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RESEARCH ARTICLE

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# Long or complicated mpox in patients with uncontrolled HIV infection

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## Abstract

To date, former research about the impact of HIV infection on mpox poor outcomes is still limited and controversial. Therefore, the aim of this study was to assess the impact of HIV on the clinical course of mpox, in a large population of patients from Spain. Nationwide case-series study. Patients from 18 Spanish hospitals, with PCR-confirmed mpox from April 27, 2022 to June 30, 2023 were included in this study. The main outcome was the development of long or complicated (LC) mpox, defined as: (i) duration of the clinical course ≥ 28 days, or; (ii) disseminated disease, or: (iii) emergence of severe complications. One thousand eight hundred twenty-three individuals were included. Seven hundred eighty-six (43%) were people living with HIV (PLWH), of whom 11 (1%) had a CD4 cell count < 200 cells/mm$^3$ and 33 (3%) <350 cells/mm$^3$. HIV viral load ≥ 1000 cp/mL was found in 27 (3%) PLWH, none of them were on effective ART. Fifteen (60%) PLWH with HIV-RNA ≥ 1000 cp/mL showed LC versus 182 (29%) PLWH with plasma HIV-RNA load < 1000 copies/mL and 192 (24%) individuals without HIV infection ($p < 0.001$). In multivariate analysis, adjusted by age, sex, CD4 cell counts and HIV viral load at the time of mpox, only plasma HIV-RNA ≥ 1000 cp/mL was associated with a greater risk of developing LC mpox [adjusted OR = 4.06 (95% confidence interval 1.57–10.51), $p = 0.004$]. PLWH with uncontrolled HIV infection, due to lack of ART, are at a greater risk of developing LC mpox. Efforts should be made to ensure HIV testing is carried out in patients with mpox and to start ART without delay in those tested positive.

**KEYWORDS**
monkeypox virus, mpox complications, people living with HIV, RNA HIV

## 1 | INTRODUCTION

Since the start of the mpox outbreak on May 14, 2022, a total of 92 783 cases of infection have been reported in 116 countries as of December 13, 2023.[1] So far, Spain is one of the countries with the highest number of cases diagnosed, accounting for 7684. According to data reported through global surveillance, the mpox outbreak continues, particularly in European region and in the region of the Americas. Following a decline in reported cases after January 2023 in Europe, sporadic infections have been documented with a substantial increase of cases in November 2023.[1] The current outbreak presents several particularities with respect to the previous ones: monkeypox virus (MPVX) transmission occurs mainly through close, intimate contact and is therefore largely related to sexual activity.[2] In fact, the vast majority of individuals with mpox are men who have sex with men (MSM), most of them live with HIV.[3–6] The clinical picture is usually mild and self-limiting and the overall mortality rate of the MPVX strain circulating in Europe is low, below 1%.[7] However, mpox-related severe outcomes may be more common in immunocompromised individuals. Available evidence concerning the impact of HIV infection on mpox poor outcomes is limited and conflicting.

Studies in Africa, before the present outbreak, highlighted that HIV-related immunosuppression and the lack of HIV viremia control might be associated with more extensive skin involvement, longer-lasting lesions, higher prevalence of complications, as well as higher mpox-related mortality.[8–11] In the present outbreak, preliminary studies pointed out that people living with HIV (PLWH) do not experience worse clinical outcomes related to mpox.[6,12] However, most patients in these studies showed optimal immunovirological control. Conversely, other works suggested that PLWH have higher rates of mpox-related clinical complications and they are hospitalized more frequently than individuals without HIV infection.[13–16] More specifically, severe forms of mpox with high mortality have been related to poor HIV control (i.e., advanced immunosuppression, nonsuppressed HIV viral loads).[17–19] However, the latter studies had a limited sample size[18,19] or did not conduct a statistical analysis of association between mpox severity and control of HIV infection.

Given the shortage of vaccines and targeted therapeutic options, it is of the greatest interest to identify populations at risk of developing severe disease, in which early therapeutic/preventive measures could be promptly implemented to avoid adverse outcomes. Because of this, further studies, including larger populations of PLWH, and analyzing in depth risk factors for poor mpox outcomes are needed.

The aim of this study was to assess the impact of HIV infection on the clinical course of mpox, in a large population of patients from Spain.

## 2 | METHODS

### 2.1 | Study design and patients

This was a nationwide case-series study. All patients from 18 Spanish hospitals, with PCR-confirmed MPXV infection from April 27, 2022 to June 30, 2023 were included in this study. Individuals were managed according to the national recommendations for mpox in force in Spain.[20] Unfortunately, tecovirimat was not available for most patients.

### 2.2 | Outcomes and definitions

The main outcome was the development of long or complicated (LC) mpox, defined as: (i) duration of the clinical course exceeded 28 days, or; (ii) disseminated disease, or: (iii) emergence of serious complications. The duration of the clinical course was calculated from the onset of symptoms until the mucocutaneous lesions were fully cleared (i.e., scabs dropping off with intact underlying skin) or the resolution of MPVX infection-related complications. Disseminated disease was defined as the presence of mucocutaneous lesions involving six or more areas of the body surface (head; neck; oropharyngeal mucosa; upper limbs, chest and abdomen, truncus dorsum, pelvis and genital, anal and gluteal, lower limbs). Severe complications included extensive superinfection of skin lesions without previous response to treatment, pain refractory to nonopioid analgesia, sepsis, odynophagia with obstructive sensation, myopericarditis, gastrointestinal bleeding, encephalitis, or ophthalmologic complications. Uncontrolled HIV infection was defined as plasma HIV-RNA load above 1000 copies/mL.[21]

### 2.3 | Data collection and laboratory procedures

Data on demographic characteristics, clinical presentation, and variables related to HIV infection control were collected. HIV related immune-virological parameters assessed within the last 3 months before mpox diagnosis were included. The diagnosis of MPVX infection was performed by real-time RT-PCR in a specimen taken from skin, genital, anal or oropharynx lesions, at the Spanish Microbiology Center reference laboratory. After June 1, 2022, laboratory confirmation was performed in local certified tertiary hospitals. HIV screening was performed to all individuals.

### 2.4 | Statistical analysis

Categorical variables are expressed as absolute and relative frequencies. Continuous variables are presented as medians (quartile 1-quartile 3). Frequencies were compared by the Chi-square test or the Fisher's test, when there was at least one cell with an expected frequency lower than five. Continuous variables were compared with the Mann–Whitney *U* test. Multivariate logistic regression was performed to assess the association between potential risk factors and the development of LC mpox. Variables associated with the main endpoint in the bivariate analysis with $p < 0.2$, along age and sex, were entered in the multivariate model. All data analyses were performed using the SPSS statistical software package release 26.0 (IBM) and Stata 15.0 Statistics/Data Analysis (StataCorp).

## 3 | RESULTS

### 3.1 | Characteristics of the study population

A total of 1823 cases of confirmed mpox were included in this study. Demographic and clinical characteristics are depicted in Table 1. Seven hundred and eighty-six (43%) individuals were living with HIV. Data on the immunovirological status at the time of mpox were available for 772 PLWH of whom 745 (97%) individuals were known to be taking antiretroviral therapy (ART) and had a plasma HIV-RNA load below 1000 copies/mL. Data on these 27 patients are provided in Supporting Information: Table 1. Of the 27 patients with uncontrolled HIV viremia, 15 (56%) were not on ART, 9 (33%) had started ART in the previous 6 months, and 3 (11%) showed a poor adherence to ART. Thirteen (0.7%) patients with HIV infection were newly detected. None of them reported recent/ever use of PrEP. Six (46%) of the 13 individuals with newly diagnosed HIV infection showed HIV viral load > 200 000 copies/mL. The median (Q1–Q3) CD4 cell count was 760 (583–973) cells/mm$^3$. Specifically, 11 (1%) PLWH had a CD4 cell count below 200 cells/mm$^3$.

### 3.2 | Clinical outcomes

Globally, PLWH did not report systemic symptoms more frequently than patients without HIV infection (585 [75%] versus 735 [72%], respectively, $p = 0.133$). Complications related to mpox were neither more common among PLWH (85 [11%] versus 109 [11%], $p = 0.848$) The median (Q1–Q3) duration of the clinical course was 21 (16–28) days for PLWH versus 21 (15–26) days for people without HIV ($p = 0.143$). PLWH were more likely to be develop disseminated disease than individuals without HIV infection, $n = 32$ (4%) versus

**TABLE 1** Baseline characteristics of the study population (*N* = 1789).

| Parameter | PLWH and viral load ≥ 1000 cp/mL (*n* = 27) | PLWH viral load < 1000 cp/mL (*n* = 745) | Individuals without HIV infection (*n* = 1015) | *p* univariate |
|---|---|---|---|---|
| Sex al birth, Male, *n* (%) | 27 (100) | 744 (100) | 1004 (99) | 0.024 |
| Age (years)[a] | 32 (26–42) | 40 (34–46) | 36 (30–43) | 0.002 |
| Sexual orientation,[b] GBMSM, *n* (%) | 24 (96) | 699 (99) | 872 (98) | 0.026 |
| Route of MPXV transmission,[c] Sexual, *n* (%) | 24 (89) | 704 (99) | 891 (96) | <0.001 |
| Nadir CD4 cell count[d] (cels/mm$^3$)[a] | 405 (298–517) | 413 (283–594) | – | 0.745 |
| HIV CDC clinical category,[e] A, *n* (%) | 13 (81) | 344 (82) | – | 1.000 |
| CD4 cell count at the time of mpox,[f] *n* (%) | 435 (259–552) | 767 (594–975) | – | <0.001 |
| Use of preexposure prophylaxis against HIV infection, *n* (%) | – | – | 373 (41) | – |
| Prior smallpox vaccination,[g] *n* (%) | 1 (5) | 65 (15) | 84 (13) | 0.352 |

*Note*: Data are number (%) of patients.
[a]Median (Q1–Q3);
[b]Available for 1622 patients;
[c]Available for 1669 patients;
[d]Available for 475 patients;
[e]Available for 434 patients;
[f]Available for 656 patients;
[g]Available for 1098 patients.

**TABLE 2** Clinical outcomes (*N* = 1789).

| Parameter | PLWH and viral load ≥ 1000 cp/mL (*n* = 27) | PLWH viral load < 1000 cp/mL (*n* = 745) | Individuals without HIV infection (*n* = 1017) | *p* univariate |
|---|---|---|---|---|
| Systemic symptoms,[a] *n* (%) | 23 (85) | 548 (74) | 721 (72) | 0.221 |
| Fever, *n* (%) | 16 (59) | 449 (61) | 516 (51) | <0.001 |
| Asthenia, *n* (%) | 6 (22) | 234 (32) | 316 (32) | 0.760 |
| Lymphadenopathies, *n* (%) | 6 (22) | 242 (33) | 417 (42) | <0.001 |
| Duration of the clinical course,[bc] | 28 (24–40) | 21 (16–27) | 21 (15–26) | 0.001 |
| Anogenital lesions present,[d] *n* (%) | 15 (60) | 509 (70) | 723 (73) | 0.135 |
| Disseminated disease,[e] *n* (%) | 6 (22) | 27 (4) | 22 (2) | <0.001 |
| Mpox- related complications, *n* (%) | 4 (15) | 111 (15) | 159 (16) | 0.899 |
| Hospital admission, *n* (%) | 5 (19) | 28 (4) | 17 (2) | <0.001 |

*Note*: Data are number (%) of patients.
[a]Available for 1763 patients;
[b]Median (Q1–Q3);
[c]Available for 821 patients;
[d]Available for 1746 patients;
[e]Available for 1789 patients.

*n* = 22 (2%), respectively (*p* = 0.009). Likewise, a higher proportion of PLWH required hospitalization (32 [4%]) compared to individuals without HIV infection (18 [2%], *p* = 0.002).

Regarding plasma HIV viremia control status, a greater proportion of PLWH with plasma HIV-RNA ≥ 1000 copies/mL showed systemic symptoms than the remaining patients, except for lymphadenopathy (Table 2). Besides, mpox was more frequently disseminated and lasted longer in PLWH with uncontrolled HIV infection than in the other two subpopulations (Table 2). No differences were found in terms of frequency of complications related to mpox. Complications developed

in the study patients are displayed at Table 3. A total of 50 (3%) patients were admitted to the hospital. Admission was more common among PLWH with HIV-RNA ≥ 1000 copies/mL (Table 2). Only one (0.1%) patient received antiviral therapy. Specifically, tecovirimat was approved for one individual with a mpox-related ophthalmic complication. One patient (0.1%) without HIV infection. The cause of death was attributed to encephalitis.

One hundred and seventy-eight (28%) PLWH showed the composite outcome LC mpox compared to 211 (26%) individuals without HIV infection ($p = 0.272$). LC mpox was developed more frequently by PLWH with CD4 < 350 cells/mm$^3$ than by PLWH with CD4 ≥ 350 cells/mm$^3$ or people without HIV infection (Table 4), however these differences were not statistically significant. A greater proportion of PLWH with HIV-RNA ≥ 1000 copies/mL developed LC disease compared to PLWH with plasma HIV-RNA load < 1000 copies/mL and individuals without HIV infection (Table 4). In multivariate analysis, adjusted by age, sex, route of transmission, CD4 cell count and plasma HIV viral load at the time of mpox, only HIV-RNA ≥ 1000 copies/mL and not CD4 cell counts was associated with a greater risk of developing LC disease (Table 4).

**TABLE 3** Complications of mpox ($n = 191$).

| Type of complication | *n* (%) |
|---|---|
| Superinfection of skin lesions | 123 (64) |
| Pain refractory to nonopioid analgesia | 33 (17) |
| Odynophagia with obstructive sensation | 7 (4) |
| Paraphimosis | 7 (4) |
| Gastrointestinal bleeding | 4 (2) |
| Ophthalmologic complications | 2 (1) |
| Sepsis | 1 (1) |
| Myopericarditis | 1 (1) |
| Encephalitis | 3 (1) |
| Others | 10 (5) |

*Note*: Data are number (%) of patients.

## 4 | DISCUSSION

The present study suggests that, in the subset of the current mpox outbreak, PLWH as a whole are not at greater risk of LC mpox. However, those with uncontrolled HIV infection, largely due to lack

**TABLE 4** Factors associated with developing a long or complicated mpox ($N = 1452$).

| | Categories | LC mpoxn/*N* (%) | *p* bivariate | Adjusted OR (95% CI) | *p* multivariate |
|---|---|---|---|---|---|
| Sex at birth | Male | 389/1433 (27) | 1.000 | 1.02 (0.30–3.40) Ref. | 0.976 |
| | Female | 4/14 (29) | | | |
| Age (years) | <37 | 160/654 (25) | 0.060 | 1.01 (1.00–1.03)[a] | 0.051 |
| | ≥37 | 229/793 (29) | | | |
| Prior smallpox vaccination | No | 233/747 (31) | 0.536 | – | – |
| | Yes | 20/75 (27) | | | |
| CD4 cell count at the time of mpox virus infection (cels/mm$^3$) | HIV negative | 178/720 (25) | 0.151 | Ref. 1.02 (0.46–2.29) | 0.959 |
| | ≥350 | 148/507 (29) | | | |
| | <350 | 11/33 (33) | | | |
| HIV viral status at the time of mpox virus infection | HIV negative | 192/799 (24) | <0.001 | Ref.4.06 (1.57–10.51) | 0.004 |
| | HIV-RNA <1000 c/mL | 182/623 (29) | | | |
| | HIV-RNA ≥1000 c/mL | 15/25 (60) | | | |
| STIs coinfection | No | 275/1041 (26) | 0.259 | – | – |
| | Yes | 109/370 (29) | | | |

*Note*: Table shows patient characteristics associated with a greater probability of developing LC mpox. For the bivariate analysis, continuous variables were categorized according to the median value or using clinically significant cut-off points. Variables associated with the main endpoint in the bivariate analysis with $p < 0.2$, along age and sex, were entered in a multivariate analysis, and a logistic binary regression was conducted. Age was entered as a continuous variable, and all other parameters were entered as categorical variables. For the multivariate analysis, variables related to CD4 cell count and HIV viremia were dichotomized and the two categories used were: patients without HIV infection and PLWH with CD4 cell count ≥ 350 cels/mm$^3$ or with HIV viremia < 1000 copies/mL versus PLWH with CD4 cell count <350 cels/mm$^3$ or with HIV viremia ≥ 1000 copies/mL. The model was built using an automatic procedure. Results are expressed as OR and their 95% CI. In total, two variables, along with age and sex, were included in the final model. The Hosmer–Lemeshow test was used for goodness of fit for logistic regression with $p = 0.419$.

Abbreviations: LC, Long or complicated; Ref, reference.

[a]For one increase year.

of ART, seem to develop more severe outcomes. More precisely, PLWH with HIV viral load above 1000 copies/mL experienced a longer duration of the disease or more commonly disseminated involvement. Finally, PLWH required admission to the hospital more frequently, mainly those with uncontrolled HIV infection. With regard to clinical expression, MPXV infection behaves as an opportunistic infection associated with HIV, with a greater severity in those with uncontrolled infection.

Since the onset of the mpox epidemic, several studies have demonstrated that this 2022 mpox outbreak has specific features that markedly differ from the larger African outbreaks. MPXV transmission has mainly been driven through sexual intercourse and infection has largely affected young MSM. The disease course was predominantly mild and the hospital admission rate was low.[3–6] However, severe clinical cases have been occasionally found, particularly in the subset of patients with advanced immunosuppression. Globally, the present study supports these findings. The most relevant aspect of this work is that it reveals the impact of uncontrolled HIV infection on the clinical expression of mpox.

Indeed, PLWH with plasma HIV-RNA viral load > 1000 copies/mL are more vulnerable and experience a worse clinical course. To date, recently case series from high and middle-income countries have not evidenced an excess of severe illness among individuals with HIV infection considered as a whole.[4–6,12] However, the vast majority of PLWH were on effective ART in these settings. Besides, these studies were limited because PLWH were analyzed altogether without considering whether HIV infection was well-controlled or not. More recent published works, suggest that PLWH with either immunodeficiency or lack of control of viremia may develop more complications or might be at a greater risk of hospitalization.[13–19] Nevertheless, several issues should be highlighted in these studies. Some of them only provided descriptive data.[13,17] Others were performed at a smaller-scale and the number of PLWH included was low.[14,18,19] Finally, hospitalization may have been the result of greater clinician concern instead of more severe disease. It is worth mentioning that, in the present study, the 26 unsuppressed individuals with HIV infection were not on ART (20 newly-detected HIV infections), showed poor ART adherence, or ART had been started in the previous 6 months. These findings underscore two important issues: on the one hand, HIV testing must be performed in all patients with mpox, and individuals with newly-diagnosed HIV infection should initiate ART immediately, although the benefit of this approach will have to be demonstrated in clinical trials. On the other hand, because PLWH with uncontrolled HIV infection experience a more prolonged illness, they may also be infectious for longer periods. This is one more reason that supports that PLWH must be prioritized for vaccination against mpox and to receive tecovirimat, whenever indicated.

The determination of disease severity in mpox poses a challenge due to the absence of globally accepted criteria. Indeed, the definition of LC disease differs slightly from the criteria employed for defining "severe disease" by the CDC. In the absence of standardized guidelines, our approach to formulating these criteria was grounded in a consideration of Spanish guidelines and other non-standardized frameworks.[20] The criteria proposed by the CDC, encompassing conditions such as hemorrhagic disease, confluent lesions, necrotic lesions, severe lymphadenopathy, and involvement of multiple organ systems, are comprehensive and reflective of the severe spectrum of mpox. However, the global heterogeneity in mpox presentations necessitates a nuanced approach to severity definitions. In our study, we aimed to capture severity not only through the lens of immediate complications but also by considering the potential for a more protracted or disseminated disease course.

An additional noteworthy point of this work is the high prevalence of HIV newly-diagnosed infections. As these diseases share the same routes of transmission, it is not surprising that individuals with mpox are at greater risk to acquire HIV infection.[3] More specifically, in six (30%) of the 20 newly diagnosed HIV infections, individuals showed an HIV viral load > 200 000 cp/mL, which could suggest that the two viruses were both transmitted at a similar date.

Because the mpox outbreak has predominately struck young people, in this work we found a low frequency of individuals previously vaccinated against smallpox. Epidemiological studies conducted in the 1980s found that vaccination against classical smallpox conferred 85% protection against mpox virus infection and prevented from severe mpox.[22,23] The present study shows that prior smallpox vaccination does not entirely protects against severe MPXV infection, as preliminary small series have shown.[24] Furthermore, nearly 30% of patients who were historically vaccinated developed a LC disease. As the number of individuals vaccinated was low, we could not determine the effect of smallpox vaccination according to HIV control status. In any case, it can be hypothesized that, as seen in the setting of other vaccine-eligible diseases, the response to smallpox vaccination might be impaired in PLWH.[25] As a result, they could be at greater risk of developing more severe disease, especially those with advanced immune deficiency. Further studies should address this subject.

This study has some limitations. First, because of the design of this study, which uses convenience sampling, mpox cases included herein might not be representative of the whole spectrum of the disease. Namely, some mild or asymptomatic cases may have not been diagnosed. However, because of PLWH and individuals in PrEP usually show proper adherence to clinical visits, underdiagnosis is very unlikely to be high in this setting.[26,27] Thus, even underdiagnosed, asymptomatic or paucisymptomatic mpox would be more prevalent among individuals without HIV infection, which would be consistent with our results. Second, some factors related to the clinical course were recorded on the basis of the self-reported information. As usually happens in these studies, we cannot rule out recall biases, thus earlier symptoms may have been missed, limiting the accuracy of data. In contrast, as far as we know, this is the first study to compare the emergence of disseminated and prolonged disease among patients without HIV infection, well-controlled PLWH and PLWH with lack of viral suppression, in the present international outbreak. In addition, the analyzed sample of mpox in PLWH is one of the largest reported so far. These are the main strengths of this study.

In conclusion, patients with uncontrolled HIV infection, due to lack of effective ART, are at higher risk of developing more severe outcomes related to mpox. As this outbreak is not over, and the virus continues to find pockets of susceptible individuals, efforts should continue to be made to ensure HIV testing carried out, to link PLWH to care and to counsel about PrEP those without HIV infection. In this setting, ART must be immediately started. Besides, PLWH, especially those with lack of HIV infection control, must be prioritized to receive mpox treatment, when deemed appropriate. Further studies are needed to clarify the potential effectiveness of smallpox vaccination in the prevention of mpox and severe disease.

## AUTHOR CONTRIBUTIONS

*Conceptualization*: Anaïs Corma-Gómez, Juan Macías, and Juan Antonio Pineda. *Methodology*: Anaïs Corma-Gómez, Juan Macías, Juan Antonio Pineda. *Formal Analysis*: Anaïs Corma-Gómez, Juan Macías, Juan Antonio Pineda. *Investigation*, *Resources*, *Data curation*, *Visualization*, *Writing—Review and Editing*: All authors. *Writing—Original Draft*: Anaïs Corma-Gómez, Juan Macías, Juan Antonio Pineda. *Supervision*: Juan Macías, Anaïs Corma-Gómez, Juan Antonio Pineda. *Project Administration*: Anaïs Corma-Gómez. *Funding acquisition*: Juan Macías and Juan Antonio Pineda.

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## CONFLICT OF INTEREST STATEMENT

The author declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

Anaïs Corma Gómez and Juan Macías had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The data that support the findings of this study are available from the corresponding author (A. C. G.), upon reasonable request. The data that support the findings of this study are available from the corresponding author upon reasonable request.

## ETHICS STATEMENT

This study was conducted according to the Helsinki declaration and was approved by the local Ethics Committee (1435-N-22).

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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