Supplementary Appendix

§ The Movie Group:

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Arnau Monforte, MD [8]
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Ramona Hervas Perez [15]
Laura Clotet Romero, MD [15]

First name	Surname
José	Ramón Santos
Lucía	Bailón
Susana	Benet
Jorge	Arroyo Andres
Lorena	Calderón Lozano
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Carla	Budria Serrano
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Supplementary Methods

Instructions for patients for self-collection of samples-

Lesion swab (DO NOT CONFUSE THE TUBE FOR LESION SWEAB and THE TUBE FOR PHARYNGEAL / RECTAL SWAB)

1. Wash and dry your hands.
2. Take the tube labeled as “lesion” and one of the swabs.
3. Rub the swab on a lesion, making some pressure and rolling the swab over the lesion 6 times. Make sufficient pressure to extract fluid from within the injured tissue.
4. Repeat the process on a minimum of three lesions (if possible).[1]
5. Immediately, insert the swab into the tube of medium labeled as "lesion", breaking the top of the swab so that the tube can be closed with the swab inside.

Oropharyngeal swab (DO NOT CONFUSE THE PHARYNGEAL SWAB TUBE and THE LESION/RECTAL SWAB TUBE)

1. Wash and dry your hands.
2. Take the tube labeled as “Pharyngeal” and the second swab.
3. Open your mouth keeping your tongue at the bottom. Rub the swab firmly through the throat (oropharynx) during five seconds.
4. Immediately insert the swab into the tube of medium labeled as "PHARYNGEAL."

Rectal swab (DO NOT CONFUSE THE RECTAL SWAB TUBE with the LESION / PHARYNGEAL SWAB TUBE!)

1. Wash and dry your hands.
2. Take the tube labeled as “Rectal” and the third swab.
3. Introduce the swab through the anal sphincter 3 cm into the rectum and rotate the swab against the anal crypts for five seconds.
4. Immediately insert the swab into the tube of medium labeled as "RECTAL."

[1] Patients were orally instructed to perform the swab in the primary/biggest lesion, and two others if present, until they were in the scar phase. When lesions were cured, patients were asked to perform the swab in the same location(s) where they presented lesions.

Nucleic acid extraction and qPCR

Nucleic acid extraction was performed using the Nimbus platform (Hamilton Company, Reno, US), according to the manufacturer's instructions. Dried blood spot samples were eluted in 1·3 mL of molecular lysis buffer for 30 min at room temperature and after digestion with proteinase K during 1·5 h at 80ºC. qPCR was performed using the LightMix Modular Monkeypox Virus assay (TIB MolBiol, Berlin, Germany) with LightMix Modular MSTN Extraction Control (TIB MolBiol, Berlin, Germany) as the internal control. A thermocycler QuantStudio™ 5 Real-Time PCR System (Applied Biosystems) was used to amplify a 106-base-pair-long fragment of the J2L/ J2R gene from monkeypox virus.[16] Applied Biosystems Interpretive Software was used for detection and data analysis.

Viral culture protocol

We conducted cell culture using a subgroup of specimen selected based on the following criteria. First, we purposively sampled all specimens from a subset of six individuals (regardless of PCR results). This group included three individuals with proctitis, two with tonsilitis and four individuals with HIV. Second, we purposively sampled an additional 96 specimens from the remaining participants to ensure representativeness of sample types, CT values and timepoints. For cell culture, an aliquot of 250 µL was decontaminated using gentamicin and amphotericin B and inoculated into 24-well plates onto Vero E6 cells (ATCC CCL-81) and cultured in Medium 199 supplemented with L-glutamine and 10% foetal bovine serum (complete medium). After sample inoculation followed by a 2 h incubation period, plates were washed twice with PBS 1x, and one mL of complete Medium 199 was added to each well. Plates were incubated in a 5% carbon dioxide atmosphere for 5 days. All experiments included positive controls (i.e., treated with a positive sample with Ct<20, or the supernatant of a positive culture with Ct<15), and negative controls (i.e., untreated cells or mock infection, or treated with a negative sample). Cultures were examined daily for the development of a cytopathic effect.

Linear mixed effects model

Statistical model of viral kinetics

We used a linear mixed effect models to describe the log viral load in the N=77 infected individuals and infer the time to undetectability. The model writes as follows:

$$y_{ijk} = f(t_{ijk}, \psi_{ik}) + e_{ijk} \qquad (1)$$

where y_{ijk} is the j^{th} observation of subject i in compartment k (blood, lesion, pharynx, rectum or semen) at time t_{ijk}, with $i \in 1, \ldots, N$. The function $f(t_{ijk}, \psi_{ik})$ describes the predicted viral load at time t_{ijk} of subject i in compartment k and is written as follows:

$$f(t_{ijk}, \psi_{ik}) = \beta_{0ik} - \beta_{1ik} t \qquad (2)$$

β_{0ik} is the (log) viral load at symptom onset and β_{1ik} is the slope of (log) viral load in compartment k in subject i. The vector of individual parameters ψ_{ik} depends on a fixed effect vector and an individual random effect vector, which follows a normal centered distribution with diagonal variance-covariance matrix Ω_k. We assumed a lognormal distribution for both parameters to ensure positivity. The residual gaussian error e_{ijk} is of constant standard deviation σ_k. Correlation between random effects between were added and kept only if they were above 0.7 and did not deteriorate the relative standard errors of population parameters by more than 50%. All compartments were considered independent and fitted separately. Values under limits of detection were considered left-censored. A limit of detection of 4.04 $\log_{10}$ copies/mL was used in the blood compartment and of 2.9 $\log_{10}$ copies/mL for others. The standard errors were calculated by asymptotic approximation and the inverse of the Fisher Information Matrix. Parameters were estimated using the stochastic approximation expectation maximisation algorithm implemented in Monolix 2018 R2.

To evaluate the assumption that all compartments are independent we added the correlation matrix between individual parameters of the different compartments, relying on the Empirical Bayes Estimates (Figure S6, Appendix 1, page 15). We verified the lognormal distributions and Gaussian residual errors, diagnostic plots are shown in Figure S7, Appendix 1, page 16 (BLQ prediction, IWRES, and the observed data vs prediction).

Sampling the time to virus clearance

The probability of detectable virus in each compartment was calculated by simulations, sampling 500 population parameters in their asymptotic estimation distribution accounting for parameter uncertainty. Then, for each set of population parameters, we sampled 300 individual parameters (leading to a total 150,000 individual parameters per compartment), and calculated the time to viral load clearance in each individual. We then derived the proportion of detectable virus in each dataset at each time, and obtained the mean and the 95% confidence interval from the distribution observed in the simulated datasets.

Table S1. Detailed characteristics of study participants and clinical presentation

	n (%) or median [IQR]
Gender, n (%)	
Female	1 (1)
Male	75 (97)
Trans-woman	1 (1)
Origin, n (%)	
Spain	36 (47)
South/Latin America	31 (40)
Other European Countries	9 (12)
West Africa	1 (1)
Sex orientation, n (%)	
Bisexual men	3 (4)
Heterosexual men	2 (3)
Heterosexual women	2 (3)
MSM	70 (91)
Site of recruitment, n (%)	
Hospital Universitari Germans Trias i Pujol	38 (49)
Hospital 12 de Octubre	18 (23)
STI Clinic BCN Checkpoint	14 (18)
STI Clinic Drassanes-Vall d'Hebrón	7 (9)
Concomitant STIs, n (%)	
Lymphogranuloma venereum	0 (0.0)
Herpes simplex virus	0 (0.0)
Warts	0 (0.0)
STIs in the last 12 months, n (%)	
Gonorrhoea	25 (33)
Chlamydia	13 (17)
Lymphogranuloma venereum	1 (1)
Syphilis	20 (26)
Herpes simplex virus	1 (1)
Warts	3 (4)
Number of sexual partners in past 3 months, median (IQR)	5.0 [3.0, 15.0]
Number of sexual partners in past 14 days, median (IQR)	2.0 [1.0, 3.0]
CLINICAL VARIABLES, n (%)	
Systemic illness	73 (95)
Malaise	55 (71)
Arthralgia/Myalgia	43 (56)
Asthenia	53 (69)

Fever >38ºC	49 (64)
Headache	51 (66)
Odynophagia	33 (43)
Vomiting	3 (4)
Abdominal pain	2 (3)
Tonsillitis	17 (22)
Complications	31 (70)
Pneumonia	0 (0)
Eye involvement	0 (0)
Deep tissue abscess	0 (0)
Encephalitis	0 (0)
Scars	13 (17)
Bacterial skin abscess	17 (22)
Penile oedema	7 (9)
Exanthem	7 (9)
Treatment required	69 (91)
Analgesic	51 (66)
Anti-inflammatory	43 (56)
Antibiotic	21 (27)
Others (antihistamines, gabapentine)	6 (8)
Topic Analgesic	22 (27)
Topic Anti-inflammatory	8 (10)
Topic Anaesthetic	7 (9)
Other topic treatments (corticosteroids, medicinal plant cream)	6 (8)

Table S2. Summary of patients' positivity profile in serial samples, by locations.

Profile	Blood	Lesion	Pharynx	Rectum	Semen
Participants (n)	77	77	77	76	71
All samples negative (n, %)	50 (65)	1 (1)	11 (14)	19 (25)	27 (38)
All samples positive (n, %)	0 (0)	15 (20)	2 (3)	3 (4)	2 (3)
Intermittent shedding (n, %) ǂ	11 (14)	13 (17)	17 (22)	6 (8)	3 (4)
Persistent clearance (n, %) §	15 (20)	47 (61)	47 (61)	48 (63)	35 (49)
Single negative sample (n, %)	0 (0)	1 (1)	0 (0)	0 (0)	2 (3)
Single positive sample (n, %)	1 (1)	0 (0)	0 (0)	0 (0)	2 (3)

ǂ Negative PCR results that became positive in the following time point collected.

§ Positive PCR results that became negative in the following time points.

Table S3. Time until the viral load is below 6.5 log10 copies/mL, by sample type.

Location	Time to viral load below 6.5 log_{10} copies/mL in 50% of patients Days (95% CI)	Time to viral load below 6.5 log_{10} copies/mL in 90% of patients Days (95% CI)	Time to viral load below 6.5 log_{10} copies/mL in 95% of patients Days (95% CI)
Blood	0 (0 – 0)	0 (0 – 0)	0 (0 – 1)
Semen	0 (0 – 0)	2 (0 – 11)	8 (0 – 19)
Rectum	0 (0 – 5)	10 (8 – 14)	12 (9 – 17)
Pharynx	0 (0 – 0)	5 (0 – 10)	9 (2 – 16)
Lesion	9 (8 – 10)	14 (11 – 17)	16 (13 – 20)

Figure S1. Schematic representations of symptom onset and duration

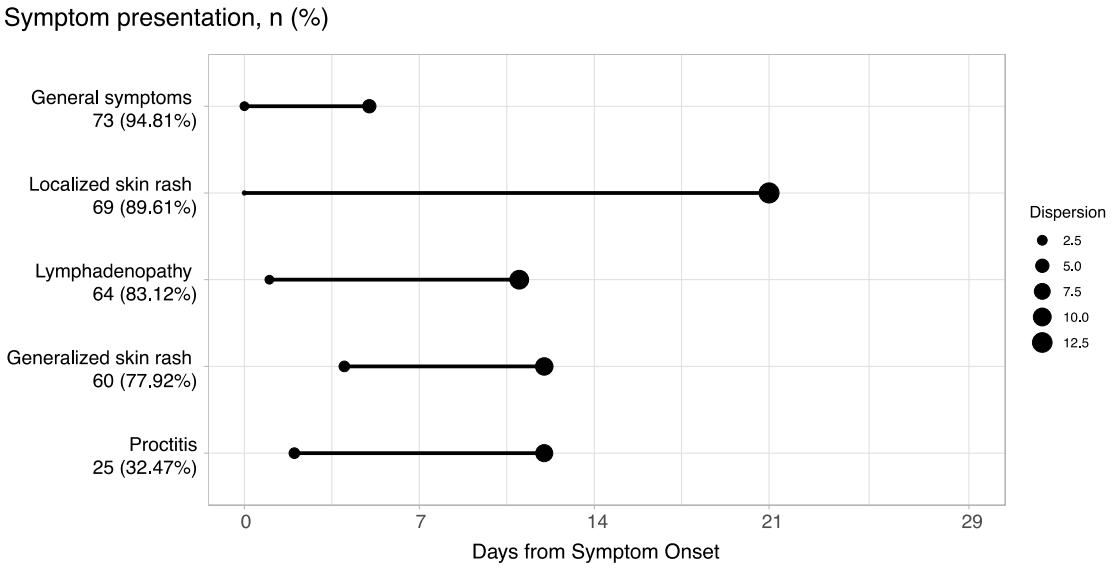

Figure S1. Schematic representations of symptom onset and duration. Each line represents one of the five symptoms measured in the study: systemic illness, localized rash (in the anogenital and/or perioral region), lymphadenopathies, generalized rash (at a distant site from the inoculation point) and proctitis. The number of patients presenting each symptom is shown, more frequent symptoms are located at the top of the graph and less frequent symptoms at the bottom. Each line starts at the median date of symptom appearance and finishes at the median day of symptom resolution. These dates are shown relative to the appearance of the first clinical signs (days from symptom onset). The size of the black circle at the beginning and the end of each line represents the dispersion (IQR) on date of symptom appearance and resolution between patients. Location [Median dates of symptom appearance (IQR) – Median date of symptom resolution (IQR): Systemic illness [0 (2) – 5 (5)]; Localized rash [0 (1) – 21 (13)]; Lymphadenopathies [1 (2) – 11 (11.25)]; Generalized rash [4 (3) – 12 (9.5)]; Proctitis [2 (3) – 12 (9)].

Figure S2. Proportion of samples positive at different timepoints

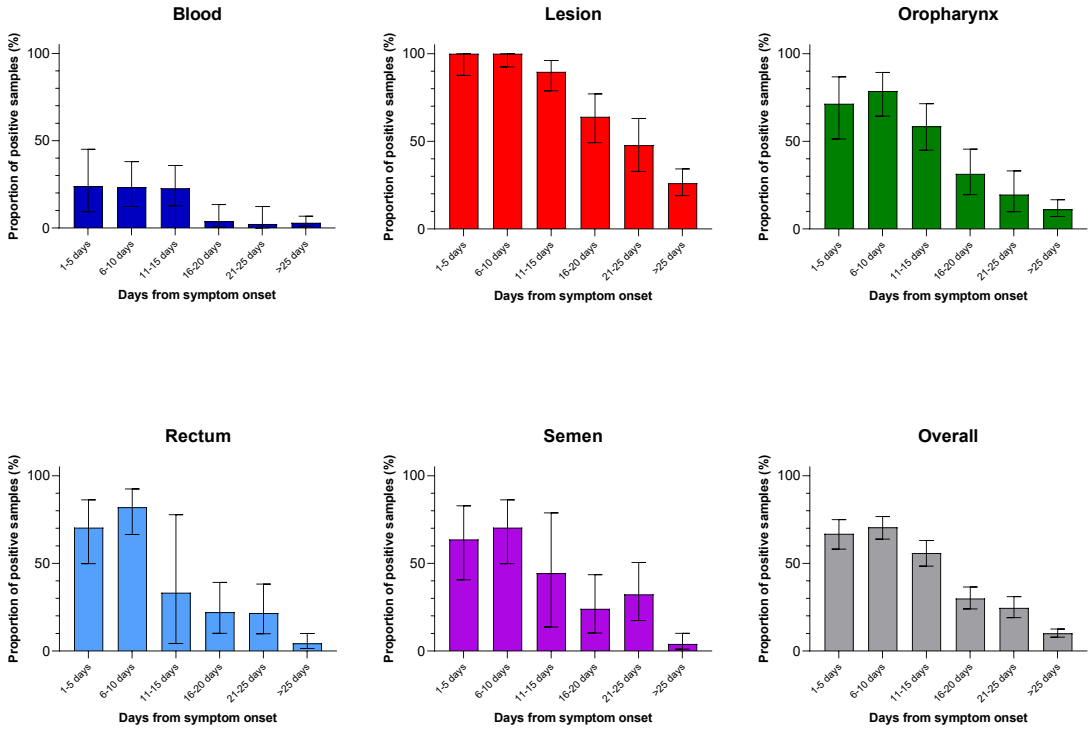

Figure S2. Proportion of samples positive at different timepoints. Proportion of samples where viral DNA was detected by qPCR, grouped in 5-days intervals since symptom onset. Error bars show 95% CI.

Figure S3. Individual Model fits

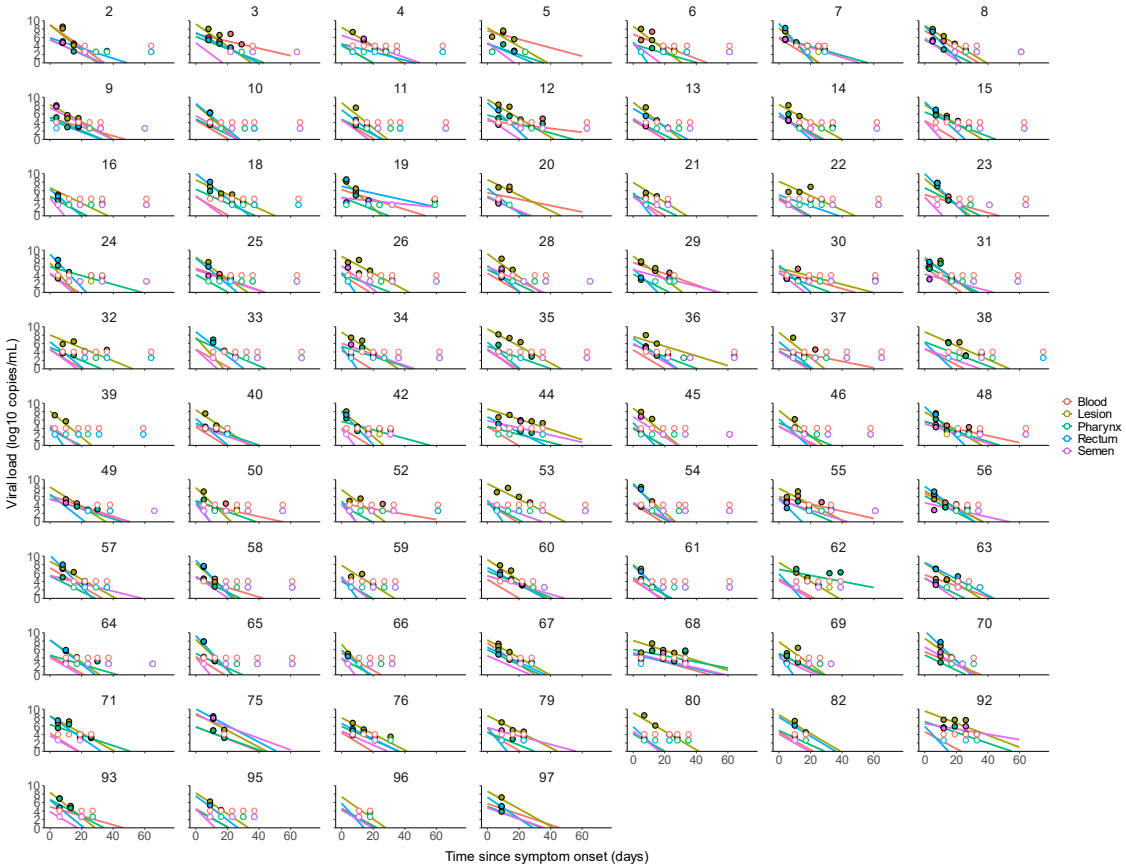

Figure S3. Individual Model fits. Each panel shows individual patients' samples. Solid lines represent model prediction. Empty dots are data under the limit of detection (4.0 $\log_{10}$ copies/mL for the blood compartment and 2.9 $\log_{10}$ copies/mL for all others).

Figure S4. Impact of HIV status (top) and Age (bottom) on the time to viral clearance in each compartment.

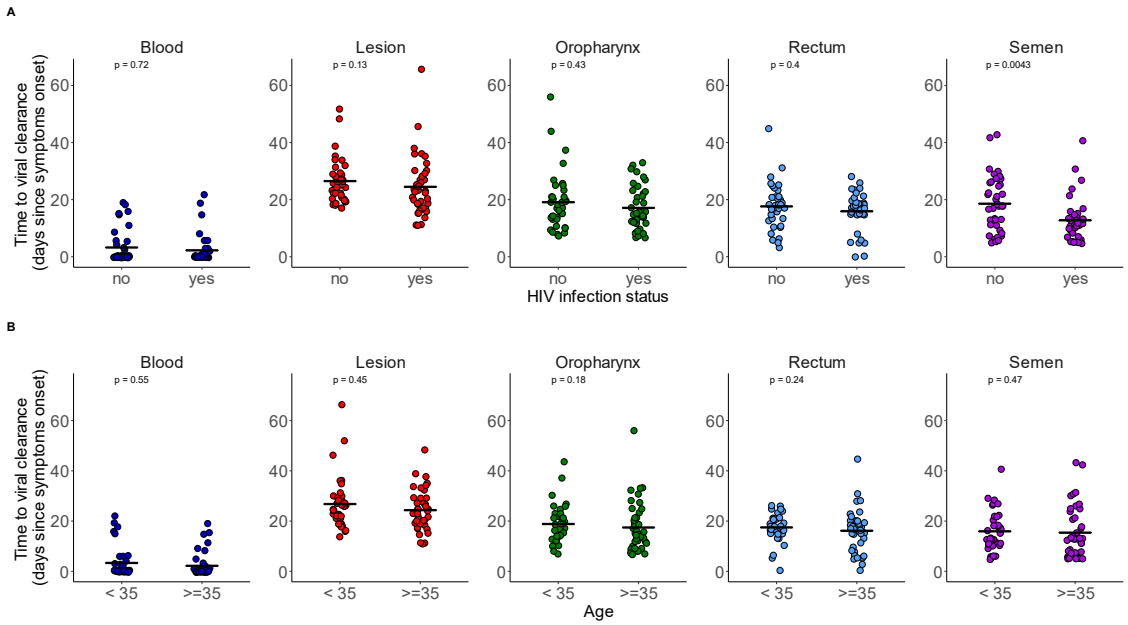

Figure S4. Impact of HIV status (top) and Age (bottom) on the time to viral clearance in each compartment. Age was considered as either below or higher than 35, the median age in the cohort.

Figure S5. Individual profiles showing PCR positivity and viral load for each patient and each sample type

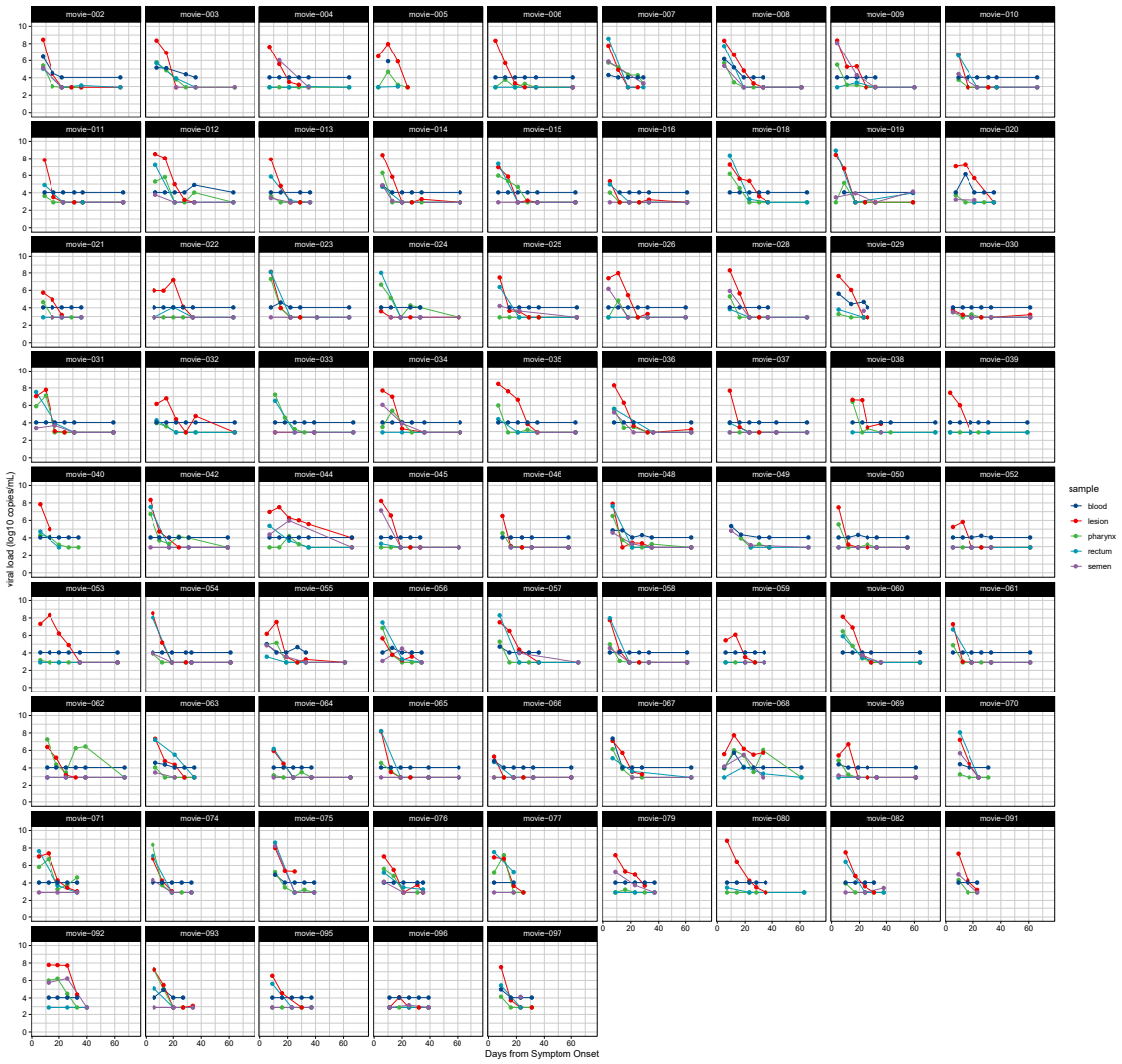

Figure S5. Individual profiles showing PCR positivity and viral load for each patient and each sample type. Viral load measures are represented in viral copies/mL (mL of viral transport media for lesion, pharynx and rectum, mL of blood, and mL of semen). The limit of detection for blood samples was 4.0 $\log_{10}$ copies/mL and 2.9 $\log_{10}$ copies/mL for the rest of the samples. For each patient, the sample collection day was corrected for the date of symptom onset.

Figure S6. Correlations between individual parameter of different compartments.

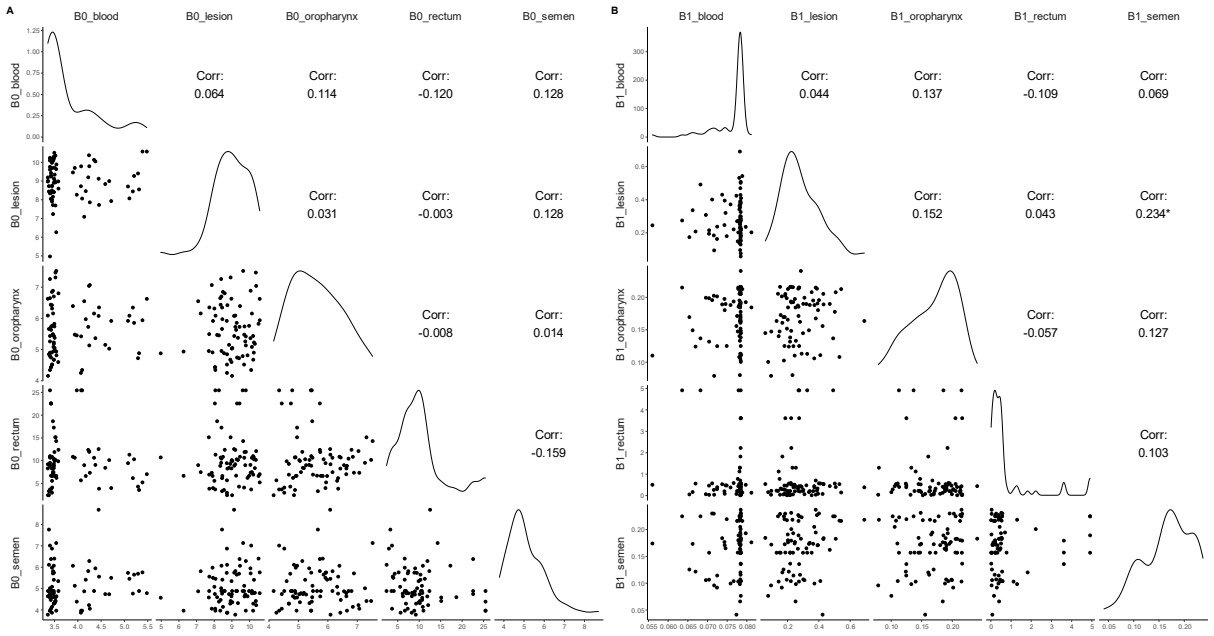

Figure S6. Correlations between individual parameter of different compartments. β_0 is the baseline viral load at symptom onset and β_1 is the decrease rate of the viral load. We present person correlation coefficient. A star indicates a P-value<0.05.

Figure S7. Diagnostic plots for each compartment.

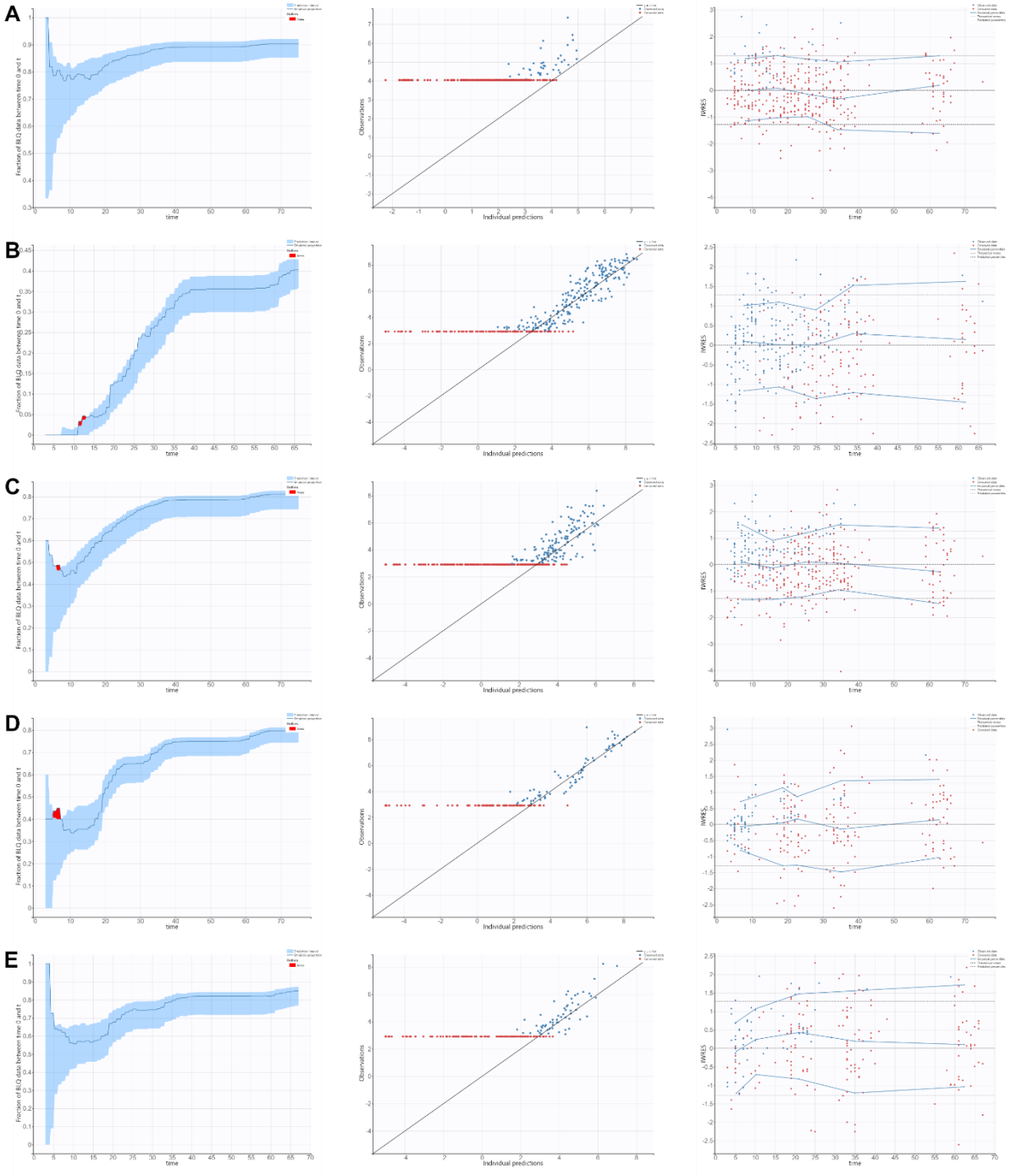

Figure S7. Diagnostic plots for each compartment. A, B, C, D, E, are for blood, lesion, oropharynx, rectum and semen compartment respectively. We represent (from left to right) the BLQ prediction, the observed data vs the predicted value by the model and the IWRES.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA

Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9 & Figure 1
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9, table 1
		(b) Indicate number of participants with missing data for each variable of interest	9, figure 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Figure 1
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	9-10
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10, Figure 2, Table 2, Figure 3
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Figure s4
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	8

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

MoViE Study Protocol

Viral Clearance and Epidemiological characteristics in Patients with Monkeypox

Code: MoViE

Version1.2, 14th September 2022

Coordinating investigator:

Oriol Mitjà Villar, MD PhD

Germans Trias i Pujol University Hospital, Badalona, Spain

Sponsor:

Fundació Lluita contra les infeccions

Ctra. de Canyet s/n Hosp. Germans Trias i Pujol, 2a planta Maternal, 08916 Badalona, Barcelona

Previous version:	Not Applicable
Summary of changes from the previous version:	Addition of three new variables (virus viability, viral sequence variation and serum neutralization capacity) to be studied in the collected samples to answer three new secondary objectives Addition of sample 57 collection for all patients Addition of details on monkeypox vaccinations status Addition of Annex I with a list of Sub-investigators

1 SYNOPSIS

Title	Viral Clearance and Dynamics in Patients with Monkeypox
Code	MoViE
Primary objective	The primary aim of the study is to describe the time to viral clearance in patients with monkeypox. Objectives: • Measure time to viral clearance from **skin lesions** in patients with monkeypox • Measure time to viral clearance from **blood** in patients with monkeypox • Measure time to viral clearance from **throat** swabs in patients with monkeypox • Measure time to viral clearance from **rectum** swabs in patients with monkeypox • Measure time to viral clearance from **semen/vaginal** discharge in patients with monkeypox
Secondary objectives	Analyse the association between clinical features (including symptom resolution) and time to viral clearance. Examine the association between clinical features and demographic and epidemiological factors. Identify behavioural factors associated to monkeypox acquisition and barriers and facilitators for health services access. To evaluate monkeypox specific humoral and cellular responses in a subset of individuals and its association with time to viral clearance and/or reinfection. To describe time to viral clearance in patients with monkeypox considering viral viability as the measure of clearance To evaluate intra-host viral evolution in distinct locations during infection evolution
Study Design	Prospective observational study. Viral load will be measured at days 1, 8, 15, 22, 29 and 57. For the immunology subset, each participant will be followed at 91 and 182 after the monkeypox infection diagnose.
Number of subjects	75 confirmed patients with monkeypox virus infection 50 confirmed patients for the immunology subset

	Movie-CC: 70 confirmed patients with monkeypox virus infection and 140 controls matched to the primary cases (2controls/case).
Inclusion Criteria	1. Adult male or female individuals of ≥18 years old 2. Examined by a specialist on STI and found to have lesions suggestive of monkeypox 3. Symptoms onset date ≤10 days prior to screening/baseline visit. 4. Willing to comply with the requirements of the protocol and available for follow-up for the planned duration of the study. 5. Understands the information provided and is capable of giving informed consent.
Exclusion Criteria	1. Severe disease – defined as requires admission to hospital 2. Inability to consent and/or comply with trial protocol 3. An alternative confirmed diagnosis that can fully explain the illness
Statistical Methods	We will describe the time to clearance of viral DNA from each 'compartment' (i.e skin lesions, blood, throat, rectum, semen, or vaginal fluid). Time to clearance will be described using mean and standard deviation and/or median and interquartile range. Time to clearance between the different compartments will be compared with a logrank test after estimating the Kaplan-Meier. In exploratory analyses we will evaluate variables associated with time to clearance including clinical features of the current illness (for example extent of skin lesions at enrollment, presence or absence of systemic symptoms) and with demographic and co-morbidity data from participants (for example age and HIV status). We will assess the extent to which clinical indicators of disease resolution (for example cessation of fever, re-epithelization of skin) are associated with clearance of the virus. We will use descriptive methods to assess the epidemiological and clinical characteristics of each episode, including the incubation period and the extent of viral dissemination. By using descriptive statistical techniques, including multiple regression analysis, we will identify factors associated with both the acquisition and access to health care We will use descriptive methods to describe time to viral clearance in patients with monkeypox considering viral viability as the measure of clearance; to evaluate intra-host viral evolution in distinct locations during infection evolution and to evaluate virus neutralisation on serum extracted from dry blood spots.
Participating Sites	• Hospital Universitari Germans Trias I Pujol

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2 TABLE OF CONTENTS

3 RATIONALE AND BACKGROUND

Monkeypox is a zoonotic Orthopox virus normally found in West and Central Africa[1]. In these settings a wide range of animal including monkeys and rodents act as reservoirs. Spillover events to humans are well described. These normally result in only small chains of onward transmission, but larger outbreaks have occurred[2,3]. Imported monkeypox has previously been reported in a number of countries, normally associated with travel to an endemic region or occasionally the importation of infected animals[4–6].

Starting in early May 2022 a large number of cases of Monkeypox have been reported in non-endemic countries. Although initial cases appeared to be linked to travel, the majority of subsequent cases appear to have no travel associated risk factors and these cases have predominantly occurred amongst Men who have Sex with Men (MSM) suggesting autochthonous transmission associated with sexual networks[7–9].

Monkeypox is known to be transmitted by close contact with skin lesions of infected individuals and/or via droplets. It is known that the virus can be detected from skin lesions, in blood, in throat swabs and on occasion urine samples. There is limited information as to whether the virus can be detected or persist in other sites including semen. Serial virological monitoring has only been conducted in a small number of individuals and demonstrates that prolonged shedding for at least 2-3 weeks appears to be relatively common[5]. To help control the current outbreak health authorities have utilised a number of strategies including identifying and isolating cases of monkeypox combined with contact tracing and limited use of ring-vaccination strategies[10]. Because the number of cases seen outside of endemic areas has previously been limited there is inadequate data to guide decision making about the duration of isolation, but this is critical to the management of the current outbreak.

We propose an observational study to understand the dynamics of viral clearance amongst patients with confirmed monkeypox to better inform decision making about patient management and isolation guidelines. We will assess the dynamics of viral clearance considering Monkeypox viral DNA detected and the presence of replicating virus in the collected samples. Also, immune analysis will be performed in a subset of individuals to describe humoral and cellular responses to monkeypox in a population expected not to be previously vaccinated against smallpox. Immune analysis will help to understand if whether localized or disseminated /systemic presentation of monkeypox disease is associated with the degree of immune response upon infection in the acute phase (baseline and first month analyses). Analysis at 3 and 6 months after diagnoses will help to explore durability of monkeypox-induced responses and explore its protective effect against reinfections. The neutralization capacity of patients will be also evaluated using the dry blood spot samples self-collected by the patients. Finally, we will also evaluate variations on the Monkeypox viral DNA by sequencing the virus presence in each sample and timepoint.

4 RESEARCH QUESTION AND OBJECTIVES

5 Primary objective

The primary aim of the study is to describe the time to viral clearance in patients with monkeypox.

Primary objectives:

1. Measure time to viral clearance from skin lesions in patients with monkeypox
2. Measure time to viral clearance from blood in patients with monkeypox
3. Measure time to viral clearance from oropharyngeal swabs in patients with monkeypox
4. Measure time to viral clearance from rectum swabs in patients with monkeypox
5. Measure time to viral clearance from semen/vaginal discharge in patients with monkeypox

6 Secondary objectives

a) We will evaluate the association between clinical features (including symptom resolution) and the time to viral clearance.
b) In addition, we will examine the association between clinical features (local or disseminated rash) and demographic and epidemiological factors.
c) Participants will be invited to participate in a structured interview to assess both the factors associated with MPVX acquisition and access to health care (Movie-CC substudy – Annex 1)
d) Analyze humoral and cellular responses against monkeypox at presentation, 1, 3, and 6 months later in a subset of participants

e) To describe time to viral clearance in patients with monkeypox considering viral viability as the measure of clearance
f) To evaluate intra-host viral evolution in distinct locations during infection evolution

The variables to be considered include demographic characteristics, sexual behaviour, travel, exposure to pets, and health care seeking behaviour, typical or atypical clinical Monkeypox presentations, and epidemiological characteristics (incubation period, interval between successive clinical cases). Additional variables that will be considered will include: presence of viable virus in the collected samples and viral DNA sequence, viral neutralization in dry blood spots.

7 RESEARCH METHODS

8 Study design

This is an observational study enrolling patients with monkeypox infection. Following acceptance of participation, eligibility will be confirmed, data collection will begin, and patients will be trained on self-collection of samples. Samples will be obtained at different timepoints and sent to the central laboratory for monkeypox viral load quantification.

Patients must meet all of the following inclusion criteria and none of the exclusion criteria in order to be eligible for the MoViE study:

9 Inclusion Criteria

1. Adult male or female individuals of ≥18 years old.
2. Examined by a specialist in STIs and found to have lesions suggestive of monkeypox.
3. Symptomatic with symptoms onset date ≤10 days prior to screening/baseline visit.
4. Willing to comply with the requirements of the protocol and available for follow-up for the planned duration of the trial.
5. Has understood the information provided and capable of giving informed consent.

10 Exclusion criteria:

1. Severe disease – defined as requires admission to hospital
2. Inability to consent and/or comply with trial protocol
3. An alternative confirmed diagnosis that can fully explain the illness

11 Setting

Patients will be recruited from the following clinics:

- Hospital Universitari Germans Trias I Pujol

  Carretera de Canyet, s/n, 08916 Badalona, Barcelona

- Hospital Universitario 12 de Octubre

  Av. De Córdoba, s/n, 28041 Madrid

- Atenció Primària Metropolitana Nord, Sabadell, Spain

  CAP Sant Fèlix, Ctra de Barcelona 473, 08204 Sabadell (Barcelona)

- BCN Checkpoint

  Comte Borrell 164-166 08015 Barcelona

- Unitat de Medicina tropical i Salut internacional Drassanes
  Carrer de Sant Oleguer, 17, 08001 Barcelona
- Hospital Universitario Fundación Jiménez Díaz

  Av. De los Reyes Católicos, 2, 28040 Madrid

- Instituto de Investigación Sanitaria Hospital 12 de Octubre

  Av. de Córdoba, s/n, 28041 Madrid
- The University Court of the University of Glasgow

  University Avenue, Glasgow G12 8QQ

CEEISCAT Will be in charge of secondary objective (c), the Movie-CC Substudy.

IrsiCaixa will be in charge of secondary objective (d) in the immunology subset.

Instituto de Investigación Sanitaria Hospital 12 de Octubre will be in charge of secondary objective (e).

The University Court of the University of Glasgow will be in charge of secondary objective (f) and (g).A complete list of sub-investigators is shown in Annex 1.

12 Variables/Endpoints

- Site, Location
- Monkeypox viral DNA detected (lesional swab, blood, oropharyngeal swab, rectal swab, semen / vaginal discharge)
- Age, sex
- History of HSV or HIV infection
- Transmission rank (Index, Secondary, Isolated)
- Exposure setting (household, friends, intimate, sexual)
- Exposure risk factor (skin cuts, sores, or ulcers before exposure)
- Number of sex partners in the past 14 days
- Date of exposure (range is acceptable)
- Date of prodrome symptoms start
- Date of vesicular rash start (date of the first vesicle)
- Prodrome (fever, night sweats, headache lymph node swelling)

- Approximately maximum number of concurrent skin lesions (e.g., 1, 30, 100)
- Distribution of lesions (face, scalp, trunk, arms, hands, legs, feet, soles, palms, penis, scrotum, labia majora, groin, buttocks)
- Distribution (localized to 1 region, 2 regions, more than 2 regions)
- Distribution in generalized rash (centrifugal, centripetal, even distribution)
- Development (monomorphic, pleomorphic)
- Proctitis manifestations
- History of smallpox vaccination
- History of MVA-BN vaccination: dose, route (ID/SC), number of vaccines administered (1/2), date of vaccination to address time since vaccination to Monkeypox onset.
- Travel history and mass-gathering event attendance (including sexual private parties)
- Symptom evolution (complete resolution of the lesions, persistence of crusted lesions, persistence of vesiculo-pustular lesions, new vesiculo-pustular or ulcerativev lesions, development of complications that require hospitalization).
- Chlamydia, gonorrhoea, syphilis, herpes or trichomoniasis concomitant tests results.
- Use of PrEP
- Treatments received for MKP
- New episodes of monkeypox in follow-up visits at day 91 and 182 for the immunology subset
- Immune endpoints will include: determination of monkeypox-specific antibodies by ELISA, virus neutralization assays using a viral neutralization assay with MKP clinical isolates, quantification of IFNg positive responses by ELISPOT and/or Flow cytometry followed by intracellular staining (TBC upon reagents availability)
- Further variables will be collected regarding the recent history of sexual relationships and health seeking behaviours
- Viral viability
- Viral evolution at different sites
- Viral neutralization capacity from dry blood spot sampling during the firsts weeks of infection

13 Visits and data collection

Candidates will be recruited in community health facilities and hospitals of the participating sites in Spain. At the time of initial diagnostic testing patients will be approached to discuss potential study participation. Interested candidates will be directed to the screening/baseline visit to obtain informed consent and assess eligibility. In addition, patients will be offered and asked to consent to a telematic interview to collect exposure-related data and health care seeking behavior.

14 Screening/baseline (day 0)

The screening/baseline visit will be an in-person visit, in a clinical setting or at home, with a study investigator.

The procedures will be the following:

- In-person information of study details
- Informed consent form obtention

- Interview the patient: clinical features of the current illness, demographic and co-morbidity data from participants.

Eligibility: verification of inclusion and exclusion criteria. If the patient is not eligible, the study staff will inform the patient of the reason and arrange for the necessary medical care.

If the patient is determined to be eligible, the study staff will instruct the patient on how to collect the samples:

1. Self- collection of vesicle fluid from one or more vesicles or ulcers, or from a dry scraping of the scab
2. Blood collection: using a finger prick and a Dry Blood Spot
3. Self-collection of a buccal and oropharyngeal swab.
4. Self-collection of a rectum swab.
5. Instruct the patient on how to collect a semen sample (males) / Self-collection of a vaginal discharge sample (females).

Patients will be provided with 6 kits to collect the subsequent samples at days 1, 8, 15, 22, 29 and 57. The semen/vaginal discharge sample and the rectal swabs will be collected only at days 1, 15, 29 and 57.

For individuals recruited in a clinical setting with available sample processing and storage laboratory will be invited to participate in the immunology subset and if accepted, 40ml blood draw will be performed for plasma and PBMC isolation. Recruitment for the immunology subset will be concluded once reached the foreseen number of patients.

MoViE study patients will be also invited to participate in the Movie-CC study (annex 1). An independent informed consent will be obtained for the patients who are interested in participating in the Movie-CC study (Annex 2).

15 Sample collection: Days 1, 8, 15, 22, 29, and 57

Participants will be required to conduct self-collection procedures:

1. Self- collection of vesicle fluid from one or more vesicles or ulcers, or from a dry scraping of the scab
2. Blood collection: using a finger prick and a Dry Blood Spot
3. Self-collection of a buccal and oropharyngeal swab.
4. Self-collection of a rectal swab (only on days 1, 15, 29, and 57)
5. Collection of a semen sample / Collection of a vaginal discharge sample (only on days 1, 15, 29, and 57)

The samples will be picked up by courier at the patient's home, taking into account the stability of each sample.

Patients who test negative for all samples at day 1 will not be required to submit further specimens and will be withdrawn from the study.

16 Follow-up visits: Day 29

On day 29, the research team will contact the patient to gather data on symptom evolution.

17 Immunology subset follow-up visits: Days 29, 91, and 182

Participants in the immunology subset will be scheduled for a clinical visit and a 40ml blood draw at the clinical site at days 29, 91 and 182. Information on new monkeypox infections will be recorded.

18 Schedule of Procedures

	Screening/ Baseline	Day 1*	Day 8	Day 15	Day 22	Day 29	Day 57	Day 91#	Day 182#
Allowable window (days)	0	+/-1	+/-2	+/-3	+/-3	+/-3	+/-5	+/-7	+/-7
Informed consent signature	X								
Symptom data	X					X		X#	X#
Exposure data	X								
Inclusion / exclusion criteria	X								
Lesional swab / dry scraping		X	X	X	X	X	X		
Blood collection (Dry Blood Spot)		X	X	X	X	X	X		
Oropharyngeal swab		X	X	X	X	X	X		
Rectum swab		X		X		X	X		

Semen/ Vaginal discharge sample		X		X		X	X		
Blood draw (40ml) #	X#					X#		X#	X#

* Patients who test negative for all samples at day 1 will be withdrawn from the study.

Immunology subset only. Baseline sample has a window of +/-3 days provided that baseline samples is still within ≤10 days from the onset of symptoms (i.e. fulfills with Inclusion criteria 3). Participants can be also recruited for the immunology subset at day 29 in those cases in which baseline sample was not possibly taken for logistic reasons.

19 Data sources

Data sources will consist of the patient medical health records and the laboratory results.

20 Laboratory tests and procedures

Test	**Type of Sample**	**Description**	**Location**	**Visit**
Quantitative measurement of Monkeypox viral load	Lesional swab dry scrap Blood Oropharyngeal swab Rectal swab Semen / Vaginal discharge sample	Quantitative PCR of Monkeypox	Microbiology Service of the HUGTiP	Day 1, 8, 15, 22, 29 and 57
Measurement of viral viability	Lesional swab Oropharyngeal swab Rectal swab Semen / Vaginal discharge sample	Viral culture, cellular toxicity and replication measuremente	Instituto de Investigación Sanitaria Hospital 12 de Octubre	Day 1, 8, 15, 22, 29 and 57
Viral sequencing	Lesional swab Oropharyngeal swab Rectal swab Dry blood spot	Sequencing of Monkeypox Viral DNA	The University Court of the University of Glasgow	Day 1, 8, 15, 22, 29 and 57

	Semen /Vaginal discharge sample			
Serum neutralization capacity	Dry blood spot	Monkeypox Virus neutralization assay	The University Court of the University of Glasgow	Day 1, 8, 15, 22, 29 and 57
Storage	Leftovers of: Lesional swab / dry scrap Blood Oropharyngeal swab Semen / Vaginal discharge sample	Future Investigations	Microbiology Service of the HUGTiP (during the study) Collection registered at the ISCIII Registro Nacional de Biobancos	Day 1, 8, 15, 22, 29 and 57 (if applicable)
Humoral responses to monkeypox *	Plasma	Serology and virus neutralization assays	IrsiCaixa	Day 1, 29, 91 and 182
Cellular responses to monkeypox*	PBMC	T cell based assays (ELISPOT +/- Flow cytometry with intracellular staining)	IrsiCaixa	Day 1, 29, 91 and 182
Storage*	Leftovers of plasma & PBMC	Future Investigations	IrsiCaixa	Day 1, 29, 91 and 182

*Immunology subset only

21 Study size

Being a descriptive exploratory study, this study aims to include 75 patients with confirmed monkeypox infection.

Immunology subset will include approximately 50 participants from recruiting sites with available laboratories to process and store PBMC and plasma within 4h from venopucture.

Movie-CC: 70 confirmed patients with monkeypox virus infection and 140 controls matched to the primary cases (2controls/case).

22 Data management

Results of laboratory analysis will be collected in a database by laboratory study-staff, with personal system of access by username and password. Clinical data will be collected in an independent database by the investigator or delegated study staff with a personal system of access by username and password. Based on the study ID, databases will be merged to create the final study database.

A data management system will be set up and procedures will be implemented to warrant homogenization, traceability, and data quality. Quality control procedures will be put in place for data checking. Consistency checks will be created to reduce errors during data entry.

Data management team and investigators will be the only ones to access the database. The backup of the data will be done on a timely basis. The final data for the analysis will not contain any personal identifiable data of the participating patients. Consequently, those receiving the final data for analysis will not have access to any information that might help to physically identify patients.

Each participant will be assigned a unique study identification number and all data will be recorded and analyzed with this unique identification number. All information will be stored in a coded fashion in an encrypted password-protected database, using unique patient identifiers. All devices and servers that store protocol data with personal identifiable information will use full drive encryption, require OS-level and application-level authentication, field-level data encryption, and limit authenticated access through the use of user profiles and groups. All transmitted data will be encrypted at source and decrypted at destination over secure channels.

23 Data analysis

We will describe the time to clearance of viral DNA from each 'compartment' (i.e skin lesions, blood, throat, rectal, semen, or vaginal fluid). Time to clearance will be described using mean and standard deviation and/or median and interquartile range. Time to clearance between the different compartments will be compared with a logrank test after estimating the Kaplan-Meier. In exploratory analyses we will evaluate variables associated with time to clearance including clinical features of the current illness (for example extent of skin lesions at enrollment, presence or absence of systemic features) and with demographic and co-morbidity data from participants (for example age and HIV status). We will assess the extent to which clinical indicators of disease resolution (for example cessation of fever, re-epithelization of skin) are associated with clearance of the virus.

Associated factors to both acquisition and access to health care will be identify by descriptive statistical techniques including multiple regression analysis.

All analyses will be done with the R statistical package, version 4.1 or higher, under a significance level of 0.05. The characteristics of the study population will be described using frequencies for categorical variables and using mean and standard deviation and/or median and interquartile range for quantitative variables. We will use the chi-square test for categorical variables and the Mann-Whitney U-test for continuous variables. The linear association between variables will be assessed by means of the Spearman correlation. Virological reduction will be determined by comparing the mean reduction of the viral load between consecutive timepoints. Intragroup comparison (signed rank wilcoxon test) will be performed to assess the viral load evolution between consecutive timepoints. The viral load will be provided in logarithmic scale; if less than 15% of specimens presents undetectable viral load at a given follow-up assessment a value of 3 log10 copies per mL (i.e., lower limit of detection) will be assigned for the purpose of statistical analysis. Otherwise, we will consider undetectable viral loads as left-censored values.

24 Quality control

Quality control mechanisms (e.g., verification of data completeness, validations, and edit checks), which will be automated at time of data entry, will be built into the database. The clinical data will be entered by the investigators themselves and/or authorized personnel directly in database. Laboratory data will be entered by laboratory staff and/or authorized personnel directly in database

There will be a training before the start of data collection where the principal investigator and collaborators and laboratory staff and collaborators will be trained on the following topics:

- The background and objectives of the study
- Study procedures
- Safety reporting
- Ethical regulations
- Data entering

25 Limitations of the research methods

The main threat for the development of this study is the lack for patients' adherence to collect all samples across the study visits. This threat will be mitigated by compensating patients for loss of productivity.

26 PROTECTION OF HUMAN SUBJECTS

This study will be carried out following the ethical principles recovered in the Declaration of Helsinki from Brazil, October 2013 and according to the Spanish regulatory (Orden SAS/3470/2009 and the instructions of the regions involved).

The protocol will be, at least, approved by one Ethics Committee. The participation of the investigators in this study is free, voluntary and independent.

27 Benefit/Risk evaluation

Not applicable

28 Patient information and informed consent

The investigator will provide all necessary oral and written information on the study to each patient, so that the patient can understand the scope of the study and give, if he/she wishes, his/her written consent to participate. Before making the decision, the patient will be given sufficient time to discuss any question they may have and for those questions to be resolved. Written information will be provided by means of the patient information sheet. Written consent will be obtained by means of the informed consent form.

Participating patients have the right to withdraw their previously given consent any time they want, with no need to provide explanations and without affecting their medical care in any way. In the informed consent form, it will be stated that if consent is withdrawn, any data collected before withdrawal of consent will be kept to ensure the validity of the research and to comply with legal duties. One original signed informed consent form will be kept at the investigator site file, and one will be provided to the patient.

If new information should emerge during the conduct of the study that might require a change in the patient information sheet, this will be provided as soon as possible to the patient so that he/she can give his/her consent again if they agree.

The informed consent will be obtained during the screening/baseline visit, and study procedures will start after the patient has signed the informed consent form. The investigator will keep a call record of the informed consent process.

29 Confidentiality

The processing of the data to be compiled by the Sponsor will be performed in accordance with Spanish Organic Law 3/2018, which develops the General Data Protection Regulation 2016/679

on data protection and privacy for all individuals within the European Union. The patient will be guaranteed anonymity, and must be informed that all communication will take place between him/her and the investigator – not the Sponsor of the clinical trial. The patient will be identified in the records by the corresponding unique code number, not associated with any of his/her personal data.

In the study database pseudonymized data will be collected and stored. The database will be accessible to the Sponsor, the data management team, the investigators, and the study staff with data entry privileges. For data safety and audit trail purposes each person using any of the defined study databases will be required to define clear data access. Individual user/password codes will be available for each person with access privileges and different roles will be established for data entry and/or revision.

To allow audits and inspections, access to data to Health Authorities (Spanish Agency for Medicines and Health Products, AEMPS), the Ethics Committee and personnel authorized by the Sponsor will be guaranteed while maintaining the confidentiality thereof according to current legislation.

Data collected will be stored in a study database, that will be hosted at a secure data centre with appropriate series of protocols to test and maintain network security, and to provide access management policies for network drives, databases, and remote access.

Data transmitted to third countries, and other countries, will in no case contain personal data. If such transfer occurs, it will be for the same purposes of the study described and ensuring confidentiality, at least to the level of protection of the law in Spain.

30 Prescription habits interference

Not applicable.

31 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Not applicable.

32 PLANS FOR DISSEMINATION AND COMMUNICATING RESULTS

The discoveries generated from this study will be disseminated within the scientific community via publications in peer-reviewed scientific journals. Given the novelty of the research field and its potential impact isolation policies for monkeypox infected patients, we anticipate one-two high impact publications as a result of this study. All publications resulting from this funding will be published in open access repositories. Data, software, algorithms, workflows and sequences will be available as supplementary materials in these publications as well as in open science repositories (GitHub, OpenAire). Results from this project will also be presented in prestigious national and international scientific conferences in the field of emerging infectious diseases. Our team also works closely with Ministries of Health and Public Agencies. The findings of this project will be communicated to these authorities for their translation into future programmatic impact.

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ANNEX 1: LIST OF PARTICIPATING SUB-INVESTIGATORS

Attached separately.

Version 1.0 14th September 2022

Site	**Sub-Investigators**
Hospital Germans Trias i Pujol - UITS	Clara Suñer, Maria Ubals, Andrea Alemany, Xènia Oller, Martí Valls, Adrià Mendoza
Hospital Universitario 12 de Octubre	Eloy José Tarín Vicente
BCN Checkpoint	Pep Coll, Àngel Rivero, Adrià Mendoza
Unitat de Medicina tropical i Salut internacional Drassanes	Vicent Descalzo
Laboratori de Biología Molecular Hospital Germans Trias i Pujol	Pere Joan Cardona, Àgueda Hernández, Cristina Casañ
CEEISCAT	Jordi Casabona, Héctor Martínez, Cinta Folch, Cristina Agustí, Ibrahim Sönmez
Hospital Germans Trias i Pujol - UMI	Bea Mothe
Fundació Lluita contra les Infeccions	Susana Benet
Atenció Primària Àrea Metropolitana Nord de Barcelona	Núria Prat
IRSICaixa	Christian Brander, Jorge Carrillo Molina, Nuria Izquierdo-Useros, Jordana Muñoz Basagoiti
Instituto de Investigación Sanitaria Hospital 12 de Octubre	María Dolores Folgueira, Margarita Robles
The University Court of the University of Glasgow	Emma Thomson, Ana da Silva Filipe, Paul Ellis, David Robertson