated form of mpox infection with 15% mortality in individuals with advanced HIV-related disease characterised by CD4 cell counts below 200 cells per mm³. This fulminant form of mpox is characterised by massive necrotising skin, genital and non-genital cutaneous and mucosal lesions (appendix pp 30–52), and is sometimes accompanied by lung involvement with multifocal nodular opacities or respiratory failure and severe cutaneous and bloodstream secondary bacterial infections. The severities of oral and anogenital complications were more marked than previously described.[4–10,19] As described in the CDC classification, disseminated forms of coccidioidomycosis, histoplasmosis, and mycobacterium avium complex are considered to be AIDS-defining illnesses.[20] We describe that people with the lowest CD4 counts (<100 cells per mm³) and highest HIV viral loads (>log4 copies per mL) had disseminated and necrotising forms of mpox, strongly suggesting that this severe form of mpox with systemic involvement could also be an AIDS-defining condition (appendix p 28).[20] We describe in detail the clinical course of 27 people with CD4 cell counts of less than 200 cells per mm³ who died, including ten people who had completed one or two full courses of tecovirimat. We also wish to raise awareness of the 57% mortality rate in those in whom immune reconstitution inflammatory syndrome was suspected following ART initiation or reinitiation.

These data build on the observations of the altered natural history and course of mpox that is emerging. During the 2022 multicountry outbreak, most information about the intersection of HIV and mpox reports on people with well-controlled HIV infection.[4–13] Even the largest series either did not report on CD4 cell count[21,22] or included very few people living with HIV and CD4 cell counts of less than 350 per mm³ (12%) or less than 200 cells per mm³ (3%).[4] We hypothesised that mpox might have a different clinical presentation in individuals with advanced immunosuppression, as can be the case with some pathogens. Although the self-limiting clinical course in individuals with well-controlled HIV is very similar to that of individuals without HIV, our series provides evidence that the disease is very different in those with advanced HIV. The protracted duration and larger number of skin lesions in these individuals also raises the possibility of a more prolonged period of infectivity, but additional studies are needed to investigate this.

Previous work has shown that people living with HIV with high CD4 cell counts (>350 cells per mm³) mount a poxvirus-specific T-cell response that is similar to those without HIV infection,[23] but there are no data on immunological responses in those with low CD4 cell counts (<350 cells per mm³). In our series, low CD4 cell count, especially when less than 200 per mm³, was strongly associated with increasing severity of mpox disease relative to those with a CD4 cell count of 200–350 cells per mm³ and compared with previous reports in which most individuals had a CD4 cell count of more than 500 per mm³. Data from animal model monkeypox virus studies have shown that CD4 cell count depletion before immunisation of non-human primates decreased the development of protective B-cell responses and antibodies and increased infection severity after monkeypox virus challenge, which is consistent with our findings.[24] In our series, the effect of a low CD4 count on severity or death varied with the HIV plasma viral load, with higher viral loads associated with increased frequency of severe illness in any given CD4 cell count

	Total (n=382)	CD4 <100 cells per mm³* (n=85)	CD4 100–200 cells per mm³ (n=94)	CD4 201–300 cells per mm³ (n=128)	CD4 >300 cells per mm³ (n=75)
(Continued from previous page)					
Antimicrobial and antiviral treatment					
Antibiotics	144 (38%)	52 (61%)	34 (36%)	38 (30%)	20 (27%)
Tecovirimat (oral)	52 (14%)	21 (25%)	11 (12%)	15 (12%)	5 (7%)
Tecovirimat (intravenous)	15 (4%)	13 (15%)	1 (1%)	1 (1%)	0
Intravenous immune globulin	6 (2%)	6 (7%)	0	0	0
Cidofovir or brincidofovir	7 (2%)	5 (6%)	2 (2%)	0	0
Genotypic resistance to tecovirimat, n					
Samples sequenced	5	4	1	0	0
Presence of F13L mutations conferring resistance	3	3	0	0	0
Immune restitution inflammatory syndrome					
Antiretroviral started or restarted	85 (22%)	40 (47%)	23 (24%)	15 (12%)	7 (9%)
Deterioration consistent with immune restitution inflammatory syndrome	21 (5%)	15 (18%)	6 (6%)	0	0
Immune restitution inflammatory syndrome treatment provided	19 (5%)	14 (16%)	5 (5%)	..	..

Data are in median (IQR) or n (%), unless specified otherwise. *For the purpose of the table, seven individuals were classified as CD4 less than 100 cells per mm³ despite not having formal CD4 counts: three individuals from Peru did not have information on CD4 counts due to absence of testing reagents but had US Centers for Disease Control and Prevention stage C disease on the basis of an opportunistic infection;four patients from Nigeria were tested using a qualitative CD4 cell count test (Visitect CD4 lateral flow assay, visually interpreted result of above or below 200 cells per mm³) with a result of less than 200 cells per mm³. †The categories within a group of organ involvements are not mutually exclusive; therefore, an individual might present with multiple manifestations of the group. ‡Among the 12 patients with dyspnoea, two had a normal chest x-ray, and ten either had no radiology examinations done or the report was unavailable. §All individuals who died received intensive care unit-level care.

Table 2: **Clinical data**

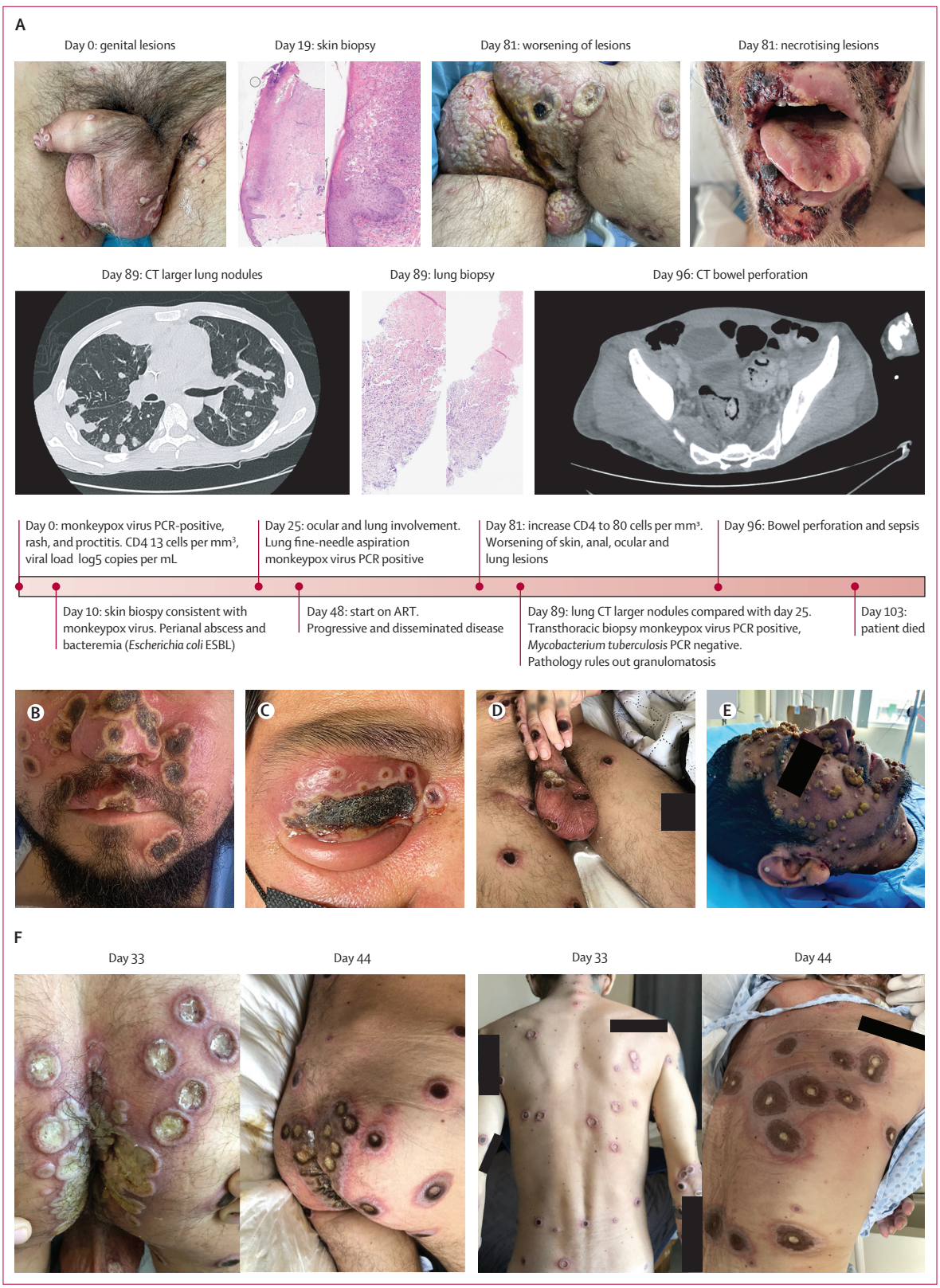

Figure 1: **Skin presentation of mpox in advanced HIV disease**

(A) Disease progression in a patient with a CD4 cell count of 13 cells per mm³ and HIV viral load log5 RNA copies per mL, with PCR-confirmed lung involvement, bowel perforation, immune reconstitution inflammatory syndrome, and death, despite having received two courses of intravenous tecovirimat and one course of intravenous cidofovir. (B–E) Photographs of necrotising lesions (lesions of the skin and mucous membranes) in multiple patients. (B) Necrotic ulcers in the perilabial and nasal areas, and ulcer with tissue destruction on the right upper lip. (C) Umbilicated vesiculopustular-like lesions on upper eyelid surrounding an extensive necrotic ulcer, and eyelids and nasal radix with oedema and erythema. (D) Necrotic ulcers with raised edges, some confluent, on the scrotum, dorsum of the fingers, groin, and thighs. (E) Numerous verrucous, excrescent, yellowish facial lesions. (F) Before and after lesions, with progression to severe confluent target-shaped ulcers with dark necrotic centre surrounded by a vesiculopustular halo and peripheral oedema, in the perianal area and back. ART=antiretroviral therapy. ESBL=extended spectrum β-lactamase *Escherichia coli*.

group. Previous work has shown that replicating HIV virions target antigen-specific T cells that are activated to combat other pathogens, resulting in impaired T-cell responses.[25–27] Thus, it is possible that a substantial proportion of monkeypox virus-specific CD4 T cells might die or be impaired due to either complete or abortive HIV infection. Other studies have shown impaired immune responses to hepatitis B and other vaccines in those with low CD4 cell counts and unsuppressed HIV virus replication, providing additional evidence that HIV replication can interfere with the immune response to other pathogens.[27,28] On the basis of our findings, we believe that a severe necrotising form of mpox with systemic manifestations exists. This form of mpox affected people with CD4 cell counts less than 200 cells per mm³—the precise CD4 threshold considered to be AIDS-defining in international guidelines (appendix p 28). Given the 15% mortality in this group, strong consideration should be given to designating this disseminated form of severe mpox as a new AIDS-defining condition in definitions and guidelines.

Several limitations of our research need to be highlighted. Our data are derived from an observational retrospective convenience case series from countries with high numbers of mpox infections. We were, therefore, unable to assess how well our cohort represents the entire population of people living with HIV who developed mpox infection. Study sites might have been more likely to include individuals with more severe outcomes, which could have biased the relationships between both CD4 cell counts and HIV viral load and clinical outcomes. Individuals included in this case series had symptoms that led them to seek medical care; therefore, people who were asymptomatic, had milder symptoms, or did not have access to medical care could have been missed and we could have overestimated illness severity.[29] Additional, outcomes might have been missed if people reattended with severe disease at different sites that were not part of the case series. Due to data collection from multiple sites, some characteristics might have been collected in a heterogeneous manner. Laboratory techniques also differed between sites. Many of the cases had a concomitant opportunistic infection and it might be difficult to differentiate many of the outcomes of mpox from those of the other infections. For example, some health-care settings included did not have access to some radiological and microbiological investigations so we cannot be certain of the role of mpox (as opposed to other opportunistic infections). However, we suggest that the coincident perivascular non-cavitating lung nodular pattern described by two radiologists and seen in 11 people, without a documented suspicion or microbiological evidence of a co-opportunistic pathogen, could be a manifestation of mpox disease and further research into this is warranted. Many of the deaths were associated with multiorgan system failure but the relative contribution of the mpox to death is unclear. We have raised the possibility

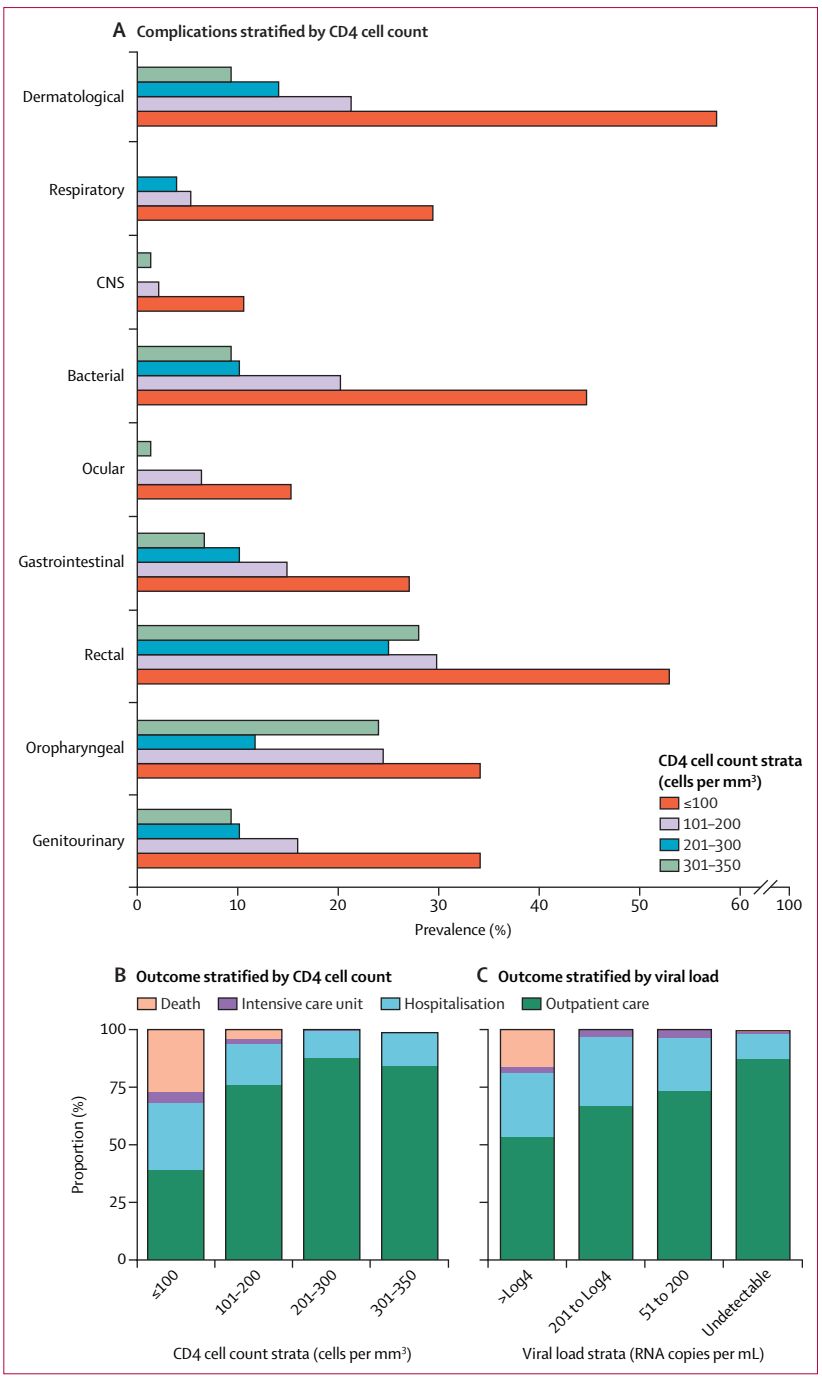

Figure 2: **Complications and outcomes of mpox in people living with HIV**
Complications stratified by CD4 cell count (A) and outcomes stratified by CD4 cell count (B) and viral load (C).

of immune reconstitution inflammatory syndrome reactions with the initiation of antiretroviral therapy; however, in the absence of a strict definition and in the absence of details on confounding conditions that might have contributed to adverse outcomes, the data are uncertain. Data are currently not available from randomised controlled clinical trials on the impact of

monkeypox virus antivirals or preventive vaccines on the course of mpox, and, with the limited use in this series, their role cannot be evaluated.

Our data reinforce the recommendation that HIV testing (in addition to testing for other sexually transmitted pathogens) and CD4 cell counts measurement be performed in every case of mpox. When immune suppression is detected, a different course of action should be followed in terms of infection prevention and control, the potential use of antivirals, and consideration of immune reconstitution inflammatory syndrome. Physicians caring for people with mpox and advanced HIV disease must be made aware of the severe outcomes and high mortality that can occur, especially when cutaneous and bloodstream bacterial superinfection sets in. Clinical trials tailored to this group are needed to evaluate the effect of antiviral agents and preventive vaccines to modify disease outcomes. In the absence of these data, people with HIV and low CD4 cell counts who need to be hospitalised with mpox should be considered for expanded access to these therapies where available and specific guidelines with best practices should be developed. We have shown that, among people with advanced HIV, the risk of deterioration and death after initiation of antiretroviral therapy is 57%. This risk needs to be considered when caring for people with HIV and advanced disease with mpox who are not on therapy. Additional research into the role of immune reconstitution inflammatory syndrome is necessary to better understand the role of potential interventions, such as early versus delayed initiation of ART, and the concomitant use of steroids or other immunomodulatory strategies leading to a reduction in the frequency of immune reconstitution inflammatory syndrome.

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

Contributors

OM and CMO conceived and designed the study. CMO and OM coordinated the global collaboration. AA and CG-C managed the global data collection. CMO, OM, AA, MM, and CG-C developed the case report form. MM and OM analysed and interpreted and the data. All authors except MM and CMO submitted cases. OM, CMO, AA, CG-C, and MM drafted the first draft of the manuscript. CG-C and JV-G prepared the image library. CMO, OM, AA, MM, and SW edited the final manuscript. Pictures were courtesy of JV-G, MFPV, and JCR-A, and CAL, KCC, JV, and GR (SHARE-NET writing group). All authors reviewed the manuscript. All authors were responsible for the final decision to submit for publication and have seen and approved the manuscript. CMO, MM, and OM had full access to all data.

Declaration of interests

We declare no competing interests.

Data sharing

Deidentified participant data collected, including individual participant data, will be made available from the corresponding author on reasonable request.

Acknowledgments

We thank Roser Escrig (Fight Infectious Diseases Foundation, University Hospital Germans Trias i Pujol, Badalona, Spain) for her assistance in administering data sharing agreements, and Gerard Carot-Sans (Fight Infectious Diseases Foundation, University Hospital Germans Trias i Pujol, Badalona, Spain) for providing comments to the manuscript. We would like to thank the Swiss HIV Cohort Study network who made possible and facilitated data collection. We wish to acknowledge Maria Beiras-Garcia (Department of imaging and Radiology, Complejo Hospitalario de Pontevedra, Pontevedra, Spain) for reviewing and commenting on the radiological images. We thank the individuals with mpox and families of deceased individuals who graciously consented to contribute data to improve the knowledge of this disease.

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