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MAJOR ARTICLE

Clinical characterisation and outcomes of human clade iib mpox virus disease - a European multicentre observational cohort study (MOSAIC)

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Background The global mpox outbreak which started in May 2022 was caused by a novel clade IIb variant of the mpox virus (MPXV). It differed from the traditional Western and Central Africa disease in transmission patterns and clinical presentation.

Methods To address the need for detailed clinical and virologic data, we conducted an observational cohort study (MOSAIC) during May 2022-July 2023 in individuals with confirmed MPXV infection enrolled in six European Countries. Case-management decisions were left to the attending physician. Participants were monitored for up to six months for clinical signs/symptoms and clinical and virologic outcomes through hospital visits, phone interviews, and self-administered questionnaires. Outcomes included time-to-lesion resolution, clinical status, and virus clearance.

Results The 518 participants not receiving any specific treatment (“untreated”) were diagnosed a median 5 days from symptom onset; 90% were managed as outpatients. Lesions were mostly cutaneous (88%) as and peri-genital (74%). By Day 14 from the first PCR-positive sample, 39% had resolved lesions. Time-to 95% unculturable virus was longest in cutaneous lesions (52 days). A putative systemic antiviral was available for 57 participants, 44% as in-patients, 34% and 58% had resolved lesions by D14 from the first PCR-positive sample and from treatment start, respectively. Time-to 95% unculturable virus was 60 days in skin and oropharynx. No death or recrudescence occurred by Day 180.

Conclusion MOSAIC provides comprehensive insights into the clinical and virologic characteristics of mpox caused by the clade IIb variant. The study forms the basis of clinical characterisation for ongoing mpox outbreaks.

Key words Mpox; Clade IIb; viral load; Lesion resolution; Observational cohort

Key points An observational study of 575 mpox cases from six European countries; 39% of untreated participants (90% managed as outpatients) had lesions resolved 14 days from

laboratory-confirmed infection; skin lesions still had culturable virus in 5% of participants by day 52.

INTRODUCTION

Between July 2022 - May 2023, the World Health Organization (WHO) declared a Public Health Emergency of International Concern (PHEIC) for a multi-country outbreak of mpox caused by a novel clade IIb variant of the mpox virus (MPXV). This outbreak was substantially different from the typical Central and Western Africa outbreaks in terms of transmission patterns. It marked the first large-scale global mpox event and the first time with extensive, sustained human-to-human transmission. The clinical presentations were also different: rather than a rash covering most of the body, often with non-specific symptoms including fever, fatigue and lymphadenopathy (1), clade IIb MPXV appeared milder, patients typically presented with localised rashes (2, 3), and intimate contact was the primary route of transmission, in adults usually associated with sexual activity (3).

While knowledge was rapidly generated on clinical characterisation and outcomes from retrospective case-series (4-8), a need was recognised to establish a protocolised, multi-country evaluation of the clinical characteristics and outcomes of clade IIb mpox infection. To respond to this need, following a request from the European Medicines Agency (EMA) Emergency Task Force (ETF), we initiated a multi-country observational cohort study in May 2022 (9, 10), with the primary objective of describing the clinical and virologic characteristics and outcomes of participants with laboratory confirmed MPXV primarily in the European region.

METHODS

Study design

MOSAIC was designed as a multi-country observational cohort study to describe natural history, clinical presentation, and clinical and virologic outcomes of clade IIb MPXV disease – including both participants who were administered a systemic putative antiviral product and those who were not. MOSAIC was approved as an observational cohort study in the UK, Switzerland, and Singapore, but was classified as a Low Intervention Clinical Trial (LICT) in participating EU countries, according to EU Clinical Trial Regulation (CTR) 536/2014.

MOSAIC enrolled inpatients and outpatients with either laboratory-confirmed MPXV infection or with clinically-suspected mpox pending laboratory confirmation – those testing negative were subsequently withdrawn. Participants were enrolled at any time following diagnosis or suspicion of mpox and followed for up to six months. Treatment decisions were left to treating physicians according to national guidelines and drug availability.

Data on clinical signs and symptoms were collected on Day (D)1, D14, D28, D60, D180 from the date the first sample was taken that returned a positive PCR result for MPXV. Data were also collected for all days of hospitalisation for inpatients up to D180. Data could be collected retrospectively or prospectively, depending on the time elapsed between the collection of the diagnostic sample and participant's consent. Data were collected via participant interview during hospital visits or by phone, as well as from the participant's hospital record or from participants' responses to self-administered questionnaires.

Two lesion swab samples (skin or mucosal), one oropharyngeal swab sample, and one blood sample were to be collected on D1, D4, D8, D14 and D28, as permitted by local and national infection prevention and control measures.

The data dictionary is available in **Supplementary Appendix 1**. All data were recorded on REDCap (version 13.1.30) (11, 12).

Setting

MOSAIC was approved in 51 hospitals in seven countries: Belgium, France, Italy, Singapore, Spain, Switzerland, and the UK. Singapore did not enrol any participants.

Outcomes

The primary outcome measure was time-to-lesion resolution – defined as the first day on which on which any of the following criteria were met: all lesions are resorbed, scabbed, or desquamated, and mucosal ulcers healed – without any serious complications by D14 – defined as a Serious Adverse Event (SAE) that is life-threatening, results in hospitalisation, prolongation of existing hospitalisation, disability, incapacity, or a congenital anomaly; or any other medically-significant complication.

Secondary outcome measures evaluated clinical and virologic outcomes. Clinical status was assessed on D14 and D28 according to a four-point ordinal scale: a) all lesions are resolved and no serious complications, b) active lesions and no serious complications, c) serious complication and/or hospitalisation due to mpox, or d) death.

Evidence of recrudescence or relapse was also assessed at D60 and D180 either in-person or remotely.

The number and type of Serious Adverse Events (SAEs), Suspected Adverse Reactions (SARs), and Suspected Unexpected Serious Adverse Reactions (SUSARs) were assessed up to D28 and assessed by the study medical monitor.

Virologic outcomes were assessed on D4, D8, D14 and D28 and included changes in cycle threshold (Ct) value from baseline in blood, lesion, throat and anal samples.

Statistical methods

Due to the descriptive nature of this study and the challenges in predicting the trajectory of case numbers during an outbreak, no formal sample size calculation was conducted.

The overall analysis population includes all participants who met the eligibility criteria and had at least one lesion at baseline.

Data and analyses are presented for the overall population and by treatment status. Participants who received an mpox-specific systemic antiviral product – defined as administration of systemic active antiviral treatment: tecovirimat, cidofovir, or tecovirimat plus cidofovir – within 14 days of their first mpox PCR positive sample are classified as “treated participants”. Any other participant is classified as “untreated participants”.

Time-to-event analyses were done for all participants considering as baseline the date of the first MPXV PCR-positive sample. The same analyses were repeated for treated participants counting from the first day of antiviral treatment.

Time-to-lesion resolution is presented by treatment status using Kaplan-Meier (KM) curves until D28. KM estimates were used to compute the percentage and 95% confidence interval of participants with lesions resolved without complications at D14 and D28. Clinical status at D14 and D28 is presented as number and percentage of participants according to the above-mentioned four-point ordinal scale for all eligible participants and according to treatment status.

Sankey diagrams summarising change in clinical status from D14 to D28 are presented for treated and untreated participants who attended both follow-up visits. For treated participants, two Sankey diagrams are presented showing D14 and D28 from (a) treatment initiation and (b) the date the first sample was taken that returned a positive PCR result for mpox.

A linear mixed-effects model was used to describe the kinetics of the Ct values in mpox-infected individuals for each treatment group, and to estimate the time to Ct ≥ 40 (indicative of virus undetectability) as well as the time to Ct ≥ 30 (used as a proxy for shedding of culturable virus) in plasma and skin, oropharyngeal, and rectal/peri-anal swabs (see **Supplementary Methods** for detailed statistical methods).

The probabilities of detectable and culturable virus were calculated by simulations (see **Supplementary Methods** for detailed statistical methods).

The MedDRA System Organ Class (SOC) and Preferred Terms (PT) are presented for each adverse event (AE) and SAE for the treated and untreated cohorts using the MedDRA Web-based Browser v27.0 (13). Analyses were performed using R Statistical Software (v4.1.2; R Core Team 2021).

Virology lab methods

All procedures on MPXV infectious samples were conducted under strict biosafety conditions, according to national regulations and WHO recommendations. MPXV-specific real-time PCR assay was performed on samples using the local procedures available in each country. A PCR signal with Ct value ≥ 40 was considered negative.

Ethics and regulatory approval

The study was registered on the EU Clinical Trials Register (2022-501132-42-00) and approved by the local ethics committees in each participating country (**Supplementary Appendix 2**).

RESULTS

During June 2022 - July 2023, 602 participants were enrolled in Europe across 37 hospitals out of the 51 outpatient and inpatient facilities that had been activated. Details of enrolment by country are reported in **Supplementary Results Table S1**.

Of the participants enrolled, 27 were subsequently excluded from the analyses either because they had no lesions at baseline or because their lesions had already resolved (**Fig 1**). Of the 575 participants with unresolved lesions included in the final analysis, 57 (10%) were treated with a putative mpox-specific systemic antiviral (classified as “treated”) within 14 days of their initial presentation. As case-management decisions were left to the attending physician and depended on drug availability, findings in the two cohorts are presented separately, and no between-groups comparison is made.

Fig 1. Flowchart summarising study enrolment, eligibility and inclusion in the analysis population

Untreated participants

Participants' median age was 37 years (IQR 32–44), 99% were male (**Table 1**); 106 (22%) participants had a concomitant active sexually-transmitted infection; 220 (43%) had a history of HIV/AIDS diagnosis, of whom 210 (95%) were on antiretroviral treatment – their median of CD4-T at last follow-up was 743/ μ l with 19/188 (10%) having CD4<350. The 153 (51%) participants who did not have an HIV diagnosis were taking HIV pre- or post-exposure prophylaxis (PREP, PEP).

Table 1. Baseline demographic and comorbidities characteristics of untreated and treated participants

A median of five days (IQR 3–8) had elapsed from symptom onset to the date when the PCR sample was taken for diagnosis; 90% were managed as outpatients (details in **Table 2**).

Lesions were mostly cutaneous (450/511, 88%): 50% of participants presented skin lesions only and 38% both skin and mucosal lesion, 12% had exclusively mucosal lesion(s); 53% of cases had 5 or fewer lesions and 93% had 25 or fewer, in 74% of cases in the peri-genital or peri-anal region. Active skin lesions were mostly vesicles (77%) and pustules (63%). Bacterial superinfection of the lesion occurred in 7% of cases. Lymphadenopathy was found in 48% of participants, fever in 47%, proctitis in 26%, pharyngitis in 15%.

For details see **Table 2**. Additional demographic and baseline characteristics can be found in **Supplementary Results Table S3 and S4**.

Table 2. Baseline disease characteristics of untreated and treated participants

Symptoms in participants with HIV or concomitant STI were not different from those without (**Supplementary Results Table S5**).

Table 3. Description of mpox-specific treatments received among treated participants

For the primary outcome measure, the KM-estimated proportion of participants with resolved lesions at D14 since the first PCR-positive sample taken was 39% (95% CI: 34% - 43%) (**Fig 2**).

Fig 2. Estimated cumulative probability of lesion resolution based on Kaplan-Meier estimates for a) untreated participant from the date of PCR diagnosis to D28 and b) treated participants from either date of PCR diagnosis to D28 or treatment initiation to D28

The proportion of participants with all lesions resolved and no serious complications increased from 35% on D14 to 68% on D28; one and two participants, respectively required hospitalisation (**Table 4**; **Fig 3** (**Table 5**; **Fig 4**). No evidence of recrudescence or relapse was observed at D60 and D180. No deaths were observed throughout the follow-up period to D28.

Table 4. Clinical outcomes of participants

Fig 3. Clinical scales at D14 and D28 among participants who attended the 14- and 28-day-outcome visits by treatment status

Fig 4. Sankey diagrams from D14 to D28 (from treatment start and PCR diagnosis) among participants who attended the 28-day-outcome visit in the treated and untreated cohorts

At least one Ct value result was available for 214 participants from a plasma sample, 361 from a skin lesion, 347 from oropharyngeal swab and 180 from an anal swab (**Fig 5**). Details on model specifications are in **Supplementary Results**. The models for each compartment closely replicated the observed data (see individual fits in **Supplementary Figures S1 and S2**).

Table 6 presents the simulated predicted times to 50%, 90% and 95% of participants reaching viral undetectability ($Ct \geq 40$) and non-culturable virus ($Ct \geq 30$) and **Figure 6** time to undetectability in the different samples. The predicted time-to-non-culturable virus reached by

95% of participants was 10 days since symptom onset in blood, 30 in anal, 31 in oropharyngeal, and 52 days in skin samples.

One SAE was reported by 12 participants (2%) between the point of consent and D28 (**Table 5**), the most frequent being pain at skin or mucosal lesion sites (5 cases) and proctitis (4); there were 5 AEs (**Supplementary Results Table S6**).

Fig 5. Spaghetti plots of Ct values over time for untreated and treated participants with at least one virological sample in one of the compartments of interest (days since symptoms onset)

Fig 6. Simulated cumulative incidence of undetectability (mean and 95% confidence intervals) for untreated (panel A) and treated (panel B) participants.

Treated participants

Case management differed across countries: mpox treatment with systemic antivirals ranged from none (Belgium, Spain), to 29% (Switzerland), and hospitalisation from none (Belgium) to 36% (Spain) (**Supplementary Results Table S2**). Overall, 22/57 (38.6%) required hospitalisation for clinical needs, including 2 requiring intensive care (**Table 2**). A median of 4 days (IQR 2–8) had elapsed from symptom onset to PCR diagnosis and 4 (IQR 3–5) from diagnosis to treatment start. Treatment was tecovirimat (49, 9%), cidofovir (6, 1%) or tecovirimat plus cidofovir (2, 3%) (**Table 3**).

The demographic and baseline characteristics of the treated cohort generally overlapped with those of untreated participants. As for presenting symptoms, 73% had lymphadenopathy, 56% fever, 33% fever, and 28% pharyngitis/tonsillitis; 33% had >25 lesions with 8% presenting >100. (**Table 2**)

The KM-estimated proportion of participants with resolved lesions at D14 since the first PCR-positive sample taken was 34% (95% CI: 20% - 45%) and 59% (95% CI: 44% - 70%) at D14 following treatment initiation. The proportion of participants with resolved lesions with no serious complications increased from 33% on D14 to 72% on D28; 9 (16%) were hospitalised due to a serious complication of mpox infection, and one remained hospitalised at D28 (**Table 4**).

Viral clearance was shortest from blood and longest for skin and anal samples. The predicted time to nonculturable virus by 95% of participants was 20 days in blood, 43 in oropharyngeal samples, and 60 days in skin and anal samples (**Table 6**).

Fifteen (26%) participants experienced a total of 16 SAEs. The most frequent events were pharyngitis and proctitis (3 each). One SAE was an increase in alanine aminotransferase which was judged to be possibly treatment. There were 7 AEs. (**Supplementary Results Table S6**). Tecovirimat treatment was discontinued for one participant following an SAE, a hepatobiliary

disorder, and two following an a liver injury and a hepatic cytolysis AE (**Supplementary Results Table S7**).

Table 5. Summary of Serious Adverse Events (SAEs) per treatment group

DISCUSSION

This paper describes clinical presentations and clinical and virologic outcomes of a cohort of mostly adult individuals with laboratory-confirmed clade IIb MPXV infection and active disease, about one-tenth of whom were treated with a systemic antiviral – tecovirimat and/or cidofovir. Compared to previous case-series, MOSAIC is the first study to adopt a protocolised approach applied to both prospectively-followed participants and retrospectively-collected data with a structured case record form, and to have enrolled a large number of cases in the European region. Having in place harmonised, always-on clinical characterisation protocols is of immediate relevance, given the new ongoing PHEIC and the complexity of mpox spread involving different clades, variants, and lineages (14).

Presenting signs/symptoms are consistent with other case-series; almost nine in ten participants had skin lesions, alone or with concomitant mucosal lesions. Half of the participants had mucosal lesions, but mucosal-only lesions were found in only about one-tenth. Lesions were mostly vesicles and/or pustules on presentation and were in three-quarters of cases in the peri-genital and perianal areas. Half of the participants had few (≤ 5) lesions.

HIV status appeared not to influence clinical presentation and outcomes. Participants living with HIV had generally normal CD4 cell counts and almost all were on antiretroviral treatment; about half of those who were HIV-negative were on pre- or post-exposure prophylaxis. Pre- or post-exposure vaccination against smallpox and/or mpox was uncommon.

Cases could mostly be managed on outpatient basis with no specific treatment. Participants treated with a systemic antiviral (predominantly tecovirimat) had proportionally more lesions and almost half of them required hospitalisation; this reflects greater propensity to offer treatment to more severe cases, particularly as supplies of antivirals were limited. National treatment guidelines and practices differed and might have been variably followed by individual clinicians (examples are provided in **Supplementary Appendix 3**), translating into variation across countries in terms of both proportion of cases on systemic antivirals and of cases hospitalised, and complicating a formal comparison of treated vs untreated (**Supplementary Results Table S2**).

Viral kinetics are key to understanding disease outcome and transmission potential. We used simulations to calculate the probability of detectable virus (set at $\geq \text{Ct}40$) and of culturable virus ($\geq \text{Ct}30$). Modelled data replicated observed data and are similar to those reported earlier in a smaller cohort from Spain (15), though that study reported viral load in copies per mL, while we

used Ct and calculated time-to-culturable virus as a proxy for virus viability and transmission potential. Viral clearance was fastest from plasma and slowest in skin lesions – where it is predicted to take on average about three weeks for half of untreated mpox participants to reach viral clearance and two weeks to have non-culturable virus from symptom onset. A small proportion of participants (5%) may however still carry virus with infectious potential beyond 7 weeks from skin and oropharyngeal lesions. These findings could inform recommendations on reducing risks of onward transmission.

Current options for treating mpox and other orthopoxviruses are limited. Tecovirimat, cidofovir and its prodrug brincidofovir are variably recommended based on very incomplete evidence-base (16, 17). Tecovirimat (18) is registered by the European Medicine Agency (EMA)(19) and the UK Medicine & Healthcare products Regulatory Agency (MHRA) for smallpox, mpox and cowpox as well as vaccinia complications for adults and children weighing ≥ 13 kg. Since the authorisation is based on experimental data and human safety data “under exceptional circumstances” with obligation for “additional monitoring” by the EMA, data generated from this study contribute to safety information of the drug, indicating a potential for altered liver functions. Tecovirimat and brincidofovir are also approved by the US Food and Drugs Administration (FDA) for the treatment of smallpox under the ‘animal rule’ (20).

Despite several interventional and observational studies ongoing or planned (21), the evidence-base on the effectiveness of mpox treatments remains limited. For the treatment of clade Ia disease, the PALM 007 trial in the Democratic Republic of the Congo (DRC) found tecovirimat to be safe but not reducing the duration of mpox lesions over placebo, though the full analyses are not yet available (22). For clade IIb, available data on tecovirimat in clade IIb mpox are inconclusive and randomised controlled trials are still recruiting at the time of writing (21). There still remain uncertainties about standardised lesion assessment and disease outcomes that make between-study and between-clade comparisons challenging(23-25).

These results should be seen in the context of study-specific and broader challenges. While the study protocol was developed quickly and enrolment started within seven weeks from the first cases being reported and before the WHO declared the mpox outbreak a PHEIC (26), complex regulations significantly slowed down the study setup in several participating countries under the current European Clinical Trials Regulation, which could only begin enrolling participants when cases were dwindling. In a related paper we describe these shortcomings and propose improvements (27). MOSAIC offers important lessons for the clinical research community in terms of observational data collection and helped ISARIC adapt its standardized tools for the rapid and harmonized collection of data and biological samples (28) that are made freely available and can now be applied to the new ongoing PHEIC.

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Fig 1. Flowchart summarising study enrolment, eligibility and inclusion in the analysis population

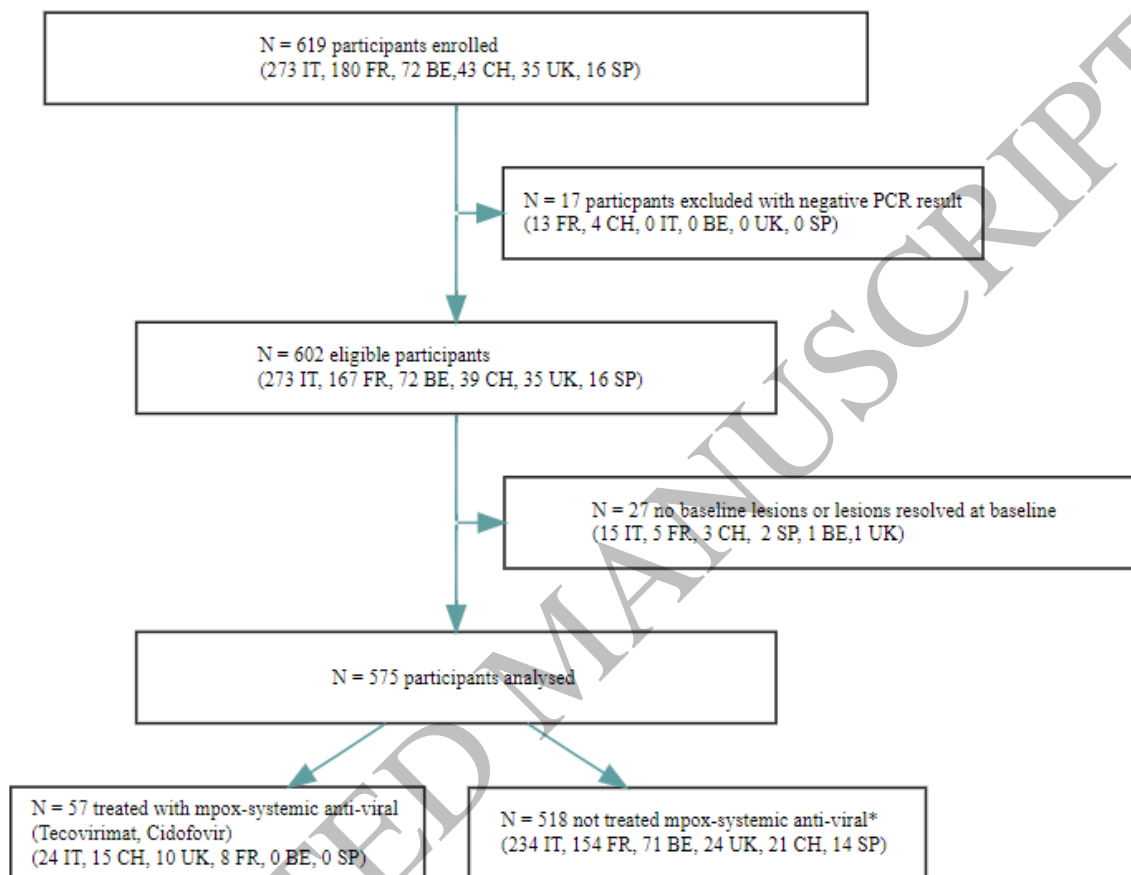
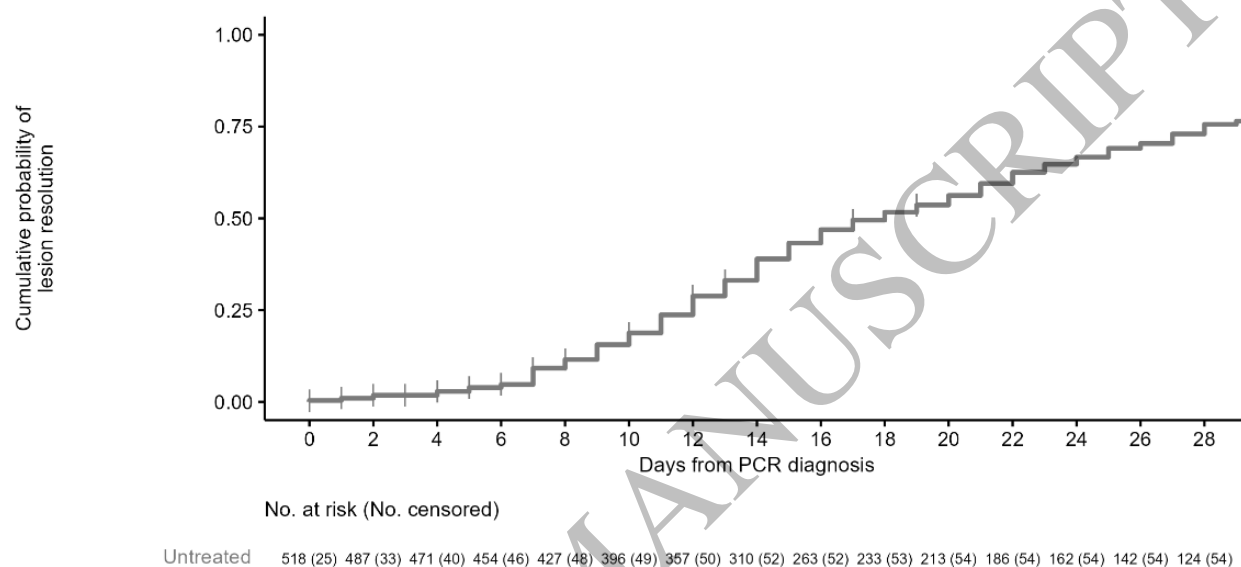


Fig 2. Estimated cumulative probability of lesion resolution based on Kaplan-Meier estimates for a) untreated participant from the date of PCR diagnosis to D28 and b) treated participants from either date of PCR diagnosis to D28 or treatment initiation to D28

a. Untreated



b. Treated

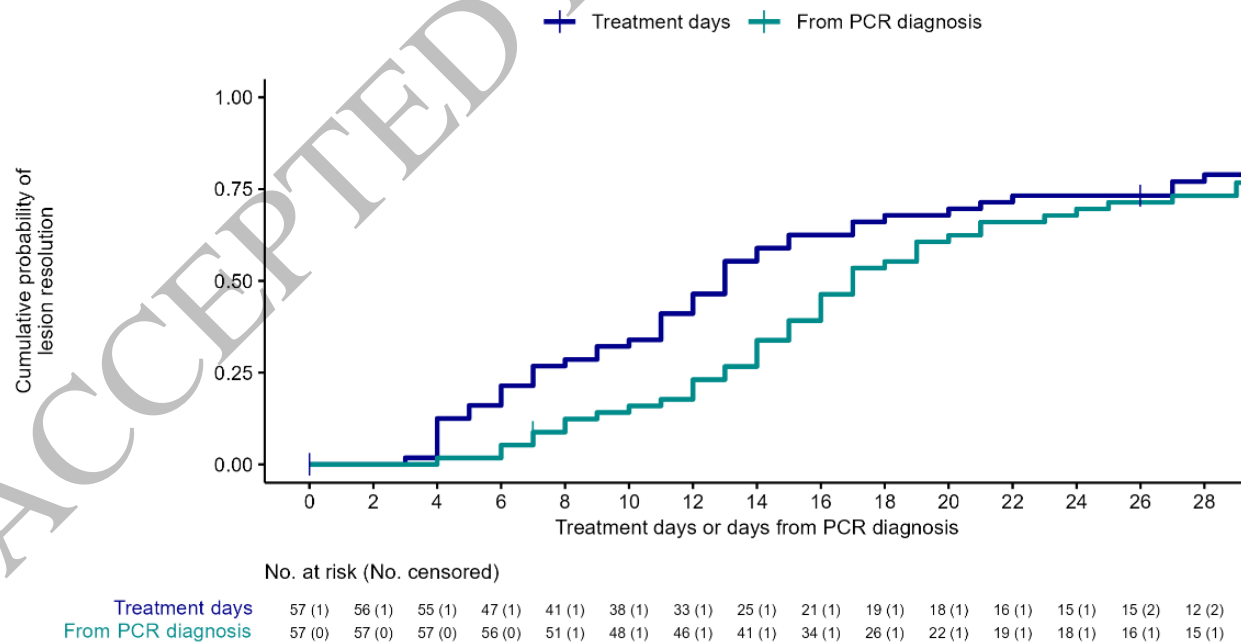
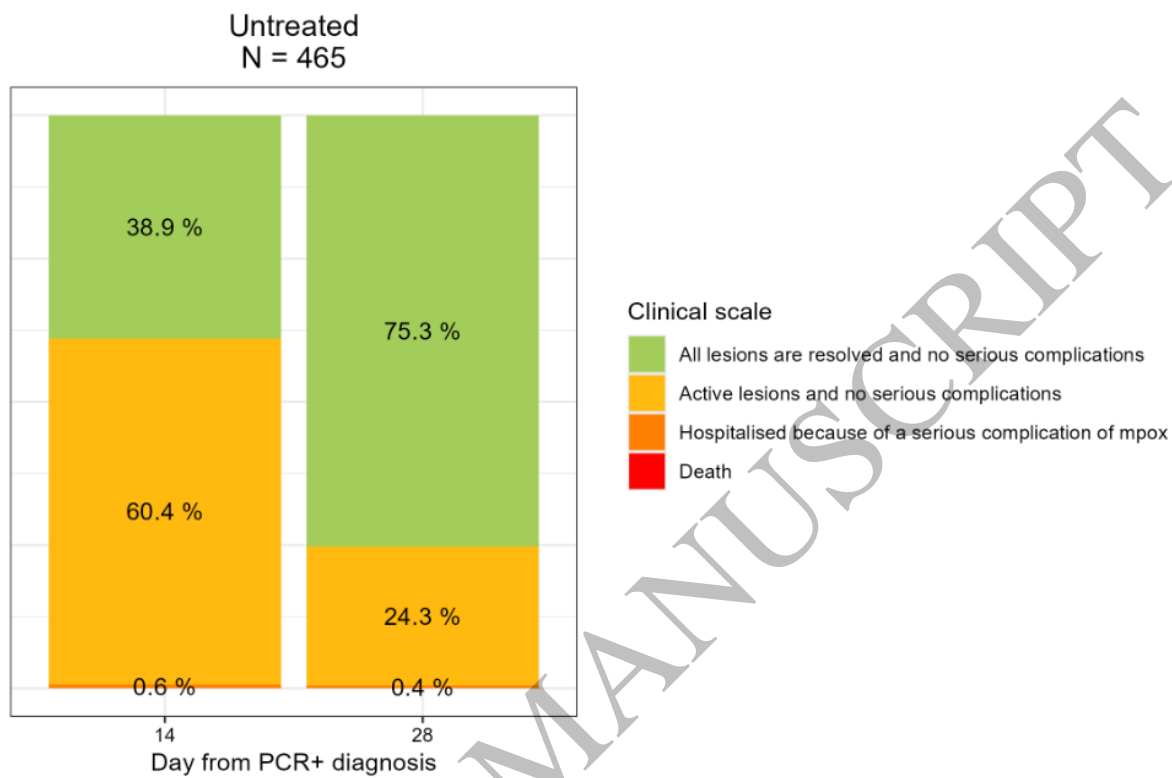
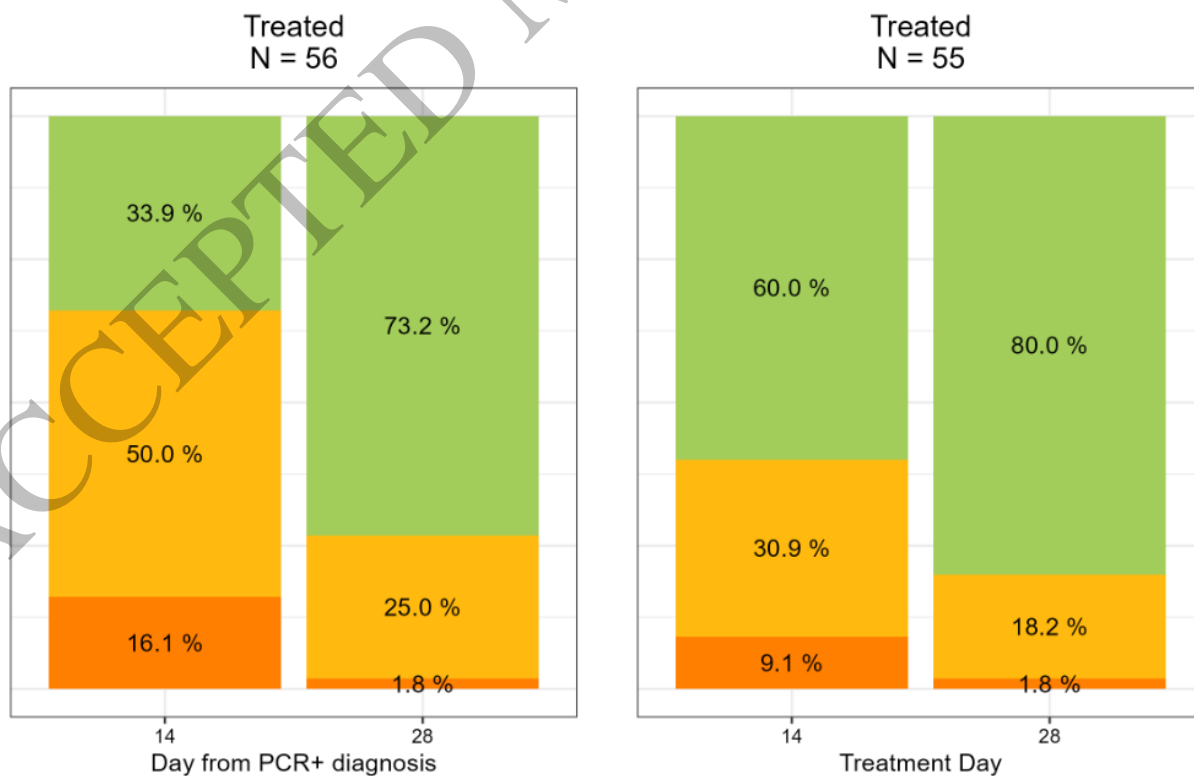


Fig 3. Clinical scales at D14 and D28 by treatment status for participants attending the D14 and D28

a.



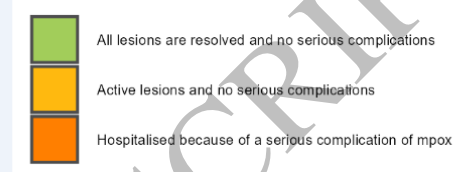
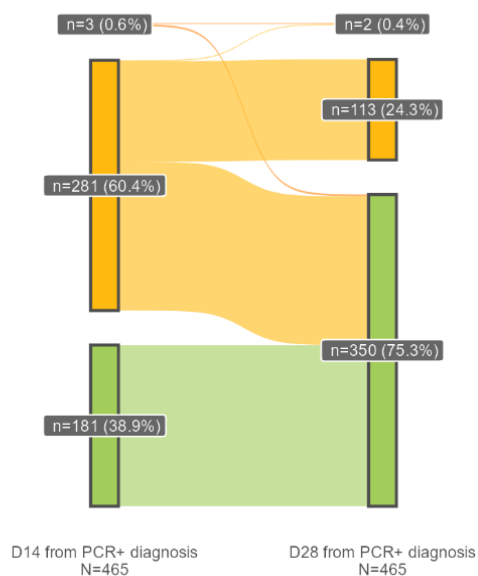
b.



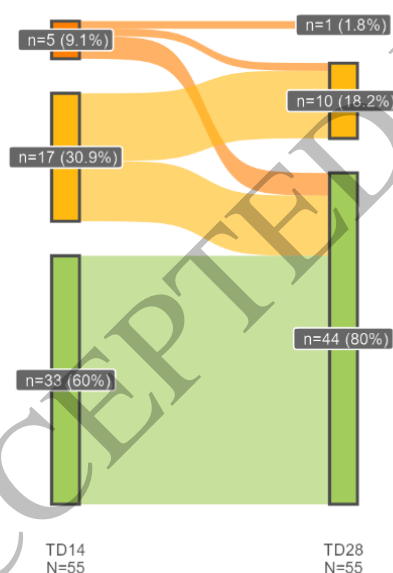
follow-up visits

Fig 4. Sankey diagrams from D14 to D28 for participants attending the D14 and D28 follow-up visits

a. From PCR diagnosis in untreated participants



b. From treatment start in treated participants



c. From PCR diagnosis in treated participant

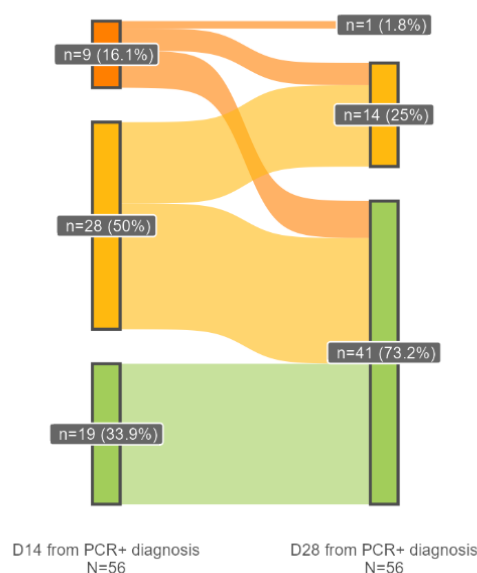


Fig 5. Spaghetti plots of Ct values over time for treated and untreated participants with at least one virological sample in one of the four compartments of interest (days since symptoms onset)

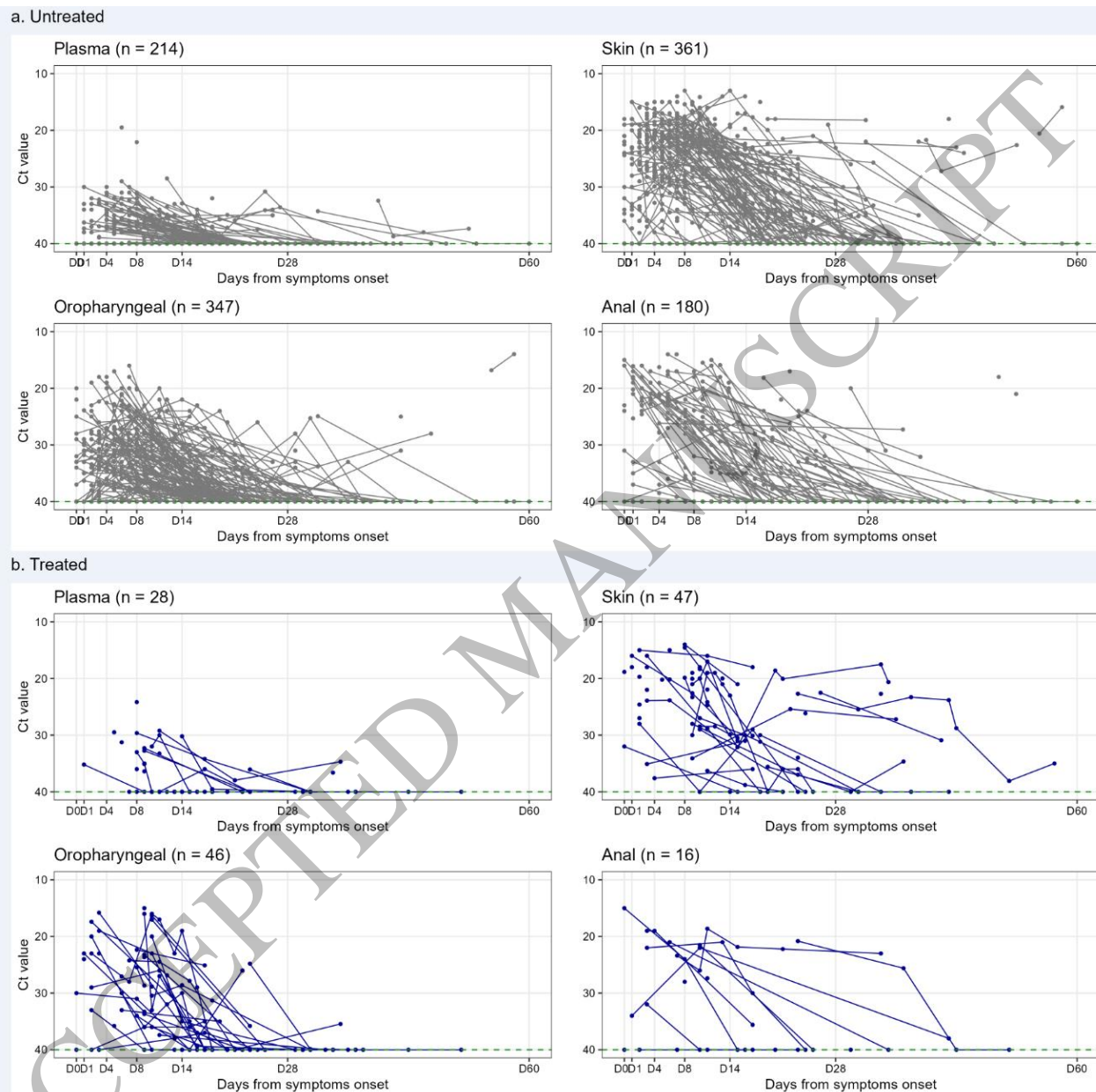
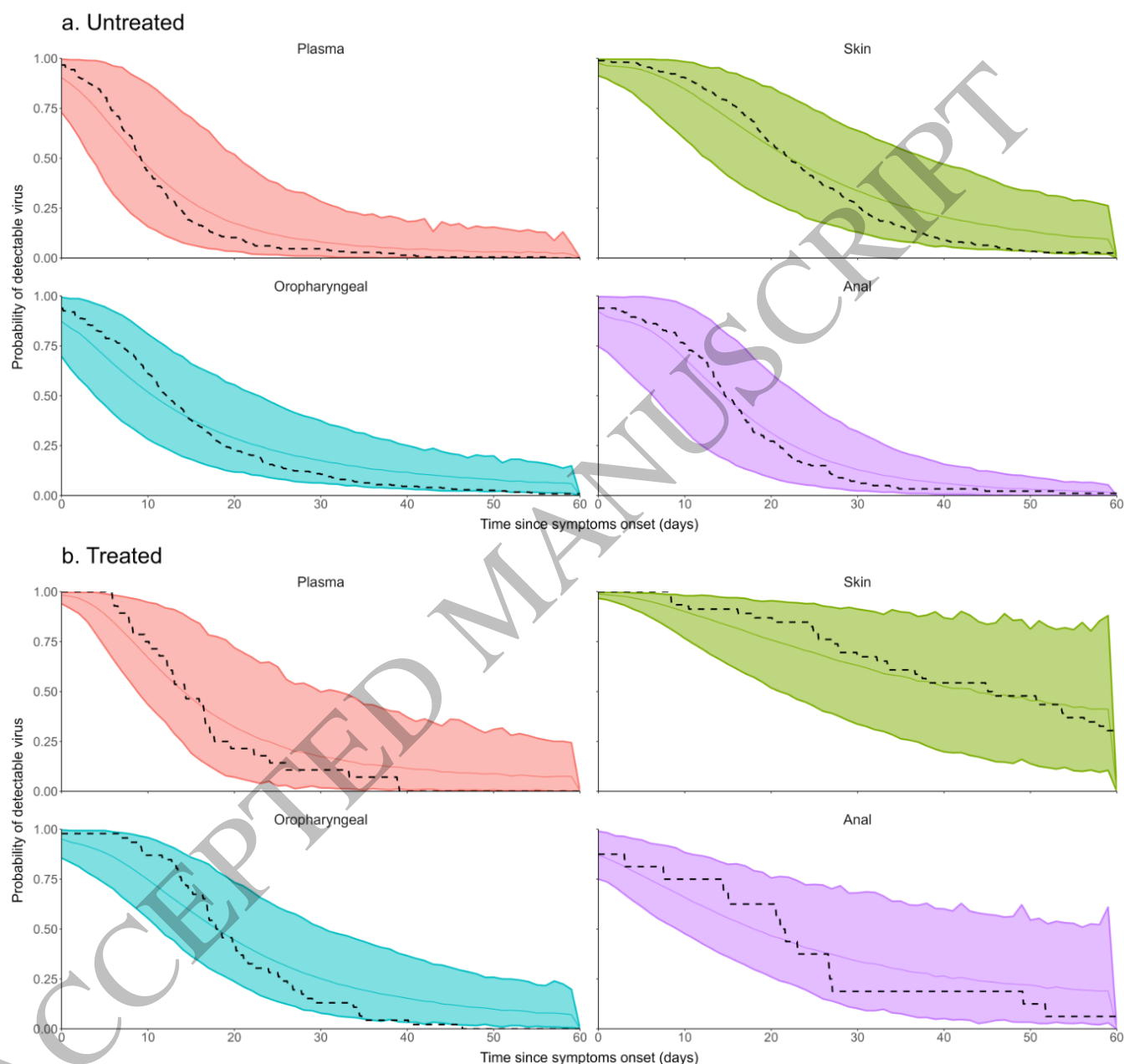


Fig 6. Simulated cumulative incidence of undetectability (mean and 95% CIs) for (a) untreated and (b) treated participants.



Caption: Mean and associated 95% confidence interval are depicted with solid lines and shaded area respectively. The dashed line represents the cumulative incidence calculated on the fitted individuals.

Table 1. Baseline demographic and comorbidities characteristics of untreated and treated participants

	Untreated (N=518)	Treated (N=57)
Demographics		
Age - Median (IQR) - yr	37 [32 ; 44]	36 [32 ; 43]
Female sex - no/total no (%)	5/515 (1)	1/57 (2)
Concomitant active sexually transmitted infection	106/514 (22)	7/56 (12)
Syphilis	51/106 (48)	2/7 (29)
Mycoplasma genitalium	6/106 (6)	3/7 (43)
Chlamydia	19/106 (18)	0/7 (0)
Hepatitis B	3/106 (3)	0/7 (0)
HSV	7/106 (6)	0/7 (0)
Gonorrhoea	33/106 (31)	0/7 (0)
HPV	2/106 (2)	0/7 (0)
Ureaplasma	3/106 (3)	3/7 (43)
Hepatitis C	5/514 (1)	0/56 (0)
HIV/ AIDS +	220/517 (43)	19/57 (33)
Receiving ARV	210/220 (95)	18/19 (95)
Viral load detectable	27/199 (14)	3/17 (18)
Viral load - Median (IQR) - cp/ml	1480 [56 ; 97662]	84 [71 ; 98]
CD4-T at last follow up - Median (IQR)/ μ l	743 [530 ; 1036]	652 [342 ; 803]
Receiving HIV PREP / PEP	153/297(51)	12/38 (32)

Table 2. Baseline disease characteristics untreated and treated participants

	Untreated (N=518)	Treated (N=57)
Management after clinical presentation - no/total no (%)		
Outpatient	465/514 (90)	32/57 (56)
Admitted to hospital ward for isolation only	12/514 (2)	3/57 (5)
Admitted to hospital ward for clinical need	36/514 (7)	20/57 (35)
Intensive care unit admission	1/514 (0)	2/57 (4)
Time from - Median (IQR), days		
Symptom onset to PCR+ diagnosis	5 [3 ; 8]	4 [2 ; 8]
PCR+ diagnosis to enrolment	0 [0 ; 0]	0 [0 ; 3]
PCR+ diagnosis to treatment start	-	4 [3 ; 5]
Symptoms - no/total no (%)		
Lymphadenopathy	243/506 (48)	40/55 (73)
Fever	239/508 (47)	30/54 (56)
Headache	103/511 (20)	18/54 (33)
Pharyngitis/tonsillitis	77/513 (15)	15/54 (28)
Lower respiratory symptoms	7/513 (1)	4/54 (7)
Ocular complications	4/513 (1)	6/54 (11)
Diarrhoea/gastroenteritis	37/512 (7)	4/55 (7)
Nausea/Vomiting	12/512 (2)	2/54 (4)
Encephalitis	1/512 (0.2)	1/54 (2)
Other complications		
Proctitis - no/total no (%)	131/511 (26)	11/55 (20)
Bacterial super-infection - no/total no (%)	21/316 (7)	8/29 (28)
Folliculitis/cellulitis	11/21 (52)	3/8 (38)
Bacteraemia	0/21 (0)	1/8 (12)
Urinary tract	1/21 (5)	0/8 (0)
Other	9/21 (43)	4/8 (50)
Mpox lesions:		
Skin / mucosal lesions - no/total no (%)		
Skin lesions only	255/511 (50)	25/56 (45)
Mucosal lesions only	61/511 (12)	5/56 (9)
Skin and mucosal lesions	195/511 (38)	26/56 (46)
Active skin lesions types - no/total no (%)		
Vesicle	226/293 (77)	31/37 (84)
Pustule	186/294 (63)	30/37 (81)
Ulcerated lesion	74/294 (25)	17/37 (46)
Haemorrhagic / bleeding lesions	4/232 (2)	1/25 (4)
Other	22/304 (7)	3/37 (8)
Lesion sites - no/total no (%)		
Head skin lesions	168/511 (33)	36/56 (64)
Ocular lesions within the orbit	1/511 (0)	1/56 (2)
Other skin lesions	266/512 (52)	37/56 (66)
Mucosal lesions	256/511 (50)	31/56 (55)
Peri-genital or peri-anal lesions	380/511 (74)	42/56 (75)

Estimated total number of active lesions- no/total no (%)		
1-5	237/450 (53)	10/51 (20)
6-25	175/450 (39)	24/51 (47)
26-100	26/450 (6)	13/51 (25)
>100	3/450 (1)	4/51 (8)
Pain score - Median (IQR) - out of 10	6 [3 ; 7]	6 [4 ; 8]
Dichotomized pain score - no/total no (%)		
pain score <6	27/66 (41)	8/19 (42)
pain score ≥6	39/66 (59)	11/19 (58)

Table 3. Description of mpox-specific treatments received among treated participants

MPOX-SPECIFIC TREATMENT	N
Tecovirimat (+/- topical treatment)	
Initiated within 14 days of diagnosis	49
Tecovirimat + Cidofovir systemic treatment (+/- topical treatment)	
Tecovirimat and cidofovir initiated within 14 days of diagnosis	1
Cidofovir initiated within 14 days of diagnosis (tecovirimat initiated later)	1
Cidofovir systemic treatment only*	
Initiated within 14 days of diagnosis	6

*Participants who received CIDOFOVIR alone received systemic treatment only – no local treatment was administered

Table 4. Clinical outcomes of participants

a. Untreated		N=518
D14, no (%)		
All lesions are resolved and no serious complications	181 (35)	
Active lesions and no serious complications	283 (55)	
Hospitalised because of a serious complication of mpox	3 (1)	
Death	0 (0)	
Loss-to-follow-up	51 (10)	
D28, no (%)		
All lesions are resolved and no serious complications	350 (68)	
Active lesions and no serious complications	113 (22)	
Hospitalised because of a serious complication of mpox	2 (0)	
Death	0 (0)	
Loss-to-follow-up	53 (10)	
b. Treated	From PCR diagnosis (N=57)	From treatment start (N=57)
D14, no (%)		
All lesions are resolved and no serious complications	19 (33)	33/57 (58)
Active lesions and no serious complications	28 (49)	18/57 (32)
Hospitalised because of a serious complication of mpox	9 (16)	5/57 (9)
Death	0 (0)	0/57 (0)
Loss-to-follow-up	1 (2)	1/57 (2)
D28, no (%)		
All lesions are resolved and no serious complications	41 (72)	44/57 (77)
Active lesions and no serious complications	14 (25)	10/57 (18)
Hospitalised because of a serious complication of mpox	1 (2)	1/57 (2)
Death	0 (0)	0/57 (0)
Loss-to-follow-up	1 (2)	2/57 (4)

Table 5. Summary of Serious Adverse Events (SAEs) per treatment group

MedDRA SOC MedDRA Preferred Term	Untreated (N=518)	Treated (N=57)
N (%) participants with at least 1 SAE	12 (2%)	15 (26%)
N SAEs reported	12	16
List of SAEs (MedDRA SOC and Preferred Terms)		
Infections and infestations	2 (<1%)	6 (11%)
Abscess	1 (0%)	0 (0%)
Eye infection intraocular ¹		1 (2%)
Laryngitis	0 (0%)	1 (2%)
Pharyngitis	1 (0%)	3 (5%)
Pharyngotonsillitis	0 (0%)	1 (2%)
Eye disorders	0 (0%)	1 (2%)
Ulcerative keratitis	0 (0%)	1 (2%)
Gastrointestinal disorders	4 (<1%)	3 (5%)
Proctitis	4 (<1%)	3 (5%)
General disorders and administration site conditions	5 (1%)	1 (2%)
Pain	5 (1%)	1 (2%)
Investigations	0 (0%)	1 (2%)
Alanine aminotransferase increased	0 (0%)	1 (2%)
Nervous system disorders	0 (0%)	1 (2%)
Miller Fisher syndrome	0 (0%)	1 (2%)
Reproductive system and breast disorders	1 (<1%)	1 (2%)
Penile oedema	1 (<1%)	1 (2%)
Skin and subcutaneous tissue disorders	0 (0%)	2 (4%)
Rash ²	0 (0%)	1 (2%)
Surgical and medical procedures	0 (0%)	1 (2%)
Microsurgery to hand	0 (0%)	1 (2%)

¹Event described as lesions on the right eyelid with progressive periorbital and conjunctival involvement

²diffuse rash with de-epithelialisation and purulent exudate

Table 6 – Predicted time to undetectability ($Ct \geq 40$) and predicted time to $Ct \geq 30$ (from simulations, in days)

		Predicted time to undetectability (Ct ≥ 40) Mean (95% CI)			Predicted time to non-culturable virus (Ct ≥ 30) Mean (95% CI)		
Sample location	N	50%	90%	95%	50%	90%	95%
Untreated							
Plasma	214	10 (4 – 21)	27 (13 – 57)	39 (17 – 60)	0 (0 – 5)	4 (0 – 36)	10 (0 – 39)
Skin	361	23 (13 – 38)	58 (33 – 60)	60 (42 – 60)	13 (4 – 28)	37 (16 – 60)	52 (22 – 60)
Oropharyngeal	347	11 (4 – 23)	44 (23 – 60)	60 (33 – 60)	2 (0 – 11)	19 (6 – 44)	31 (10 – 60)
Anal	180	15 (7 – 24)	34 (20 – 50)	44 (25 – 60)	9 (1 – 17)	23 (11 – 36)	30 (15 – 44)
Treated							
Plasma	28	15 (9 – 30)	44 (19 – 60)	60 (22 – 60)	4 (2 – 7)	13 (7 – 39)	20 (8 – 60)
Skin	46	44 (21 – 60)	60 (58 – 60)	60 (60 – 60)	22 (11 – 60)	60 (32 – 60)	60 (43 – 60)
Oropharyngeal	46	18 (12 – 31)	50 (28 – 60)	60 (35 – 60)	9 (4 – 21)	30 (15 – 59)	43 (19 – 60)
Anal	16	19 (10 – 60)	60 (31 – 60)	60 (39 – 60)	8 (4 – 25)	60 (18 – 60)	60 (24 – 60)