# Sexually transmitted diseases and HIV co-infection among adult male patients in the 2022 monkeypox outbreak: a systematic review and meta-analysis

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## Abstract

This meta-analysis estimates sexually transmitted disease (STI) and HIV rates in male monkeypox patients during the 2022 outbreak. The study examines contextual factors that increase monkeypox risk. A systematic review of PubMed/Medline, Scopus, and Google Scholar was conducted to find observational studies on monkeypox patients' demographics and medical characteristics from the 2022 outbreak. This review's meta-analysis followed the System for the Unified Management, Assessment, and Review of Information – Joanna Briggs Institute (SUMARI JBI) guidelines. All HIV and STI prevalence data for male monkeypox patients was exported into the SUMARI JBI. For point prevalence of HIV and STIs, we used the Freeman-Tukey-type arcsine square root transformation to stabilize raw proportion variances. A fixed-effects model weighted and pooled all estimates by inverse variance. We then used a random model to account for sampling variation and reported fixed-effect model effect size heterogeneity across studies. Study heterogeneity was measured using the $I^2$ test statistic and P-values. $I^2$ test results were interpreted as low (25%), moderate (50%), and high (75%). Six Spanish and English studies qualified. These studies included 541 male monkeypox patients, 214 of whom had HIV and 255 with other STIs. HIV prevalence was estimated at 40% (95% CI = 0.31%, 0.50%; $\chi 2=15$) and STIs at 43% (95% CI = 25%, 61%; $\chi 2=118$). Overall, analyses showed moderate to high heterogeneity. Four in ten male monkeypox patients in 2022 had HIV or other STIs. To prevent HIV and other STIs, public health measures should target male and female monkeypox patients.

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## Introduction

The 21st century has witnessed the emergence and re-emergence of several zoonotic viral infections such as severe acute respiratory syndrome, Middle East respiratory syndrome, and more lately Coronavirus disease 2019 (COVID-19).[1] As the world was recovering from the repercussions of COVID-19, a newly emerging zoonotic viral infection had been identified in the form of monkeypox. Originally identified in monkeys and other animals, some cases were reported among humans, however, they did not attract much attention due to the zoonotic nature of this disease and the low numbers of human cases. Most cases of monkeypox occurred in Africa with some sporadic cases occurring elsewhere. However, a noticeable surge of cases was reported in May 2022 in countries not previously known to report such infection such as Europe and North America.[2] On 4th September 2023, there were 89,752 confirmed cases and 157 confirmed deaths related to this disease.[3] It is primarily manifested as self-limiting skin lesions, however, other clinical manifestations were described in a recent systematic review which included observational studies conducted during the 21st century and these were fever, lymphadenopathy, fatigue, sore throat, and headache.[4] Despite the self-limiting nature in most cases, other disease outcomes could present in the form of severe complications such as encephalitis, pneumonia, gastrointestinal symptoms, secondary bacterial skin infection, and eye problems in the form of keratitis, blurred vision, and corneal scarring.[5] The infection is transmissible from animals to humans, and it can be transmitted among humans through multiple routes. This is well-represented by the 2022 outbreak which affected large numbers of humans in a total of 114 countries, 107 of which have not historically reported monkeypox.[6] Social activities that

involved skin-to-skin contact, contact with fomites such as bed linens, and exposure to respiratory droplets were highlighted as the main predisposing factors in this outbreak.[7] Among these social activities, sexual intercourse among men who have sex with men (MSM), stands out as the most likely risky behavior in predisposing to this infection.[8] Patients were primarily seen in sexual healthcare facilities complaining of genital lesions, which prompted concerned authorities to look into the possibility of considering monkeypox as an emerging sexually transmitted disease (STI).[2] A striking feature of the 2022 outbreak was the presence of comorbidities in the form of STIs and HIV in the affected patients. Another feature was the involvement of sexual networks whereby patients had reported multiple sexual partners (homosexual and bisexual). Considerably lower numbers of female patients were affected and these reported previous contact with males in a sexual or household context.[2] Despite the low numbers of infected women, vulnerable populations of pregnant women, breastfeeding mothers and even children were under the spotlight as potentially susceptible patients.[9] Previous studies in Africa identified people with uncontrolled HIV to have worse outcomes, including more extensive and longer-lasting lesions, more complications, and several deaths.[10] On the other hand, MSM are considered a high-risk group for STIs.[11] It is important at this stage to assess potential risk factors and identify risk groups susceptible to monkeypox. This will facilitate designing the appropriate preventive measures that target susceptible populations.

Despite the wide distribution of monkeypox in the current outbreak that involved 114 countries up to date,[12] Europe and the Americas represent the most highly affected geographic areas. The outbreak initially was identified in the United Kingdom (UK) and later in Spain and hence many studies were conducted in these two countries during the first months of the outbreak. Therefore, we conducted this meta-analysis to estimate the prevalence of STIs and HIV infection among adult male patients reported in Spain and the UK considering their epidemiological importance in the initiation and spread of the infection.

## Materials and Methods

### Eligibility criteria

Studies were considered eligible for inclusion in this review if they had the following criteria: i) studies on human monkeypox infections; ii) case series, cross-sectional, cohort studies describing prevalence of STIs and HIV among monkeypox cases in the 2022 outbreak; iii) studies from countries/geographic regions that were initially affected by the outbreak in Europe: Spain and the UK; iv) studies published in the English language; v) publication date: 1st January 2022 to 30th September 2022; vi) patients: male patients.

Studies were excluded if they were: i) clinical trials, opinion, commentary, letter to the editor, editorial, review, or case reports; ii) reporting other geographic locations.

### Information sources

Literature from the following databases was searched: PubMed/ Medline, Scopus, and Google Scholar. References of retrieved articles were searched where applicable. Further, the websites of the World Health Organization (WHO), European Centre for Disease Prevention and Control, and Centers for Disease Control and Prevention were searched for relevant keywords. A data search was conducted for literature published within the period: 1st January 2022 until 30th September 2022.

### Search strategy

The included databases were initially searched for the keywords: "Monkeypox" and "2022", using the following filters: observational studies, case series, cross-sectional studies, human studies, English language, and period from 1/1/2022-30/9/2022. The WHO website was consulted to obtain data on the most affected geographic areas by the outbreak. The retrieved articles were then searched for the following keywords: "Spain", "UK", and their references were also searched to ensure retrieving all relevant articles.

### Selection process

Two reviewers (NDO and OAH) worked independently to select eligible articles. This was done by initial screening of titles and abstracts of retrieved articles. Only relevant articles were screened for full text.

### Data collection process

Two reviewers (A. Raheem J and A. Rahman J) independently collected data from selected articles.

All collected data were further revised by a third reviewer (AAH) to confirm the accuracy of retrieved data.

### Data items

Collected data included: author(s) name; study type; country; number of monkeypox cases reported by the study; sociodemographic characteristics of patients like age, sexual orientation; disease factors including: history of HIV, history of STIs (concurrent or past), and possible transmission route.

### Study risk of bias assessment

The risk of bias (methodological quality) in included articles was determined using Joanna Briggs Institute (JBI) critical appraisal tools for case series,[13] cohort studies, and cross-sectional studies.[14] Two reviewers (NDO and AAH) worked independently to assess all studies.

### Data synthesis

A meta-analysis was considered the most appropriate approach for this study. The System for the Unified Management, Assessment, and Review of Information – JBI (SUMARI JBI) guidelines was used by author NA to conduct the meta-analysis of this review.[15] First, all data relevant to the prevalence of HIV and STIs in male patients diagnosed with monkeypox were extracted and exported into the SUMARI JBI. To assess the point prevalence of HIV and STIs, we used the Freeman-Tukey type arcsine square root transformation to stabilize the variances of the raw proportions. All estimates were weighted and pooled by the inverse variance using a fixed-effect model. We then used a random model to account for sampling variation and reported heterogeneity in effect size noted across studies in the fixed-effect model. The $I^2$ test statistic and P-values were used to measure the heterogeneity between studies. A value of $I^2$ test statistic results of 25%, 50%, and 75% was considered as low, moderate, and high respectively.

### Reporting bias assessment

Missing results were related to the reported types of STIs and their prevalence among patients. This data was determined to be influenced by the availability of data on screening for STIs or the lack of retrieved past history on previous infections with STIs.

## Results

### Study selection

A total of six articles were determined to be appropriate for inclusion in this review. The flowchart that describes the selection process is presented in Figure 1.

### Included studies and their findings

As of 30th September 2022, only six studies reported prevalence data on HIV and STIs among adult male patients with monkeypox and met all criteria for inclusion. The data for all studies were reported from two European countries (Spain and the UK) in the form of case series, cross-sectional, and cohort studies. Three studies enrolled male patients from Spain and another three studies from the UK (Table 1).

In these studies, enrollment was based on the presence of HIV and other STIs among patients diagnosed with monkeypox. Among the six studies of male patients diagnosed with monkeypox, the pooled prevalence of HIV was 40% (95% CI = 0.31%, 0.50%; $\chi^2$=15) and 43% (95% CI = 25%, 61%; $\chi^2$=118), for other STIs (Figures 2, 3). The $I^2$ test of homogeneity was highly signif-

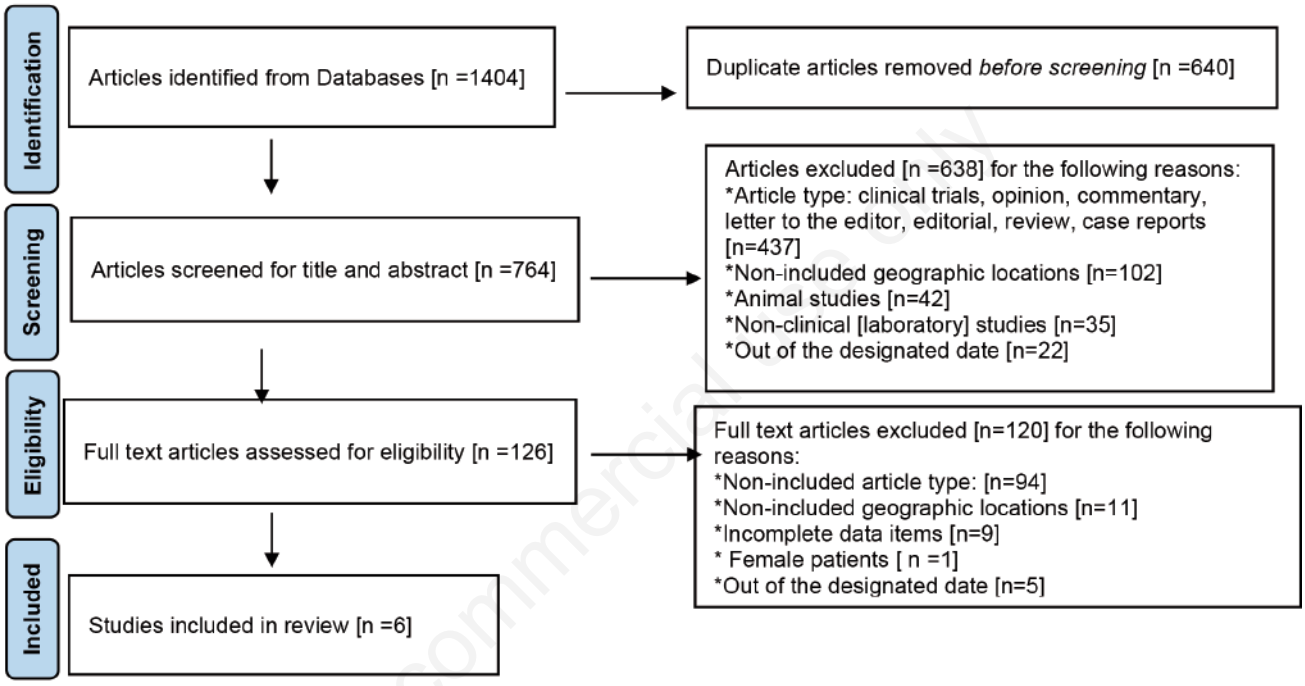


**Figure 1.** Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart displaying the identification and selection process of studies. Retrieved via: MEDLINE/PubMed, Scopus, and Google Scholar databases.

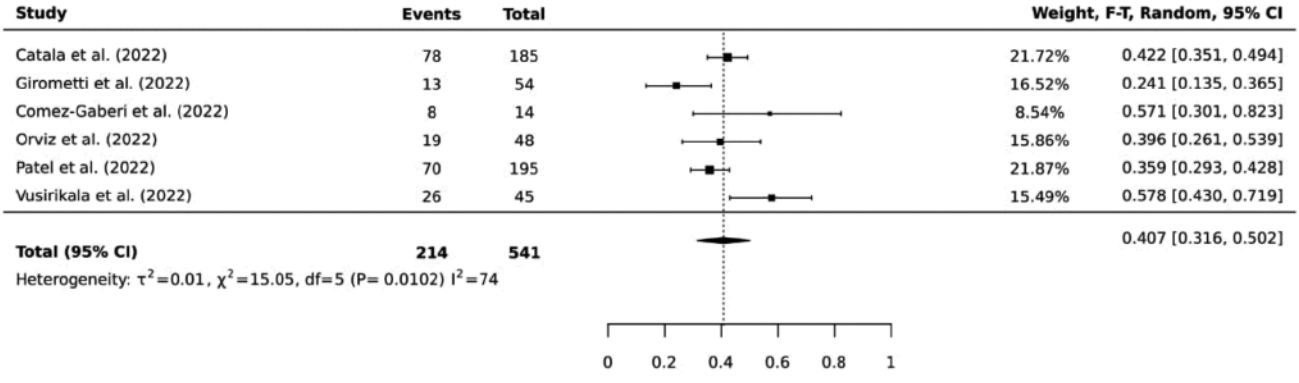


**Figure 2.** Meta-analysis and forest plot presentation of HIV among male patients with Monkeypox (based on studies from the United Kingdom and Spain on the 2022 outbreak). CI, confidence interval.

icant (P≤0.001). Accordingly, random effects estimates were used. Studies did not provide enough data to stratify prevalence based on age, race, or circumcision status, all of which can affect infection risk. Therefore, we were unable to quantify estimates of HIV and other STIs prevalence for each subgroup.

## Risk of bias assessment

Only two studies were assessed as having a low (Catala *et al.*) and a moderate (Vusirikala *et al.*) risk of bias according to the JBI critical appraisal criteria for cross-sectional studies, and case series. The reasons behind this assessment are mentioned in Table 2.

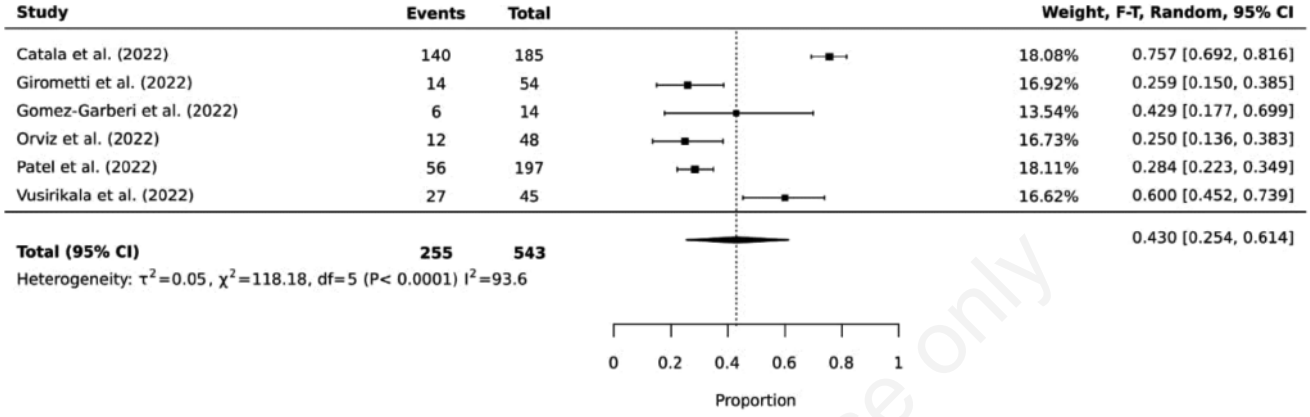


**Figure 3.** Meta-analysis and forest plot presentation of sexually transmitted diseases among male patients with monkeypox (based on studies from the United Kingdom and Spain on the 2022 outbreak). CI, confidence interval.

**Table 1.** Sexually transmitted diseases and HIV infection among adult male monkeypox patients affected during the 2022 outbreak in Spain and the United Kingdom. Studies were published up until 30th September 2022.

| Authors | Study type | Country | Patient, N | Age (years) (mean or median) | HIV+ve (N, %) | Other STIs (N, %) | MSM | Sexual route of transmission |
|---|---|---|---|---|---|---|---|---|
| Catala *et al.*[16] | Prospective cross-sectional | Spain | 185 | M=38.7 | 78 (42.0%) | 140 (76.0%) (concurrent) | 99% | 100% |
| Orviz *et al.*[17] | Cross-sectional | Spain | 48 | Med=35 | 19 (39.5%) | 12 (25.0%) (concurrent)<br>gonorrhea (6)<br>syphilis (4)<br>mycoplasma genitalium (1) | 97.9% | 100% |
| Gomez-Garberi *et al.*[18] | Prospective observational | Spain | 14 | Med=42 | 8 (57%) | 43%<br>gonorrhea (1)<br>chlamydia (2)<br>syphilis (1)<br>mycoplasma genitalium (1)<br>genital herpes (1) | 71% | 12 (85.7%) |
| Patel *et al.*[19] | Case series | United Kingdom | 197 | Med=38 | 70/195 (35.9%) | 56 (31.5%) of screened patients (concurrent)<br>gonorrhea: 34 (21.1%)<br>chlamydia: 18 (11.2%)<br>cenital herpes: 11 (7.0%)<br>syphilis: 6 (3.7%)<br>> one STI: 12 | 196/197 (99.5%) | 170/177 (96.0%) |
| Girometti *et al.*[20] | Observational | United Kingdom | 54 | Med=41 | 13 (24%) | (25.0%) (concurrent)<br>13/51 (25.0%): positive<br>gonorrhoea (9)<br>chlamydia (6)<br>gonorrhoea<br>chlamydia (2) | 100% | 100% |
| Vusirikala *et al.*[21] | Cross-sectional | United Kingdom | 45 | Med=40 | 26% | 27 (60.0%) (past history) | 44 (98.0%) | 100% |

STI, sexually transmitted diseases; MSM, men who have sex with men; M, mean; Med, median.

## Discussion

Two years have passed since the identification of the first batch of patients with monkeypox in the global outbreak that emerged in 2022. The outbreak is still ongoing and more countries are being affected, though the greatest majority of those countries are not historically known to be affected by this infection. According to the most recent data reported by the WHO on August 14th, 2023, an estimated 1020 new cases and three new deaths were reported during the period from 14th July-9th August 2023 with most of these cases being reported in the Western Pacific region.[22] Further, the risk for monkeypox at the global level is still assessed as moderate in most parts of the world including Africa, the Eastern Mediterranean region, Europe, and the Americas. Sexual orientation and occurrence of specific comorbidities in the current monkeypox outbreak with significant public health consequences prompted the performance of this study. We focused on studies from the UK and Spain because these represented the most commonly affected two countries at the outset of the outbreak. At present, after almost two years, the UK and Spain are still among the most commonly affected ten countries worldwide.[22]

Although monkeypox is not a recent disease, the re-emergence of this infection drew attention due to the changing trends in epidemiology. In their systematic review published in early 2022, Bunge *et al.* investigated the evolving epidemiology of human monkeypox in the last two decades and highlighted the changing trends in geography (outside Africa), age (adults), and severity of disease outcomes (mortality).[23] Authors attributed the increasing human-human transmission to the cessation of smallpox vaccination and a waning immunity of populations.[23] However, sexual orientation and intimate social activities were given more attention as the main risk factors in transmission in later reports.[24]

This analysis described a total of 541 male patients and the associated co-morbidities of HIV and STIs. All studies reported that a substantial proportion of patients was positive for HIV. On the other hand, all studies, except one,[21] reported that at least one in four patients had one or more concurrent STI. Patients were in their late thirties- early forties, mainly MSM and the sexual route represented the only confirmed route of transmission in most studies. This highlights the risk for transmission of HIV and STIs in general and is consistent with recent surveys that highlighted the substantial proportion of STIs among monkeypox patients. Hoffmann *et al.* described a cohort of patients in Germany in the current outbreak to be exclusively MSM; 46.7% of them had HIV and 59.0% were diagnosed with an STI during the six-months period prior to monkeypox infection.[25] Similar findings are reported from patients diagnosed in the United States where HIV prevalence was 38%, and 41% of them were diagnosed with at least one STI in the preceding year.[26]

In this review, the reported STIs were gonorrhea, chlamydia, genital herpes, syphilis, and *Mycoplasma genitalium* in descending order. It is worth noting that gonorrhea reached its lowest incidence in the United States by the year 2009.[27] Syphilis, on the other hand, was on the verge of eradication by the year 2000,[28] however, since that year a steady rise of cases was noticed with severe symptoms such as neurosyphilis and ocular syphilis being noticed among MSM.[29] It is also noticeable that as monkeypox cases were surging during May 2022, another surge in the prevalence of STIs was noticed in the post-COVID era specifically congenital syphilis, gonorrhea, and syphilis.[30] The so-called "modern" resurgence of syphilis is an important public health problem in the US and other high-income countries. Of particular interest is congenital syphilis, a major cause of severe adverse pregnancy outcomes such as low birth weight, hepatomegaly, osteolytic bone lesions that may be associated with fractures, pseudoparalysis, central nervous system infection, and long-term disabilities. A recent report warned that cases of congenital syphilis have increased by 32% in the United States in the years 2020-2021, with >2,000 cases reported in 2021 alone.[31] The public health burden of these STIs is mainly attributed to the serious adverse disease outcomes. There is also the anticipated burden of prevention and treatment outcomes on healthcare systems, which aim to integrate screening, vaccination and antimicrobial therapy in the comprehensive plan of care of patients and susceptible populations. Moreover, bacteria responsible for certain STIs are rapidly developing antibiotic resistance. It was reported recently that azithromycin resistance was more likely among MSM and among HIV patients.[32]

This analysis estimated that the reported prevalence of HIV and other STIs among patients with monkeypox was high, yet the total estimates varied widely between studies. Estimates of HIV prevalence ranged from 2% in Gomez-Garberi to 26.95% in Patel *et al.*[18,19] The STIs prevalence yields similar estimates which confirms the importance of demographic and clinical variables when considering patients who are at higher risk of developing monkeypox. Although we could not directly calculate the pooled prevalence of HIV and STIs in patients with certain clinical demographics, it would be reasonable to assume that the risk of transmission in this population is high (40% in HIV patients and 43% in other STIs' patients). The available data from earlier studies suggest that MSM subgroup is associated with a higher risk of infection. Although more data are needed to clarify the mechanism by which sexual orientation affects baseline risk of infection, based on the available data, MSM patients can be considered at higher risk of developing monkeypox than heterosexual male patients. Similar results were reported by recent studies. A recent systematic review estimated that 40.3% of monkeypox cases that were reported in epidemiological studies from 2018-2022 were HIV positive.[33]

Other demographic features like age were also characteristic. In this study, patients were in their late thirties or early forties. The last report of the WHO pointed out that the median age of patients is 34, probably due to the inclusion of children aged 0-17 years in

**Table 2.** Studies that showed a low/moderate risk of bias in methodological quality, and the reasons for this assessment.

| Study | Level of risk | Reasons: lack of diagnostic tests or assessment methods |
|---|---|---|
| Catala *et al.*[16] | Low | 1. Screening tests of concurrent STIs was not mentioned<br>2. Types of concurrent types of STIs were not mentioned |
| Vusirikala *et al.*[21] | Moderate | 1. Only past history of STIs was mentioned<br>2. Screening tests of concurrent STIs were not mentioned<br>3. Types of past and concurrent types of STIs were not mentioned |

STI, sexually transmitted disease.

the total sample of patients. At the beginning of the outbreak, the most common exposure setting was parties with sexual contact, however, in the last three months the main exposure setting was parties with no sexual contact, while the household setting constituted 14% of the cases.[22] This has serious public health implications because the risk of infection may extend to other commonly considered non-risk groups for the infection.

This review has limitations. The high heterogeneity could be considered a major limitation, therefore clinical judgment is warranted to decide whether, in fact, we included studies that were "too different" to be included, mainly in terms of diagnostic criteria of HIV and STIs, type of studies and sample size. Second, because most of the studies about HIV did not differentiate HIV from AIDS, the estimates provided included both. The estimates of STIs included also large categories of different types of infection. Finally, we could not calculate the prevalence rate of HIV or STIs for certain subgroups, such as circumcised patients, age groups, sexual orientation, or HIV-viral load due to limited data. This analysis, however, has several strengths. By using a comprehensive search strategy and *a priori* inclusion/exclusion criteria, these results provide a more updated picture of monkeypox prevalence and its association with HIV and other STIs infection. Our findings show the pooled estimates have relatively narrow confidence intervals, mainly for HIV patients and are consistent with previous epidemiologic studies.

The pooled prevalence values provided in our analysis can be used as an estimate of baseline probability in an evidence-based approach. However, more prevalence meta-analysis is needed in the future to provide healthcare professionals with baseline estimates of risk of monkeypox among certain populations.

Specific Public Health interventions have been recommended in the context of the monkeypox outbreak such as vaccination, messaging, and individual behavior modification and these may have contributed to the overall decline in cases worldwide.[30] However, more research is warranted to identify the most effective methods in preventing new cases. Further, officials are warranted to allocate sufficient funding and to adopt appropriate national strategies targeted toward sexual health promotion.[29] A comprehensive sexual health screening to conduct testing for other STIs should be included for all monkeypox patients.[34] Clinicians in different disciplines are also encouraged to be aware of the clinical features of this infection.[35] This is for two main reasons: first, patients can be identified early in the disease process which will improve the disease outcomes by offering the patient the appropriate referral and treatment plan; secondly, early identification will help prevent transmission to others which will have a great impact particularly for the sexual networks involved. Since patient education and cooperation are two main factors in prevention of disease transmission, it is also recommended to discuss safer sexual practices with at-risk groups namely MSM, and engage them in planning public health measures that could be effective in counteracting the disease.

## Conclusions

Approximately four in ten male patients with monkeypox have HIV and/or other STIs. Necessary public health programs should target male and female patients who are at risk of monkeypox infection to prevent the transmission of serious infections such as HIV and other STIs.

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