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RESEARCH ARTICLE

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Epidemiological trends and clinical features of the ongoing monkeypox epidemic: A preliminary pooled data analysis and literature review

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Abstract

An emerging outbreak of monkeypox infection is quickly spreading worldwide, being currently reported in more than 30 countries, with slightly less than 1000 cases. In the present preliminary report, we collected and synthesized early data concerning epidemiological trends and clinical features of the ongoing outbreak and we compared them with those of previous outbreaks. Data were pooled from six clusters in Italy, Australia, the Czech Republic, Portugal, and the United Kingdom, totaling 124 cases (for 35 of which it was possible to retrieve detailed information). The ongoing epidemic differs from previous outbreaks in terms of age (54.29% of individuals in their thirties), sex/gender (most cases being males), risk factors, and transmission route, with sexual transmission being highly likely. Also, the clinical presentation is atypical and unusual, being characterized by anogenital lesions and rashes that relatively spare the face and extremities. The most prevalent sign/symptom reported was fever (in 54.29% of cases) followed by inguinal lymphadenopathy (45.71%) and exanthema (40.00%). Asthenia, fatigue, and headache were described in 22.86% and 25.71% of the subjects, respectively. Myalgia was present in 17.14% of the cases. Both genital and anal lesions (ulcers and vesicles) were reported in 31.43% of the cases. Finally, cervical lymphadenopathy was described in 11.43% of the sample, while the least commonly reported symptoms were diarrhea and axillary lymphadenopathy (5.71% of the case series for both symptoms). Some preliminary risk factors can be identified (being a young male, having sex with other men, engaging in risky behaviors and activities, including condomless sex, human immunodeficiency virus positivity (54.29% of the sample analyzed), and a story of previous sexually transmitted infections, including syphilis). On the other hand, being fully virally suppressed and undetectable may protect against a more severe infectious course. However, further research in the field is urgently needed.

KEYWORDS

emerging pathogen, monkeypox, outbreak, pooled data analysis

1 | INTRODUCTION

An emerging outbreak of monkeypox infection is quickly spreading worldwide, being currently reported in more than 30 countries in Europe, the Americas, Australia, and the Middle East (https://bnonews.com/monkeypox/). The cluster of cases commenced in May 2022, mostly affecting men having sex with men (MSM), with no travel history to central and western Africa, where the infection has been endemic in 11 countries since the seventies. Cases were diagnosed mainly through primary care and sexual health clinics. So far, as of June 7, 2022, slightly more than 1000 cases (1099) have been notified: namely, 32 (2.91%) suspected, 1 (0.09%) probable, and 1066 (97.00%) confirmed cases.

Monkeypox was discovered and identified in 1958 in Denmark by the virologist Preben Christian Alexander von Magnus (1912–1973) while investigating two smallpox-like disease outbreaks that occurred in monk colonies.[1] The first known human case of monkeypox was reported on September 1, 1970, in a 9-month-old child admitted to the Basankusu Hospital in the Republic of the Congo (nowadays known as the Democratic Republic of the Congo).[2] There exist two clades: the Central African (Congo basin) and the Western African clades. The ecoregion extending from southeastern Nigeria to Cameroon, between the Cross and Sanaga rivers, may have acted as a biogeographic barrier, splitting the virus into two variants.[3]

Here, we present a preliminary pooled data analysis of monkeypox cases both from an epidemiological and a clinical perspective.

2 | MATERIALS AND METHODS

2.1 | Literature search strategy

Literature was mined without time filters or language restrictions. More specifically, two major scholarly, electronic databases, PubMed/MEDLINE and Scopus, were searched. "Medical subject headings" terms were utilized. In particular, we focused on the period from the inception of the ongoing outbreak and we compared current epidemiological trends and clinical features with those of previous outbreaks. Google Scholar was also searched to increase the chance of getting all relevant studies, not still indexed in the previously mentioned databases and to retrieve gray literature. The following keywords were utilized: "monkeypox," "monkey pox," "monkeypox virus", "monkey pox virus," "MPX," "MPXV," "variole du singe" (in French), "variole simienne" (in French), "viruela del mono" (in Spanish), "Affenpocken" (in German), "Affenpockenkrankheit" (in German), "Affenpockenvirus" (in German), and "varíola dos macacos" (in Portuguese).

The literature search was supplemented by extensive mining of websites from the major health authorities, including the World Health Organization, the US "Centers for Disease Control and Prevention," the "UK Health Security Agency," and the "European Centre for Disease Prevention and Control."

2.2 | Inclusion and exclusion criteria

Any relevant study design (case report, case series, cohort population study, clusters/outbreaks investigation, epidemiological or surveillance studies) reporting epidemiological and/or clinical data on the currently ongoing monkeypox epidemic in nonendemic countries (i.e., to say, countries outside of Africa) was considered eligible.

2.3 | Monkeypox case definition

The Portuguese Directorate-General of Health (https://www.dgs.pt/normas-orientacoes-e-informacoes/orientacoes-e-circulares-informativas/orientacao-n-0042022-de-31052022-pdf.aspx) has proposed the following working definition for suspected, probable, and confirmed monkeypox cases. A suspected case is an individual of any age, clinically presenting with a localized or generalized rash (at any stage, macular, papular, vesicular, or pustular phase) and/or anogenital complaints (such as ulcers), with sudden symptom onset since March 15, 2022, after ruling out other differential diagnoses (including other sexually transmitted infections [STIs]). Moreover, this person presents one or more of the following signs/symptoms: namely, (i) sudden onset fever (≥38.0°C), (ii) asthenia, (iii) myalgia, (iv) backache, (v) headache, and (vi) lymphadenopathy. A probable case is defined when a subject, besides meeting the previous criteria, presents also one or more of the following signs/symptoms: namely, (i) contact with a suspected, probable, or confirmed monkeypox case within 21 days before the onset of symptoms, (ii) sexual intercourse with multiple or anonymous random sexual partners within 21 days before the symptom onset, (iii) hospitalization due to a clinical condition consistent with a suspected case, and (iv) travel history to monkeypox-endemic countries within 21 days before the symptom onset. Finally, a confirmed case is an individual with a laboratory-proven monkeypox infection (in a clinical sample, using reliable and validated techniques, such as real-time polymerase chain reaction [PCR] and/or nucleotide sequencing). Similar working definitions have been proposed in other countries.

A slightly different working definition has been formulated by Bunge et al.[2]: a case is defined as suspected in presence of sudden onset of high fever, with a (vesicular or pustular) rash affecting the face, the palms of the hands, and the soles of the feet, or if at least five smallpox-like scabs are present. A case is defined as possible when it exhibits a typical rash (vesicular, pustular, or crusty), for which the primary healthcare or family provider has ruled out a diagnosis of chickenpox, if it reports a history of rash and fever, if one of the epidemiological criteria is met or raised concentrations of *Orthopoxvirus*-specific antibodies (immunoglobulin M [IgM]) have been proven, with unexplained rash and fever and two other signs/symptoms from the clinical criteria.[4–6] A case is probable if it meets the criteria of a suspected case but there is no possibility to have a laboratory confirmation, however, a robust epidemiological link to a

confirmed case exists. Finally, a confirmed case is a laboratory-proven suspected case (positivity of IgM antibodies, positive PCR testing result, and/or virus isolation). The feasibility of the working definition by Bunge et al.[2] will be discussed in the following sections.

2.4 | Statistical analysis

Relevant data (surname of the first author, journal, study country, study period, monkeypox case working definition, sample size, sex/gender and sexual orientation, age, human immunodeficiency virus (HIV) status and sexual health, epidemiological exposures, smallpox vaccination status, signs/symptoms at clinical presentation, clinical course/evolution, hospital admission, treatment/management, diagnosis, and outcome) were extracted, and when possible and appropriate, were pooled together, conducting a descriptive statistical analysis.

3 | RESULTS

Mining PubMed/MEDLINE and Scopus resulted in 907 and 1182 items, respectively. After extensively familiarizing with the literature, six relevant studies were selected,[7–12] totaling 124 subjects (11.28% of the cases notified as of June 7, 2022), and their major findings are summarized in Table 1. In the present pooled data analysis, 35 individuals affected by monkeypox were included and analyzed, since data at the individual level are available only for a subset of the entire sample: four from Italy,[7] one from the Czech Republic,[8] two from the United Kingdom,[9] another one from Australia,[10] and twenty-seven from Portugal.[11] Two relevant systematic reviews and meta-analyses were consulted,[2,13] along with the studies referenced thereby.

3.1 | Sex, gender, and sexual orientation

The subjects retained in the pooled data analysis were all males, with most reporting sexual intercourse with same-gender individuals (97.14%). Only one of the Portuguese cases[11] was a man having sex with a woman. Pooling this data together with information provided by Vivancos et al.,[12] an overall rate of 87.72% of MSM was computed.

3.2 | Age

A total of 54.29% of the individuals were in their 30s, with 8.57% and 2.86% of cases in their 40s and 50s, respectively; 20.00% of subjects were in their 20s. In a few cases (14.29%), age was unknown. The Portuguese sample[11] had a median age of 33 years, ranging from 22 to 51 years with the majority ($n = 13$, 48.15%) aged 30–39 years. Similarly, the English sample[12] had a median age of 38 years, ranging from 32 to 43 years.

3.3 | HIV status

A total of 54.29% were HIV-positive, whereas the remaining were HIV-negative generally on HIV pre-exposure prophylaxis (PrEP), either daily or event-driven/on-demand.

3.4 | Smallpox vaccination status

Two cases documented being vaccinated against smallpox: a young individual in his 30s from the Italian cluster[7] and one middle-aged from the Portuguese cluster.[11]

3.5 | Signs/symptoms at clinical presentation

The most prevalent sign/symptom reported was fever (in 54.29% of cases) followed by inguinal lymphadenopathy (45.71%) and exanthema (40.00%). Asthenia, fatigue, and headache were described in 22.86% and 25.71% of the subjects, respectively. Myalgia was present in 17.14% of the cases. Both genital and anal lesions (ulcers and vesicles) were reported in 31.43% of the cases. Finally, cervical lymphadenopathy was described in 11.43% of the sample, while the least commonly reported symptom was axillary lymphadenopathy (5.71% of the case series). The English cluster cases (5.71%) presented diarrhea.[9]

3.6 | Infection evolution

In all cases, the evolution of the lesions was asynchronous, developing in multiple stages, with some of them forming scabs and crusts while others were still in the early papular (umbilicated papulae with progressive central ulceration), vesicular, and pustular phases. Of note, most cases reported a story of previous STIs, including syphilis, hepatitis A, B, and C. Syphilis was the most commonly reported STI. Interestingly, there was a case of likely coinfection of syphilis and monkeypox.[8]

3.7 | Transmission route

Sexual exposure could be documented in 91.67% of the cases. Sexual intercourse was unprotected (condomless) with multiple, random/anonymous sexual partners. Of note, 14/16 of the Portuguese cases[11] reported sexual exposure, and in seven cases sexual encounters occurred in saunas and other venues. All four Italian cases[7] reported sexual encounters: three cases during festivals and gathering events, and one case during sex work. The Czech case[8] reported random sexual encounters during the festival/gathering event in Maspalomas (Spain).

Concerning other potential transmission routes and epidemiological exposures, three cases from the Portuguese cluster[11] had contact with animals (two cases with cats and one case with pigs), while only one case from the same cluster reported contact with another case.

TABLE 1 Major features of the studies included in the present review

Reference	Country	Study period	Sample size	Sex/ gender and sexual orientation	Age	HIV status	Previous STIs	Sexual exposure	Travel	Contact with other cases	Smallpox vaccination status	Signs/symptoms at clinical presentation	Clinical evolution	Hospital admission	Treatment	Diagnosis	Deaths
Antinori et al.[7]	Italy	17–22 May 2022	4	M; MSM	30s	2	4	4 (Sexual encounters during festivals and gathering events in 3 cases, sex work in 1 case)	4	0	1	Fever, asthenia and fatigue, myalgia, anogenital lesions, inguinal lymphadenopathy, lesions affecting the pubic area, anterior and posterior thorax, calf, back, head, legs and foot sole, arms and hands	Asynchronous	4	Oral ciprofloxacin, acyclovir, a single dose of benzylpenicillin (1); antiinflammatory and antihistaminic drugs (1)	Real-time PCR from various samples (skin, anogenital lesions, serum, plasma, semen, feces, and nasopharynx), viral quantification cycle (Cq), and DNA sequencing	0
Bížová et al.[8]	Czech Republic	May 2022	1	M; MSM	34	1	Likely concurrent syphilis infection	1 (Sexual encounters during a festival/ gathering event)	1 (To Spain)	0	NR	Tonsil ulceration, fever, chills, lymphadenopathy, anal and forehead lesions	Asynchronous	0	Cephalosporins	Vesicle fluid electron microscopy, PCR	0
Heskin et al.[9]	UK	End of April–May 2022	2	M; MSM	NR	1	NR	2	0	0	NR	Perioral white spots, perianal blistering lesions, anogenital and pubic lesions, lymphadenopathy, fever, headache, diarrhea	Asynchronous	2	High-dose antiviral and antibacterial medications, including intravenous ceftriaxone	RT-PCR from respiratory, serum, lesion, and urine samples	0

TABLE 1 (Continued)

Reference	Country	Study period	Sample size	Sex/ gender and sexual orientation	Age	HIV status	Previous STIs	Sexual exposure	Travel	Contact with other cases	Smallpox vaccination status	Signs/symptoms at clinical presentation	Clinical evolution	Hospital admission	Treatment	Diagnosis	Deaths
Hammerschlag et al.[10]	Australia	May 2022	1	M; MSM	30s	1	1	1	1 (To Europe)	0	NR	Fever, malaise, genital lesions, trunk, and to a less extent face and limbs	Asynchronous	1	Oral doxycycline, intramuscular ceftriaxone, oral and intravenous cephalexin, oral analgesia	Real-time PCR from skin, nose throat swabs, DNA sequencing, viral isolation and visualization through thin-section electron microscopy	0
Perez Duque et al.[11]	Portugal	29 April–23 May 2022	27	M; MSM (18/19), MSW (1/19)	33 (2-2–5-1)	14	NR	14/16 (7 Cases in saunas and other venues)	4 (To Spain, the UK, and Brazil)	1	1 (A middle-aged individual)	Fever, asthenia and fatigue, myalgia, headache, anogenital ulcers and vesicles, exanthema, inguinal, cervical, and axillary lymphadenopathy	At the same clinical stage (5)	3 (For their clinical condition)	NR	Real-time PCR from skin lesions (surface, exudate, and crusts) and oral mucosa, and DNA sequencing	0
Vivancos et al.[12]	UK	7–25 May 2022	89	M (79/79); gbMSM (66/79)	38 (3-2–4-3)	NR	NR	86 (Premises venues, private sex parties, and the use of geospatial dating apps)	1 (To Nigeria) and 18/86 (to multiple countries)	3 (Household cluster)	NR	NR	NR	NR	NR	PCR	0

Abbreviations: HIV, human immunodeficiency virus; M, male; MSM, men having sex with men; MSW, men having sex with women; STI, sexually transmitted infection; RT-PCR, real-time polymerase chain reaction.

3.8 | Outcomes

No deaths were so far reported.

4 | DISCUSSION

Monkeypox is a rare zoonotic disease, caused by a double-stranded DNA virus belonging to the *Orthopoxvirus* genus, the *Poxviridae* family, and the *Chordopoxvirinae* subfamily, closely related to the *variola* virus, the causative agent of smallpox. Endemic in Africa, no cases outside of the African continent have been reported until 2003 in the United States of America, when the importation of infected rodents and exotic animals from Ghana resulted in a cluster of 47 confirmed/probable monkeypox cases, after the contamination of some pet prairie dogs.[14] Subsequent clusters were described in Singapore (in 2019),[15] United Kingdom (in 2018 and in 2019),[16] and Israel (in 2018).[17] These clusters mostly exhibited a clear epidemiological link to travel to African countries, including Nigeria, being as such imported (as in Singapore, United Kingdom, and Israel), or were due to transmission to household or healthcare contacts (as in the United Kingdom).

The currently ongoing outbreak is mostly travel-unrelated, with a few exceptions, including the case traveling back to the United Kingdom from Nigeria, which was PCR-confirmed on May 7, 2022. A household cluster was reported in the United Kingdom on May 12, 2022, with the symptom onset dating back to April 17, 2022. A total of 18 cases reviewed by Vivancos et al.[12] reported a travel history in non-African countries, generally for sexual purposes. Mass gathering events can contribute to the spreading/super-spreading of infectious outbreaks. Some of these, including the "Gay Pride Maspalomas (Gran Canaria) 2022" festival, held from May 5 to May 15, 2002, in Maspalomas, Great Canary, Spain, have been linked to monkeypox cases.[18,19]

4.1 | Sex, gender, and sexual orientation

All cases included in our review were males, having unprotected sex with men, mostly in their thirties. This is in line with other studies: Vivancos et al.[12] reported that (at least) 83% of the cases they analyzed were known to be gay or bisexual. In previous outbreaks of at least two cases as well in single clusters that occurred in African countries, males represented ≥50% of the confirmed cases. In nonendemic countries, males were most affected.[2]

4.2 | Age

Generally, subjects included in the present review were in their 30s. Similarly, Vivancos et al.[12] computed a median age of their cases of 38 years (interquartile range, 32–43 years). Moreover, young individuals were more likely to be sexually active and engaged in mass gathering events/festivals. This represents a significant shift in the epidemiological trend of monkeypox: in countries where monkeypox is endemic, and in the early years (1970–1989), monkeypox was primarily a disease affecting young children, with a median age at the clinical presentation of 4–5 years. Mean age has increased to 10 years in 2000–2009 and 21 years in 2010–2019, suggesting a major role of smallpox vaccination discontinuation and waning of immunity. In the 2003 US outbreak, 10 out of 34 (29.41%) were less than 18 years.[2]

4.3 | Smallpox vaccination status

Subjects reviewed, as expected, were young because older individuals were protected against monkeypox by the smallpox vaccination. Of note, one of the four Italian monkeypox cases (25.0%), who was in his 30s, reported being vaccinated against smallpox.[7] The proportion of vaccinated subjects affected by monkeypox in both endemic African and nonendemic countries in previous outbreaks ranges from 4% to 21%, with the highest percentage reported during the US 2003 outbreak.[2]

4.4 | Transmission route

Despite the sexual transmission route is not generally associated with monkeypox infection, being skin-to-skin, or respiratory, most cases reported genital and/or (peri-)anal lesions, suggesting that sexual intercourse is likely to play a key role. Indeed, the lesions mirror the point of skin-to-skin sexual contact and the type of sexual intercourse and there is a significant temporal association of symptoms to sexual intercourse.[9] On the other hand, the Israeli case of the 2018 cluster[17] reported a lesion affecting his penile shaft and the epidemiological assessment was able to link the case to exposure to Africant infected rodent carcasses.

Concerning risk factors, the Australian case[10] reported unprotected sexual intercourse with four random sexual partners during his travel to Europe. Seven of the Portuguese cases[11] had attended a sauna. Interestingly, one of the four Italian cases was a sex worker. This occupational risk factor warrants further investigations. From a biological perspective, the seminal fluid obtained from some of the cases reviewed was found to be positive for the monkeypox virus, with quantification cycle (Cq) values comparable to those obtained for nasopharyngeal swabs. However, correlations between viral seeding in the male reproductive tract, viremia, and viral shedding/transmissibility are not obvious and still unknown. The presence of the monkeypox virus in the semen could be just a consequence of the systemic dissemination of the virus itself and the viremia, due to the imperfection of the blood–testis barrier and the immune-privileged nature of the testes ("the sanctuary site theory").

Concerning other potential transmission routes, three of the Portuguese cases reported contact with animals (a pig in one case, and cats in two cases), and one from the same cluster reported contact with another monkeypox case. Contact with other cases was

reported also for three of the English cluster,[12] documenting a household outbreak, as previously mentioned.

4.5 | Infection course

Generally, the infection course was mild, with no severe symptoms (such as dyspnea) being reported and with complications being described only in a few cases. For instance, the Australian case[10] experienced a superinfection (a superimposed bacterial cellulitis of his penile shaft and lower central abdomen). Laboratory exams (full blood-work, and biochemistry liver function tests) were in the normal ranges, with mildly increased C-reactive protein levels. Usually, in monkeypox, evolution and dissemination of the rash is monomorphic and centrifugal, with lesions concentrated on the face and peripheral extremities, but unusual presentations, with initial genital rashes and face and extremities relatively spared by the virus, are possible and have been particularly observed during the ongoing monkeypox epidemic. Of note, one of the Italian cases[7] and one of the English cases[12] presented a rash limited to the genital and pubic areas. In a few cases, there were no prodromal symptoms, atypically followed by systemic symptoms/signs.[9]

4.6 | Monkeypox virus and HIV

Another point that merits further studies is the interplay between HIV and the monkeypox virus. This topic has been relatively underlooked in the existing scholarly literature, with a few exceptions. For instance, in a study conducted in Nigeria,[20] where the monkeypox is endemic, the authors found that HIV status impacted the clinical course of the infection. Clinical variables associated with HIV positivity were genital ulcers (odds ratio [OR]: 1.94 [95% confidence interval {95% CI}: 1.38–2.72], $p = 0.015$), secondary infections and complications (OR: 3.1 [95% CI: 1.86–5.16], $p < 0.0001$), rash size, equal to or greater than 2 cm (OR: 12.7 [95% CI: 1.4–114.4], $p = 0.020$), and duration of illness, equal to or longer than 28 days (OR: 9.3 [95% CI: 1.36–63.9], $p = 0.029$). However, other variables, including age group, sex, hospital day, and outcome, had no statistically significant correlation. Mobility and rash distribution resulted in a borderline significant association ($p = 0.09$ and $p = 0.06$, respectively).

4.7 | Outcome

No fatalities were reported so far for the case series reviewed in the present study. According to Bunge et al.,[2] the case fatality rate (CFR) of monkeypox is computed at 8.7% (95% CI: 7.0–10.8), being higher for the central African clade (10.6% [95% CI: 8.4–13.3]) compared to the Western clade (3.6% [95% CI: 1.7–6.8]). When restricting the analysis to endemic countries only, Bunge et al.[2] computed a value of 4.6% (95% CI: 2.1–8.6) for the CFR of the Western clade. CFR of the US 2003 outbreak was 0% (no deaths reported for the 47 cases).

4.8 | Implications for public health

The ongoing monkeypox epidemic represents a true challenge in terms of global/public health.[21–24] Contact tracing is rather difficult and unfeasible given that most cases were engaged in risky behaviors with multiple anonymous partners. Only 28% of sexual contacts of the English cases had details that could be fully disclosed and reported.[12] For this reason, the involvement of all relevant actors and stakeholders—professional agencies, third sector organizations, LGBTQI+ associations, organizers of Pride festivals and related events, and developers of geospatial dating apps—is absolutely necessary. Furthermore, a stigmatizing approach should be avoided.[18] Besides tracing close contacts as much as it is possible, the implementation of an integrated and concerted package of public health interventions such as home isolation/quarantine, pre- (PrEP), and postexposure prophylaxis with smallpox vaccine when indicated, along with sexual health promotion should be considered. Since willingness of immunizing against smallpox seems to be rather low among at-risk groups (approximately 14%),[12] awareness campaigns should be conducted. So far, Belgium has been the first to introduce a 21-day monkeypox-induced mandatory quarantine. Finally, a standardized definition of monkeypox should be formulated, potentially updating previous working definitions and including unusual/atypical clinical presentations of monkeypox lesions.

4.9 | Study limitations

The present study has several shortcomings, that should be properly acknowledged. Data are not complete and still preliminary, drawn from a relatively small cohort/population, and the epidemic is still ongoing, with cases expected to significantly increase. On the other hand, understanding the main determinants of the monkeypox infection is of paramount importance and extremely urgent and could effectively assist the public health response to the outbreak.

4.10 | Future directions and prospects

This review should be considered a "living review" and will be updated when new data emerge.

5 | CONCLUSION

In the present study, we synthesized early epidemiological and virological data of monkeypox cases from Australia, Italy, the Czech Republic, Portugal, and the United Kingdom. The latter two countries are currently the most affected by the ongoing monkeypox epidemic. We compared epidemiological trends and clinical features of the ongoing epidemic with those of previous outbreaks. Significant changes in the transmission route, mean age, signs/symptoms at the clinical presentation, and their evolution could be detected. Even though preliminary, this report can inform practitioners as well as

policy- and decision-makers in their efforts to contain and control the outbreak. Some preliminary risk factors can be identified (being a male, having sex with other men, engaging in risky behaviors and activities, including condomless sex, HIV positivity, and a story of previous STIs, including syphilis). On the other hand, being fully virally suppressed and undetectable may protect against a more severe infectious course. However, further research in the field is urgently needed, since our findings need to be replicated and confirmed by further larger studies.

AUTHOR CONTRIBUTIONS

Nicola L. Bragazzi conceived, drafted, and revised the paper. Jude D. Kong conceived, and critically revised the paper. Naim Mahroum critically revised the paper. Christina Tsigalou critically revised the paper. Rola Khamisy-Farah, Manlio Converti, and Jianhong Wu conceived and critically revised the paper

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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