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Association between genital mycoplasmas (*Ureaplasma urealyticum* and *Mycoplasma hominis*) and HIV infection: a systematic review and meta-analysis

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Abstract

Several studies have reported the occurrence of genital mycoplasmas (Ureaplasma urealyticum, Mycoplasma hominis, Mycoplasma genitalium, and Mycoplasma fermentans) among human immunodeficiency virus (HIV)-infected patients, but findings are conflicting. The aim of this systematic review and meta-analysis was to assess the association of U. urealyticum and M. hominis with HIV infection. We searched seven databases to retrieve articles reporting the prevalence of genital mycoplasmas among HIV-infected patients. Pooled odds ratios (OR) with 95% confidence intervals (CI) were calculated and displayed by forest plots. Cochran Q and I^2 statistics were applied to assess heterogeneity. In addition, a funnel plot with an Egger's test was performed to evaluate potential publication bias. Of the 1123 articles identified, 12 studies met the inclusion criteria and were included in this meta-analysis. Our results revealed that HIV-infected patients had higher colonization rates by U. urealyticum and M. hominis (single infection) than the control group (OR = 1.526; 95% CI: 1.202-1.937; p = 0.001 and OR = 2.610; 95% CI: 1.890-3.604; p = 0,000, respectively). However, coinfection seemed to be not associated with HIV infection (OR = 1.311; 95% CI: 0.744-2.311; p = 0.348). A subgroup analysis showed that study design and geographical origin were a source of heterogeneity in the studies that reported coinfection among HIV-infected patients. However, there was no statistical evidence of publication bias. Our study revealed that genital mycoplasmas were more frequent in HIV-infected patients than healthy individuals, resulting from a decline of natural immunity due to HIV. More effort should be dedicated to the screening, prevention, and treatment of genital mycoplasmas, to curb the spread of HIV.

Keywords

Ureaplasma urealyticum. Mycoplasma hominis. Colonization rate. Meta-analysis.

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Introduction

HIV/AIDS was the ninth cause of death in low-income countries in 2019[1]. In 2021, it was estimated that approximately 38.4 million people were living with AIDS worldwide[2]. Sexually transmitted infections (STIs) increase the risk of HIV transmission, which constitutes a real public health problem[3]. Therefore, interest has been paid to STIs, including genital mycoplasmas (*Ureaplasma urealyticum*, *Mycoplasma hominis, Mycoplasma genitalium,* and *Mycoplasma fermentans*), and the integration of AIDS programs with STIs prevention and care strategies is highly advised[4].

During the course of HIV infection, one or more superantigens may be involved in the activation of the immune system. Mycoplasmas may act as cofactor stimulating the expression of these superantigens[5]. Furthermore, mycoplasmas enhance the acquisition and progression to AIDS by enhancing the HIV replication through selective activation of CD4+ T lymphocytes[6].

Genital mycoplasmas (*U. urealyticum*, *M. hominis, M. genitalium,* and *M. fermentans*), which belong to the *Mycoplasmataceae* family, within the *Mollicutes* class, are wall-less Gram-positive bacteria that colonize the human genital tract[7]. They are important emerging sexually transmitted bacterial pathogens that can also be transferred vertically from mother to offspring or through transplanted organs[8,9]. *U. urealyticum* and *M. hominis* are the most prevalent genital mycoplasmas that can cause asymptomatic, long-term, and chronic infections in the genitourinary tract such as cervicitis, pelvic inflammatory disease, and bacterial vaginosis[7,10,11]. They are also associated with pregnancy complications and increased risk of neonatal morbidity[12]. Many studies have reported that these sexually transmitted pathogens might affect human fertility[13,14]. In addition, they have been associated with diverse extragenital infections, especially in immunocompromised patients[15-17].

Over the past few decades, several epidemiological studies have investigated the association between genital mycoplasma colonization and HIV infection[18-20]. However, their results remained inconclusive and the impact of HIV infection on the occurrence of genital mycoplasmas is still a topic for discussion. The previous systematic review and meta-analysis studies have revealed a strong association between two other genital mycoplasmas, *M. genitalium,* and *M. fermentans,* and HIV infection[21,22]. However, no such study has been undertaken for *U. urealyticum* or *M. hominis*.

Hence, we aimed to perform the first systematic review and meta-analysis to investigate the prevalence of *U. urealyticum* and *M. hominis* among HIV-infected patients compared to HIV-negative individuals.

Methods

This systematic review and meta-analysis study was prospectively registered at PROSPERO (CRD42022350458) and was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMAs) guidelines[23].

Search strategy

A systematic search was conducted on PubMed, Medline, Web of Science, the Cochrane Library, Embase, Google Scholar, and CINAHL from database inception until June 2022 to look for potentially eligible articles. The search strategy was based on the following key search terms: "human immunodeficiency virus" OR "acquired immune deficiency syndrome" OR "AIDS" OR "HIV" OR "HIV-positive" OR "HIV-seropositivity" AND "urogenital mycoplasmas" OR "*Ureaplasma* spp." OR "*U. urealyticum"* OR "*Ureaplasma parvum"* OR "*Ureaplasma urealyticum"* OR "*U. parvum"* OR "*Mycoplasma hominis"* OR "*M. hominis*." All retrieval processes were performed independently by two authors.

Selection criteria

Relevant articles were screened by title and abstract after removing duplicates. Studies were eligible for inclusion if they addressed the prevalence of *U. urealyticum* or/and *M. hominis* among HIV-infected patients. The remaining studies were then examined in full-text to confirm eligibility.

Inclusion criteria for articles were: (1) case-control, cohort, and cross-sectional studies reporting the prevalence of *U. urealyticum* or/and *M. hominis* among HIV-infected patients; (2) studies with sample size ≥ 30; (3) publications reporting sufficient data to establish the odds ratio (OR) effect size; and (4) studies published as original articles. Exclusion criteria were: (1) no full-text electronically available; (2) publication in a language other than English; (3) comments, letters, editorials, protocols, guidelines, and review papers; (4) studies reporting genital mycoplasma infections

other than *U. urealyticum* and *M. hominis*; and (5) studies with insufficient outcome data.

Data extraction

Two independent authors (SB and GSS) retrieved information from the eligible articles following the inclusion and exclusion criteria, and information were collected on a standardized data sheet that included: (1) study ID (name of first author, year of publication), (2) study design, (3) country, (4) study population, (5) type of sample, (6) testing methods of genital mycoplasmas, (7) species, and (8) prevalence of *U. urealyticum* and *M. hominis* among HIV-seropositive and HIV-seronegative patients.

Quality assessment of studies

The Newcastle-Ottawa scale (NOS) was used to assess the quality of the non-randomized studies, which evaluates selection bias, comparability of the exposed and control participants, and outcome evaluation. Each criterion was assessed as 1 star or 0 stars. The total stars of the NOS checklist ranged from 0 to 9 stars for case-control and cohort studies and 0 to 10 for cross-sectional studies.

The NOS tool evaluates three sections: (1) selection of exposed (HIV-seropositive patients) and unexposed groups (HIV-seronegative patients) (max 4 points for case-control and cohort studies and 5 points for cross-sectional studies), (2) comparability of study groups (max 2 points), and (3) evaluation of outcome (max 3 points). Two independent authors (SB and GSS) assessed quality, independently, and discordances were solved by discussion. A study with a score from 7 to 9 or 10 has good quality, 4-6, fair quality, and 0-3, poor quality[24].

Statistical analysis

The statistical analyses were performed using comprehensive meta-analysis version 3 (Biostat Inc. USA). OR with 95% confidence intervals (CIs) was calculated to evaluate the association between *U. urealyticum* and *M. hominis* with HIV infection, using the Mantel-Haenszel method[25]. $p < 0.05$ was considered as the level of significance. The Cochran's Q test was used to evaluate heterogeneity among articles, with $p < 0.05$ indicating the existence of heterogeneity. To estimate the impact of heterogeneity on the meta-analysis, I^2 value was calculated. I^2 values $\geq 50\%$ and $p < 0.05$ indicated a moderate to a high degree of heterogeneity among pooled studies. A fixed-effects design was used when $I^2 < 50\%$ and $p > 0.05$; otherwise, a random-effects model was adopted[26]. We also performed subgroup and sensitivity analyses to assess the possible sources of heterogeneity. An Egger's test was conducted to evaluate publication bias. This latter was further assessed by the visual inspection of the symmetry in funnel plots.

Results

Identification of studies

The database search identified 1123 studies to be screened, of which 98 abstracts were identified as potentially eligible and retrieved for full-text review. Eligibility criteria were met by 12 articles, which were included in this systematic review and meta-analysis study. The PRISMA flowchart is shown in figure 1.

Characteristics of studies

The included articles were published between 1998 and 2021, as well as distributed among eight countries. Among 12 articles included in this systematic review and meta-analysis, ten were cross-sectional studies[18-20,27-33], one study was case-control[34], and one study was cohort (prospective study)[35]. The sample size of the included articles varied from 30 to 455 participants. The participants comprised 1382 HIV-infected patients and 1256 controls. The samples used to detect genital mycoplasmas were: urethral swabs (three studies), urine specimens (four studies), vaginal or cervical samples (five studies), and rectal swabs (one study). The detection of genital mycoplasmas was performed by culture and/or polymerase chain reaction (PCR).

Characteristics of included studies are summarized in Supplementary material: Table S1.

Quality assessment

Overall, the scores of included studies ranged from five to seven stars. Among the included studies, six were assessed to be of good quality and six articles were of fair quality. Supplementary material: Tables S2-S4 summarized the quality assessment scores for the included studies.

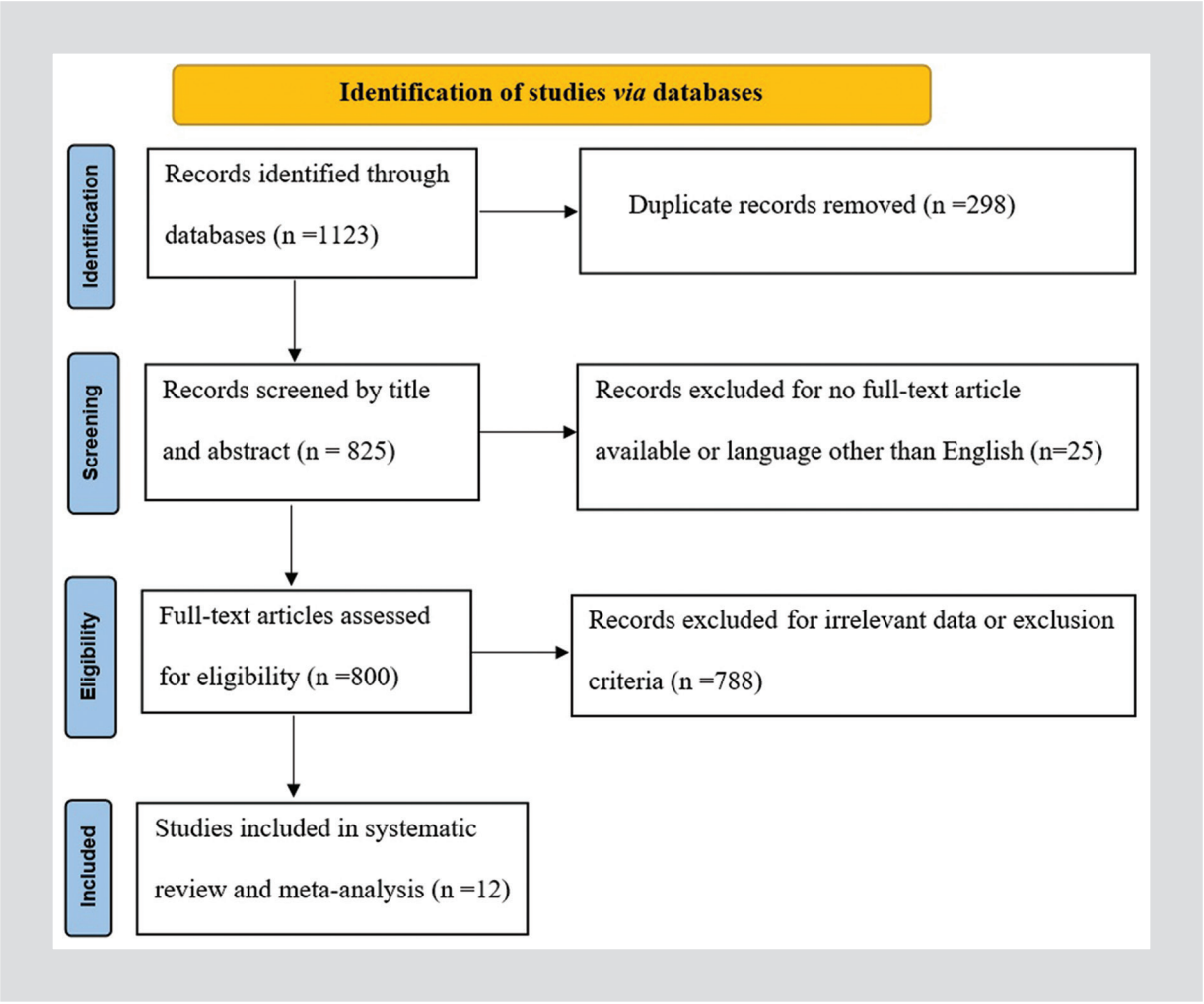

Figure 1. Preferred reporting items for systematic reviews and meta-analyses flow diagram.

Selection

Within cross-sectional studies (n = 10), all studies scored two stars. The reasons for not receiving a full quality score for the selection section were that the sample size was not justified and no description of the characteristics of the responders and the non-responders (Supplementary material: Table S2).

The case-control study scored three stars. The reason for not receiving a full quality score for the selection section was that the control group was not selected from the general community (Supplementary material: Table S3). The cohort study scored four stars (Supplementary material: Table S4).

Comparability

Within cross-sectional studies (n = 10), four studies controlled for the outcome and for additional factors (e.g., age), so they scored two stars. However, six studies controlled for only the outcome and scored one star (Supplementary material: Table S2). Both case-control and cohort studies controlled for the outcome and for additional factors (e.g., age) so they scored two stars (Supplementary material: Tables S3 and S4).

Outcome

All the cross-sectional studies adopted a validated assessment tool of the outcome (PCR or culture) and used a statistical test to analyze results and thus, they scored three stars (Supplementary material: Table S2).

While the case-control study reported the ascertainment of the outcome and used the same method of ascertainment for cases and controls, so it scored two stars (Supplementary material: Table S3). However, the

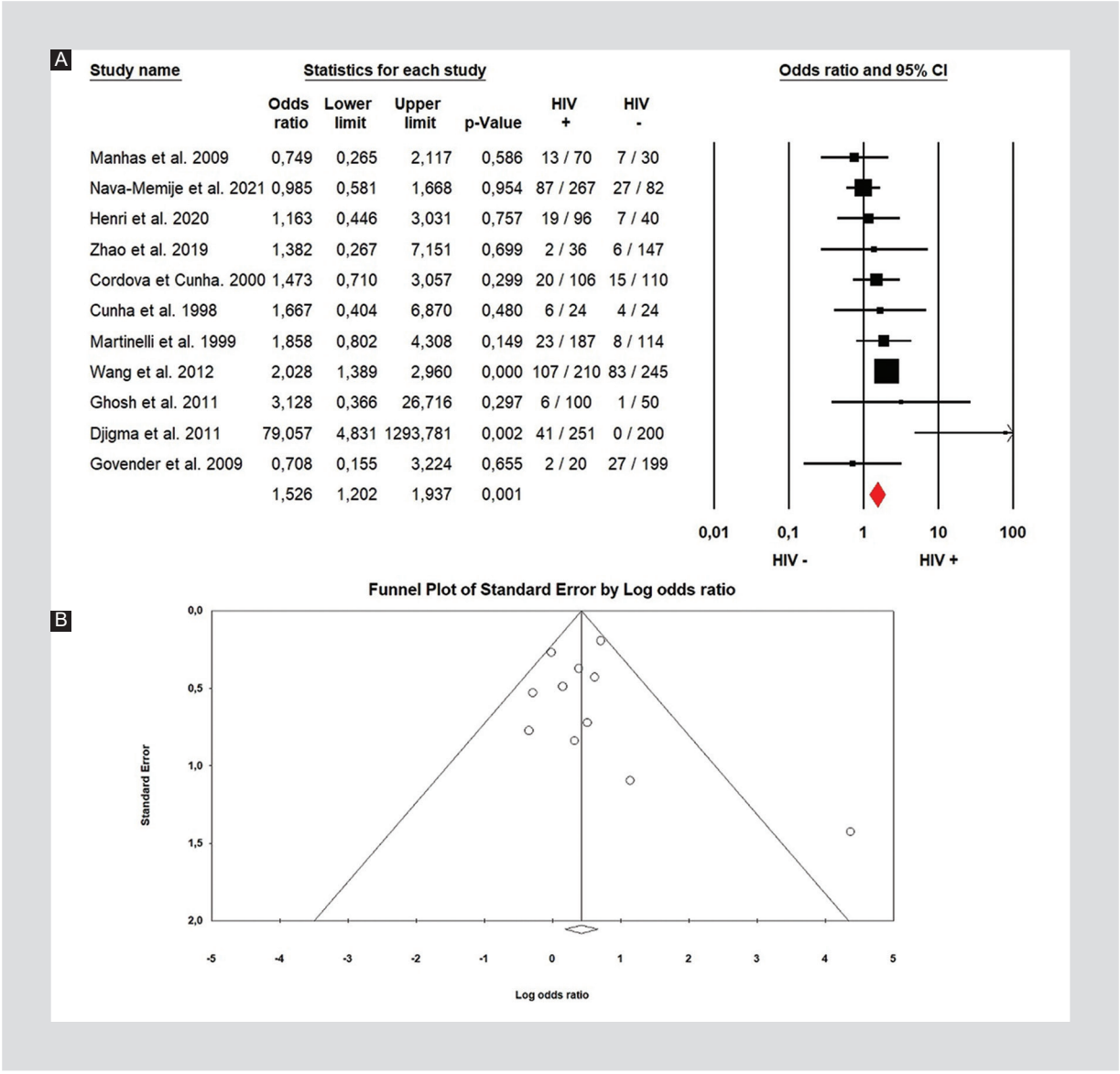

Figure 2. A: *forest plot of pooled odds ratio (OR) for U. urealyticum.* **B:** *funnel plot of pooled OR for U. urealyticum. The circles represent the 11 included studies about association between U. urealyticum and human immunodeficiency virus infection. The horizontal axis represents the size of association, while the vertical axis represents the standard error. The fixed effects that summary estimate is indicated by the vertical line, and the expected 95% confidence interval of the standard error is indicated by the two lines either side.*

cohort study scored only one star because it did not describe the follow-up period (Supplementary material: Table S4).

Outcomes

U. urealyticum

Eleven studies reported the prevalence of *U. urealyticum* among HIV-infected patients (Fig. 2A). The Cochran's Q test and I^2 statistic did not reveal a significant heterogeneity (Q-value = 16.26, p = 0.092, I^2 = 38.50%), so a fixed model was used. The forest plot analysis showed that the prevalence of *U. urealyticum* was significantly different between HIV-seropositive and HIV-seronegative groups. Indeed, *U. urealyticum* was 52% more likely to infect HIV-infected patients than control participants (OR = 1,526; 95% CI: 1.202-1.937; p = 0.001). The Egger's test was not found to be statistically significant (p = 0.751), which indicated the absence of publication bias. This finding was confirmed by the funnel plot (Fig. 2B).

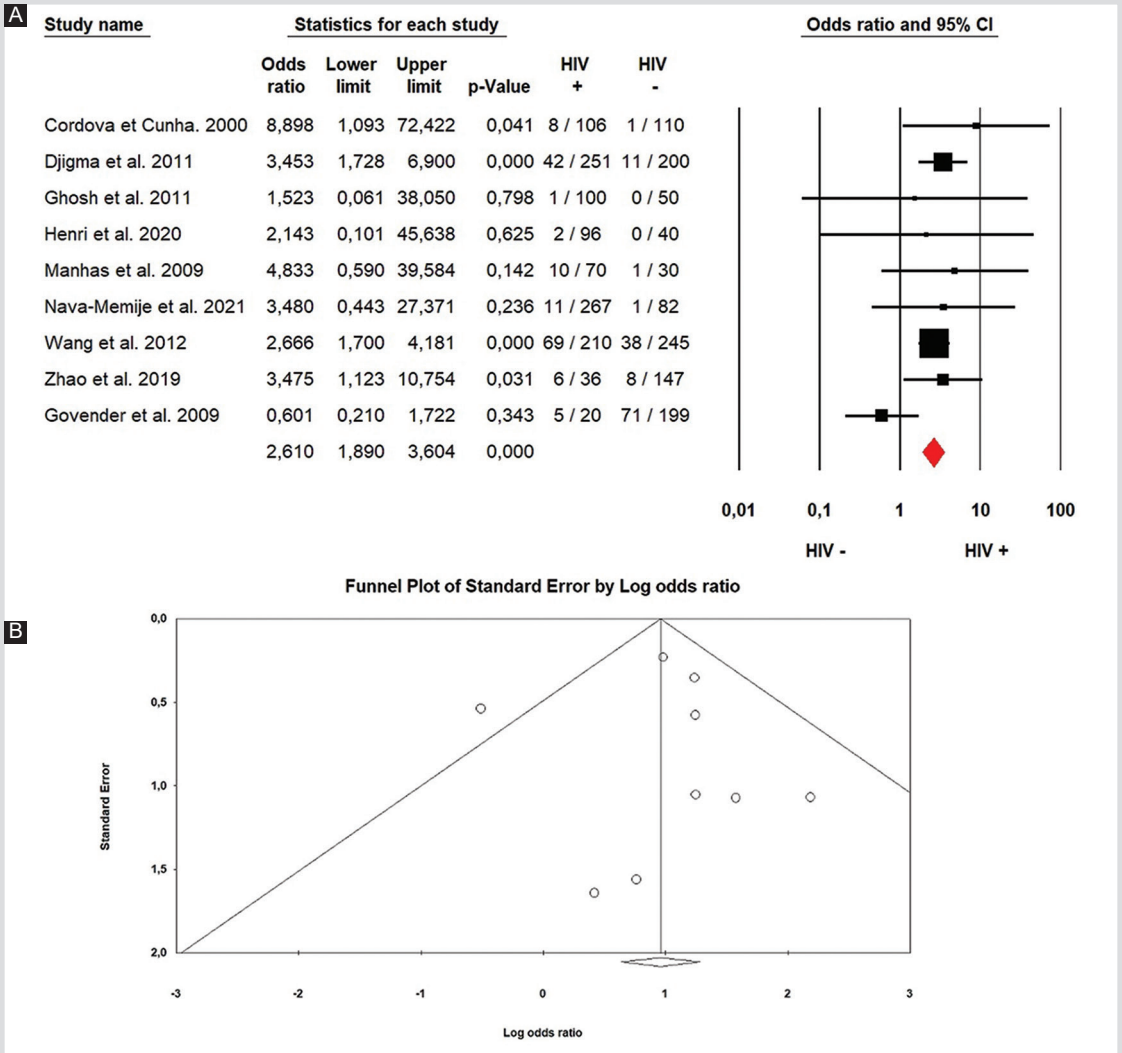

Figure 3. A: *Forest plot of pooled odds ratio (OR) for M. hominis.* **B:** *Funnel plot of pooled OR for M. hominis. The circles represent the nine included studies about association between M. hominis and human immunodeficiency virus infection. The horizontal axis represents the size of association, while the vertical axis represents the standard error. The fixed effects summary estimate is indicated by the vertical line, and the expected 95% confidence interval of the standard error is indicated by the two lines either side.*

M. hominis

Nine studies reported the prevalence of *M. hominis* among HIV-infected patients (Fig. 3A). The Cochran's Q test and I^2 statistic did not reveal a significant heterogeneity (Q-value = 10.2, p = 0.251, I^2 = 21.56%), so a fixed model was used. The forest plot analysis showed that the prevalence of *M. hominis* was significantly different between HIV-seropositive and HIV-seronegative groups. Indeed, the odds of *M. hominis* were more than 2-fold greater for HIV-infected patients than for control participants (OR = 2.610; 95% CI: 1.890-3.604; p = 0.000). The funnel plot appeared asymmetric (Fig. 3B), but Egger's test failed to show evidence of publication bias (p = 0.931).

Coinfection: *U. urealyticum* + *M. hominis*

Six studies reported the prevalence of *U. urealyticum* + *M. hominis* among HIV-infected patients (Fig. 4A). The Cochran's Q test and I^2 statistic showed a significant heterogeneity (Q-value = 15.238, p = 0.009, I^2 = 67.188%), so a random model was used. The forest plot analysis showed that the prevalence of *U. urealyticum* + *M. hominis* was not significantly different between

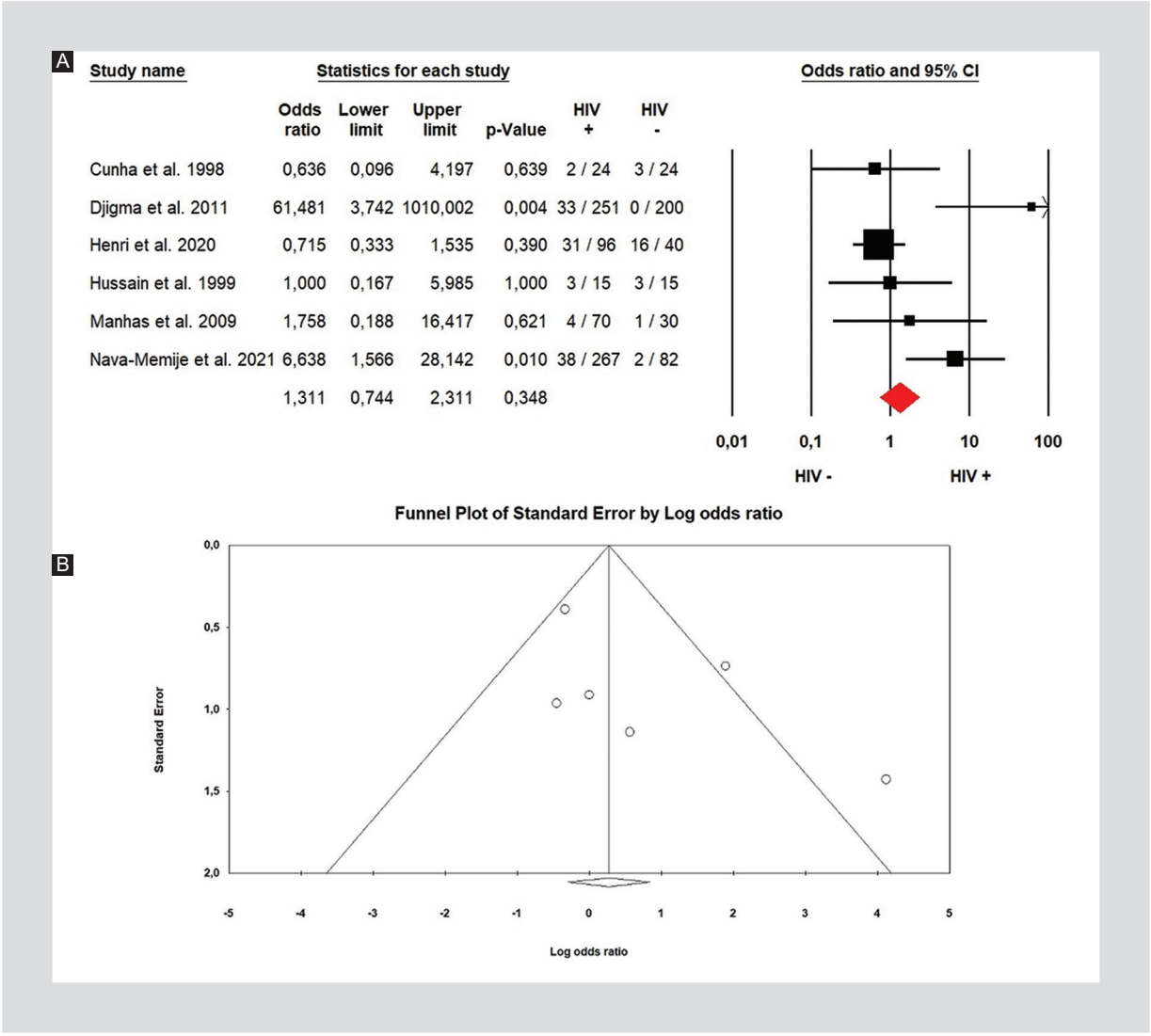

Figure 4. A: *forest plot of pooled odds ratio (OR) for U. urealyticum + M. hominis.* **B:** *funnel plot of pooled OR for U. urealyticum + M. hominis. The circles represent the six included studies about association between U. urealyticum + M. hominis and human immunodeficiency virus infection. The horizontal axis represents the size of association, while the vertical axis represents the standard error. The fixed effects summary estimate is indicated by the vertical line, and the expected 95% confidence interval of the standard error is indicated by the two lines either side.*

HIV-infected patients and control participants (OR = 1.311; 95% CI: 0.744-2.311; p = 0.348). The funnel plot appeared asymmetric (Fig. 4B), but Egger's test failed to show evidence of publication bias (p = 0.194).

Subgroup analysis

We carried out a subgroup analysis for the prevalence of genital mycoplasmas among HIV-infected patients. The ORs of the prevalence of genital mycoplasmas among HIV-infected patients were different by the period of publication, the study design, and the geographical origin of the study.

U. urealyticum

According to the period of publication, the OR of *U. urealyticum* among HIV-infected patients was approximately similar between studies published before 2010 and those published after 2010 (OR = 1.322 and 1.619, respectively, p = 0.449). Interestingly, a high heterogeneity was revealed among studies published after 2010 (I^2: 61.74%, p = 0.023). When the study design was adopted as a moderator, similar results were obtained and no significant difference was obtained between case-control, cohort, and cross-sectional studies (p = 0.134). Moreover, no significant heterogeneity

was detected across studies (p > 0.05). Regarding the geographical origin of the studies, the highest OR was observed in Europe (OR = 2.537), but no significant difference was detected between the different continents (p = 0,163) (Supplementary material: Table S5).

M. hominis

According to the period of publication, the OR of *M. hominis* among HIV-infected patients was approximately similar between studies published before 2010 and those published after 2010 (OR = 1.337 and 2.913, respectively, p = 0.100). Interestingly, a high heterogeneity was revealed among studies published before 2010 ($I^{2:}$ 70%, p = 0.034). When the study design was adopted as a moderator, similar results were obtained and no significant difference was obtained between case-control, cohort, and cross-sectional studies (p = 0.955). Moreover, no significant heterogeneity was detected across studies (p > 0.05). Regarding the geographical origin of the studies, a significant difference of OR was revealed between the different continents (p = 0.035). Indeed, the highest OR was detected in North America (OR = 5.522), followed by Europe (OR = 3.453), while the lowest OR was detected in Africa (OR = 0.688). However, no significant heterogeneity was detected across studies (p > 0.05) (Supplementary material: Table S5).

U. urealyticum + M. hominis

When the period of publication was adopted as a moderator, no significant difference was obtained between studies published before 2010 and those published after 2010 (p = 0.559). However, a high heterogeneity was revealed among studies published after 2010 (I^2 = 86%, p = 0.001). Regarding study design, the OR of both *U. urealyticum* and *M. hominis* among HIV-infected patients significantly differed between studies (p = 0.023). Indeed, the OR was significantly higher in the cohort study (OR = 6.638) compared to cross-sectional (OR = 1.743) and case-control (OR = 0.715) studies. Regarding the geographical origin of the studies, a significant difference in OR was revealed between the different continents (p = 0.022). Indeed, the highest OR was detected in Europe (OR = 61.481), followed by North America (OR = 2.790), while the lowest OR was detected in Africa (OR = 0.715). However, no significant heterogeneity was detected across studies (p > 0.05) (Supplementary material: Table S5).

Sensitivity analysis

A leave-one-out sensitivity analysis was performed to further identify the possible source of heterogeneity in the pooled analysis of OR values. The outcomes did not differ markedly when a single study was omitted, which indicated that the meta-analysis had strong reliability. Indeed, the OR of *U. urealyticum* ranged from 1.464 (95% CI: 1.130-1.720) to 1.709 (95% CI: 1.307-2.233). Similarly, the OR of *M. hominis* differed from 2.415 (95% CI: 1.677-3.478) to 3.040 (95% CI: 2.165-4.266), while the OR of *U. urealyticum + M. hominis* varied from 0.977 (95% CI: 0.527-1.808) to 1.754 (95% CI: 0.683-2.911) (Supplementary material: Table S6).

Discussion

U. urealyticum and *M. hominis* are frequently detected in the genitourinary tract and cause diverse STIs[36,37]. Despite their high incidence and clinical importance, genital mycoplasma infections are still underrated diseases. The relationships between genital mycoplasmas (*U. urealyticum*, *M. hominis, M. genitalium*, and *M. fermentans*) and HIV infection have been investigated on multiple occasions[21,22]. However, there is limited evidence regarding the impact of HIV infection on the prevalence of *U. urealyticum* and *M. hominis*.

To the best of our knowledge, this meta-analysis is the first to systematically assess the relationships between *U. urealyticum*/*M. hominis* and HIV infection.

In this meta-analysis, we analyzed 12 studies that evaluated the role of genital mycoplasmas (*U. urealyticum* and *M. hominis*) among patients with HIV infection. We observed that HIV infection was associated with a 1.526-fold higher odds of *U. urealyticum* and 2.61-fold higher odds of *M. hominis* colonization, respectively, compared to the control group. This finding validates the existing evidence on the potential role of genital mycoplasmas in the pathogenesis of HIV infection. Our results support previous meta-analysis studies that found a strong association between two other genital mycoplasmas, *M. genitalium* and *M. fermentans*, and HIV infection[21,22]. However, we also acknowledge the possibility that the occurrence of genital mycoplasmas may also indicate the presence of other STIs, such as *Chlamydia* spp., thus confounding the association between this microorganism and HIV infection[38].

The potential link between genital mycoplasmas and HIV infection has been investigated since the 1990s and an increased prevalence of *U. urealyticum* and *M. hominis* in HIV-infected patients has been reported

by several studies. Martinelli et al. revealed that the prevalence of *U. urealyticum* was higher in HIV-infected patients (18%) than in healthy individuals (7%)[19]. In the same context, Ghosh et al. demonstrated a 6% infection rate by *U. urealyticum* in HIV-infected patients compared to 2% in healthy participants[20]. Similar results have been found for *M. hominis*. Indeed, among HIV-positive and -negative individuals, the prevalence of *M. hominis* was 16.7% versus 5.5%, and 33% versus 12%, as reported by Djigma et al. 2011 and Wang et al. 2012, respectively[31,32]. The higher rate of genital mycoplasmas during HIV infection could be explained by the fact that immunodeficiency due to HIV infection could be a factor that predisposes to the risk of genital mycoplasma colonization, which could be an early event during the HIV infection[36]. Furthermore, it was indicated that infection with genital mycoplasmas potentially increases the susceptibility of acquiring and transmitting HIV, which supports the hypothesis that STIs can enhance the sexual transmission of HIV[39]. Therefore, genital mycoplasmas have been considered as cofactors that interact with HIV and contribute to the pathogenesis of AIDS[40]. Interestingly, these species are implicated in extragenital infections, especially in immunocompromised patients, causing pneumonitis, arthritis, osteomyelitis, and sternal wound infection[41-43]. Thus, by the strong association between genital mycoplasmas and HIV, these species may be playing a more important role in HIV-infected patients than the majority of physicians currently suspect. Consequently, its implication in some severe diseases in HIV-infected patients, often not diagnosed, may be underestimated. Hence, it is important to develop an adequate policy for screening.

In contrast, Govender et al. reported that a positive HIV status was seen to have no effect on colonization with *U. urealyticum* and *M. hominis*[29]. This suggests that the association between HIV infection and colonization rate with genial mycoplasmas may be influenced by the level of education and other socioeconomic and behavioral factors of each country.

Interestingly, we revealed that *M. hominis* was more prevalent among HIV-infected patients than *U. urealyticum* (OR = 2.610 vs. OR = 1.526, respectively). This finding is not surprising as *M. hominis* has several properties such as arginine depletion, cytotoxicity toward lymphoid cells, activation of monocytes, and stimulation of cytokines production that can modulate the host immune system[44]. Consequently, *M. hominis* seems to play more relevant pathogenic roles in the pathogenesis of AIDS than *U. urealyticum*. However, the mechanisms underlying the modulation of the immune system are still not known. Hence, the prevalence and the role of this species in immunosuppressed patients must be more widely studied and more research is needed to determine the specific role that genital mycoplasmas play in the pathogenesis of AIDS. In addition, adequate screening guidelines for systematic testing and treatment of genital mycoplasmas in HIV-infected patients might prove necessary to control retroviral transmission in developing countries.

Our meta-analysis has some limitations. First, a high heterogeneity was detected across studies reporting the coinfection with both species. Regarding the subgroup analysis, heterogeneity could be likely due to differences in study design and geographic location of studies. Considerable heterogeneity, which is expected in meta-analysis studies, can alter the interpretability of results[45]. Consequently, the findings of the coinfection have to be analyzed with attentiveness. Second, the included studies also had minor differences in control groups (e. g., healthy volunteers, HIV-negative men with urethritis, and HIV-negative men who have sex with men), which may have confounded the results. Third, there were limited studies included in this meta-analysis and the sample size was low. Fourth, many factors may impact the prevalence of genital mycoplasmas during HIV infection such as sex, age, hormonal status, and unprotected sexual intercourse, which leads to a higher prevalence of STIs. This confounding factor should be taken into account when interpreting our findings. Thus, further studies are required to overcome the above challenges and confirm the present results. Finally, all studies used standardized methods (PCR and culture) to identify genital mycoplasmas, which ensure standardized outcome assessment. However, these diagnostic tools constitute an important source of discrepancies in this meta-analysis because they are characterized by different sensitivity and specificity.

Despite these limitations, the major strength of our meta-analysis is the methodological quality of the included studies (good or fair quality score). In addition, the sensitivity analysis showed that the estimated OR was reliable and not affected when a single study was omitted.

In summary, this study provides the most up-to-date and comprehensive data that validating the association between genital mycoplasmas and HIV infection.

Conclusion

This meta-analysis reveals that the immunodeficiency status associated with HIV infection can lead to significant increased colonization rate of genital mycoplasmas.

In the other way, this finding highlights the need to perform more clinical research to get further insights into the role of genital mycoplasmas in the pathogenesis of AIDS. On the other hand, the testing and treatment of genital mycoplasmas in high-risk populations should be investigated as a potential HIV-prevention strategy. Knowing that genital mycoplasmas can cause several extragenital infections, it is important to develop screening and care policies as well as prevention programs to protect HIV-infected individuals from mycoplasmas exposures.

Authors' contributions

SB, GSS, and GK: conceived the design and developed the search strategy; SB and GSS: searched, screened, and appraised the studies, then extracted the data; SB analyzed the data; SB, GSS, and GK: drafted the manuscript. All authors read and approved the final manuscript for publication.

Supplementary data

Supplementary data are available at *Aids Reviews* online (10.24875/AIDSRev.22000024). These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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