Association of *Mycoplasma fermentans* and the risk of HIV-1 infection
A meta-analysis

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**Abstract**

**Background:** Previous studies have reported the association between *Mycoplasma fermentans* (M. fermentans) and the risk of human immunodeficiency virus 1 (HIV-1) infection, but the results were inconsistent. The present study aims to systematically review reported studies on *M. fermentans* and its association with HIV-1 infection, as well as to summarize the findings using a meta-analysis.

**Methods:** Studies meeting the inclusion criteria in the PubMed, Embase, China National Knowledge Infrastructure, WanFang Data, and Chongqing VIP databases up to March 2019 were identified. Cochran Q and *I²* statistics were used to assess heterogeneity. Additionally, pooled odds ratio (OR) with 95% confidence intervals (CI) were calculated and displayed by Forest plots. Also, the funnel plot, Begg test, and Egger test were used to evaluate potential publication bias. In addition, the source of heterogeneity was investigated by subgroup and sensitivity analyses.

**Results:** A total of 11 studies comprising 1028 HIV-1-positive patients and 1298 controls were ultimately included in this meta-analysis. Our results indicated that *M. fermentans* could increase the risk of HIV-1 infection among humans (OR = 3.68, 95%CI 1.26–10.64). Subgroup analysis showed that the risk of HIV-1 infection associated with *M. fermentans* was, based on the geographical distribution, 1.19 (95%CI 0.33–4.33) in Europe, 2.83 (95%CI 0.94–8.52) in United States, 11.92 (95%CI 3.93–36.15) in Asia; based on the source of the sample, 2.97 (95%CI 0.89–9.98) in blood samples, 4.36 (95%CI 1.63–11.68) in urine samples; based on the detection method, 2.80 (95%CI 0.72–10.96) with the polymerase chain reaction method, 5.54 (95%CI 1.21–25.28) with other detection methods; based on the source of controls, 1.91 (95%CI 0.53–6.89) in sexually transmitted diseases individuals, and 8.25 (95%CI 2.16–31.60) in health individuals.

**Conclusion:** Our study revealed evidence of the association between *M. fermentans* and HIV-1 infection. Considering the heterogeneity, further studies are warranted to understand the relationship between *M. fermentans* and HIV-1 infection.

**Abbreviations:** AIDS = acquired immunodeficiency syndrome, CI = confidence intervals, CNKI = China National Knowledge Infrastructure, ELISA = enzyme-linked immunosorbent assay, HIV-1 = human immunodeficiency virus 1, HPTLC = high-performance thin-layer chromatography, NOS = Newcastle-Ottawa Scale, OR = odds ratio, PCR = polymerase chain reaction, PRISMA = the Preferred Reporting Items for Systematic Reviews and Meta-Analysis, STD = sexually transmitted diseases.

**Keywords:** HIV, human immunodeficiency virus, meta-analysis, *Mycoplasma fermentans*

**1. Introduction**

To date, human immunodeficiency virus 1 (HIV-1), the cause of acquired immunodeficiency syndrome (AIDS), remains one of the established causes of infectious death in the world.[1–3] In 2017, it was estimated that 36.9 million people worldwide were living with HIV-1, including 1.8 million people newly infected with HIV-1, and 0.94 million people who died from AIDS.[4] Thus, it is widely recognized that HIV-1 infection is endangering people’s lives and safety.
Mycoplasma fermentans (M. fermentans) are wall-less Gram positive bacteria that colonize human mucosal surfaces. Some studies have reported that M. fermentans could enhance HIV-1 by inducing the viral infection. In addition, Li et al collected serum samples from 65 HIV-1-infected individuals and 117 HIV-1 negative healthy blood donors to extract M. fermentans, and found that 44.6% HIV-1-positive subjects and 1.7% HIV-1-negative healthy donors were infected with M. fermentans. Also, Horowitz et al found that M. fermentans was present in 39.6% of HIV-positive patients and in 10% HIV-negative controls (OR 5.9, 95%CI 1.46–33.88). Other studies also found that M. fermentans could increase the risk of HIV infection. Moreover, M. fermentans could promote more rapid progression from HIV infection to AIDS. However, Katser et al measured M. fermentans in blood, throat swab, and urine specimens from 117 HIV-1-seropositive patients and 73 HIV-1-seronegative controls, using a polymerase chain reaction (PCR) assay, and found no association between M. fermentans infection and HIV-1 load. Additionally, Tully et al and Hussain et al also did not find a relationship between M. fermentans and the risk of HIV-1 infection. Therefore, the relationship between the two infections was still ambiguous.

Accordingly, the aims of our meta-analysis are to systematically review the literature on the association of M. fermentans with HIV-1 infection, and to determine the risk size. The findings from this study could provide a basis for future studies and policy development towards M. fermentans prevention and control of HIV infection.

2. Materials and methods

2.1. Search strategy

We conducted this meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. In this study, we used a predefined search strategy (Fig. 1) to search the studies showing the relationship between M. fermentans and the risk of HIV infection in humans in the following databases: PubMed (1966 to March 2019), Embase (1986 to March 2019), China National Knowledge Infrastructure (CNKI, 1994 to March 2019), WanFang Data (1980 to March 2019), and Chongqing VIP (1989 to March 2019). The key search terms in this meta-analysis included “HIV”/“human immune deficiency virus”/“human immunodeficiency virus”/“AIDS”/“acquired immune deficiency syndrome” and “Mycoplasma fermentans”/“M. fermentans”/“M.f”. The complete search strategy for PubMed database was list in Appendix Table 1, http://links.lww.com/MD/D550. Additionally, we also hand searched the reference lists of eligible studies and related meta-analysis to identify the additional relevant studies. All retrieval processes were performed independently by two researchers.

2.2. Selection criteria

All the case-control studies reporting the M. fermentans infection association with the risk of HIV infection and providing sufficient data to establish the odds ratio (OR) effect size were eligible for inclusion. Language was restricted to English and Chinese. We excluded reviews, case reports, commentaries, animal studies, and studies with sample size of <30 individuals. All the searched studies were imported into the EndNote X9 library and duplicate studies were removed. At the end of the selection process, in case of divergence of opinion about the articles, a third reviewer evaluated whether the article in question was eligible.

2.3. Data extraction

The same researchers independently extracted the information of the selected studies using a predefined form. The extracted information comprised the first author, publication year, country, study design, detection method for M. fermentans, number of cases and controls, the OR, etc. When necessary, we also corresponded with the authors of the studies to obtain information that had been omitted from the publications.

2.4. Quality assessment of the studies

According to the criteria of the Newcastle-Ottawa Scale (NOS), which was recommended by the Cochrane Collaboration, the quality of the included studies was independently assessed by two reviewers. The NOS mainly contained three items, namely the selection, comparability, and outcomes. Each criterion was assessed as 1 star or 0 stars. The total stars of the NOS checklist ranged from 0 to 9 stars. In the present study, we assumed that high quality was at ≥7 stars, moderate quality was at 4 to 6 stars, and low quality was at ≤3 stars.

Finally, two studies[14,15] scored 8 stars, six studies[8–11,16,17] scored 7 stars, one study[18] scored 6 stars, and two studies[7,12] scored 5 stars. The results indicated that all studies were of moderate to high quality.

2.5. Ethical approval

Since all the data were extracted from previously published articles, there was no need for ethical approval for this review.

2.6. Statistical analyses

The outcomes were assessed using the OR, along with the 95% confidence intervals (CI). Heterogeneity was assessed by the Cochran Q test ($\chi^2$ and P-value) and $I^2$ statistic. When $I^2$ was over 50%, we considered that there was high heterogeneity among studies. Otherwise, we considered that there was low heterogeneity. When there was heterogeneity, we used the random-effect model to pool the effect size. When there was no heterogeneity, the fixed-effect model was used. To assess the publication bias, the funnel plot of the sample size of each study was used by subjective judgment, while the Beg$\rm{g}$ test and Egger test were used statistically.

Subgroup analysis and sensitivity analysis were conducted to investigate the source of heterogeneity. Sensitivity analysis was performed by sequentially excluding single studies and recalculating the pooled OR for the remaining studies. If the pooled OR without one study was within the 95% CI of the overall estimate, we deemed that the study had no influence on the overall model. A $P$-value ≤.05 was considered to be statistically significant. The meta-analysis results were analyzed using the Stata software version 12.0 (Stata Corporation, College Station, TX, USA).

3. Results

3.1. Characteristics of the included studies

The 11 included studies comprised 1028 HIV-1-positive patients and 1298 control subjects, all of whom were assigned to this strategy (Table 1). Individual studies’ sample size ranged 30 to
910 participants. Among the 11 included studies, seven studies[9,10,12,15–18] used PCR method to detect M. fermentans, four studies[7,8,11,14] used other methods to detect M. fermentans, namely enzyme-linked immunosorbent assay (ELISA),[14] metabolism inhibition,[11] high-performance thin-layer chromatography (HPTLC)+ELISA,[7] and modified immunoblotting technique.[8] Four studies[10,14,16,17] were conducted in Europe, four studies[11,12,15,18] were in United States, and the remaining three studies[7–9] were in Asia. As for the source of the sample used for the extraction or detection of M. fermentans, seven studies[7,8,10,11,14,16,18] used blood samples, four studies[9,10,12,15] used urine samples, and two studies[10,17] used other samples. All the included studies were written in English.

### 3.2. Overall results

Four studies reported that M. fermentans could increase the risk of HIV-1 infection (OR > 1), and six studies found no association between M. fermentans infection and risk of HIV-1 infection. Only one study reported that M. fermentans could decrease the risk of HIV infection. The OR effect size among the various studies ranged from 0.45 to 46.32. Significant heterogeneity was found in this meta-analysis ($Q = 63.71, P < .001; I^2 = 84.3\%$). Accordingly, a random effect model was used to pool the overall OR effect size in this meta-analysis (Fig. 2). The pooled overall OR value was 3.66 (95%CI 1.26–10.64, $Z = 2.38, P = .017 < .05$).

### 3.3. Subgroup and sensitivity analyses

In order to explore the source of heterogeneity, subgroup analysis was performed in this meta-analysis (Table 2). The source of the sample used for the detection, the pooled OR

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**Figure 1.** Flow diagram of the screening process.
was 2.97 (95% CI 0.89–9.95) in blood samples, 4.36 (95% CI 1.63–11.68) in urine samples, and 4.50 (95% CI 0.13–154.84) in other samples. Seven studies used PCR method to detect *M. fermentans*, and the pooled OR was 2.80 (95% CI 0.72–10.96); four studies used other detection methods, specifically, ELISA, metabolism inhibition, HPTLC + ELISA, modified immunoblotting technique, and the pooled OR was 5.54 (95% CI 1.21–25.28). Five studies adopted sexually transmitted diseases (STD) individuals as controls, seven studies selected health individuals as controls, and the pooled OR were 1.91 (95% CI 0.53–6.89) and 8.25 (95% CI 2.16–31.60), respectively.

Additionally, we also performed a sensitivity analysis to assess the reliability and stability of this meta-analysis by sequentially omitting each study and calculating the pooled OR again for the remaining studies. The results of the sensitivity analysis were visualized in Figure 3, and no significant difference with 95% CI for OR was observed when any of the studies was omitted. For example, after the study with children was omitted, the pooled OR was 1.91 (95% CI 0.53–6.89).
OR of remained studies with adults changed from 3.66 (95% CI 1.26–10.64) to 3.70 (95% CI 1.22–11.29).

3.4. Publication bias

The funnel plot showed a slight asymmetry among the included studies (Fig. 4). However, the Begg test and Egger test revealed that there was no publication bias for the publications ($z=0.93, P=.350; t=1.03, P=.328$).

4. Discussion

To the best of our knowledge, this meta-analysis is the first to systematically evaluate the association between $M. \ fermentans$ and risk of HIV-1 infection. In this study, we identified 11 eligible studies, which comprised 1028 patients and 1298 control individuals. All the included studies were assessed by the NOS checklist, and were of good methodological qualities. Individuals with $M. \ fermentans$ infection are at risk for HIV-1 infection with varying range, and the OR value was 0.45 to 46.32. Overall, the

| Subgroup  | No. of studies | OR Lower | OR Upper | $\chi^2$ | $P$ | $I^2$ | $Z$ | $P$ | $z$ | $P$ |
|-----------|----------------|----------|----------|---------|-----|------|-----|-----|-----|-----|
| Total     | 11             | 3.66     | 1.26     | 10.64   | 63.71| .001 | 84.3| .017| .030| .350|
| Method    |                |          |          |         |      |      |     |     |     |     |
| PCR       | 7              | 2.80     | 0.72     | 10.96   | 30.42| .001 | 84.9| .139| .30  | .764|
| Other     | 4              | 5.54     | 1.21     | 25.28   | 42.44| .001 | 76.0| .027| 1.02 | .308|
| Area      |                |          |          |         |      |      |     |     |     |     |
| Europe    | 4              | 1.19     | 0.33     | 4.33    | 10.16| .005 | 77.0| .026| .792 | .089|
| United States | 4 | 2.83     | 0.94     | 6.52    | 1.89 | .596 | 0.1 | 1.85 | .064 | .34  |
| Asia      | 3              | 3.93     | 36.15    | 0.13    | 0.77 | 61.0 | 4.38| .001| 1.04 | .296|
| Source    |                |          |          |         |      |      |     |     |     |     |
| Blood     | 7              | 2.97     | 0.89     | 9.95    | 31.68| .001 | 81.1| .176| .078 | .230|
| Urine     | 4              | 4.36     | 1.63     | 11.68   | 4.59 | .205 | 34.6| .293| .003 | .734|
| Other     | 2              | 4.50     | 0.13     | 154.84  | 5.92 | .015 | 83.1| .83  | .405 | .01  |
| Control   |                |          |          |         |      |      |     |     |     |     |
| STD       | 5              | 1.91     | 0.53     | 6.89    | 30.42| .001 | 86.9| .099| .324 | .806|
| Health    | 7              | 3.25     | 2.16     | 31.60   | 16.20| .013 | 63.0| 3.08 | .002 | .60  |

CI = confidence intervals, OR = odds ratio, STD = sexually transmitted diseases.
### Figure 3. Sensitivity analysis of the included 11 studies in this meta-analysis.

| Study               | Lower CI Limit | Estimate | Upper CI Limit |
|---------------------|----------------|----------|----------------|
| Hawkins R (1992)    | 3.51 (1.15, 10.71) |          |                |
| Hakkarainen K (1992)| 3.86 (1.20, 12.43) |          |                |
| Katseni V (1993)    | 4.74 (1.71, 13.13) |          |                |
| Tully G (1993)      | 4.12 (1.29, 13.17) |          |                |
| Kovacic R (1996)    | 4.70 (1.51, 14.69) |          |                |
| Li J (1997)         | 2.67 (0.99, 7.18)  |          |                |
| Horowitz S (1998)   | 3.50 (1.09, 11.23) |          |                |
| Hussain A (1999)    | 3.70 (1.22, 11.29) |          |                |
| Cordova C (2000)    | 3.49 (1.13, 10.83) |          |                |
| Ainsworth J (2000)  | 3.17 (1.07, 9.41)  |          |                |
| Wang B (2012)       | 3.34 (1.04, 10.68) |          |                |

### Figure 4. Funnel plot of the included 11 studies in this meta-analysis.
pooled findings support evidence for a statistically significant 3.66-fold increased odds of HIV-1 infection among M. fermentans-infected individuals.

Thirty years ago, Lo and colleagues\(^{[19,20]}\) first identified M. fermentans in AIDS autopsy material. Subsequently, numerous studies frequently detected the M. fermentans in patients with HIV-1 infection. Among the HIV-1-seropositive individuals, the prevalence of M. fermentans co-infection ranged from 5% to 23%\(^{[15,6,21-23]}\). M. fermentans was proposed as a co-factor aggravating the clinical manifestation and leading to the onset of AIDS after HIV-1 infection\(^{[24,25]}\). Therefore, it is important to understand the effect of the occurrence of M. fermentans on the risk of HIV-1 infection, and further to prevent and control the M. fermentans infection level among HIV-1 individuals.

In the present study, significant heterogeneity was detected among the included studies, thus subgroup analyses were performed to investigate the source of such heterogeneity. We found that the individuals infected with M. fermentans in Asia were at higher risk for HIV-1 infection (OR = 11.92, 95%CI = 3.93–36.15). However, individuals infected with M. fermentans in Europe and United States did not have a significant risk for HIV-1 infection. We suspect that the reason for this discrepancy is probably related to racial differences.

PCR is the primary method used for detecting M. fermentans in humans\(^{[26-27]}\). In the included studies, 64% of them used PCR method to detect M. fermentans. Earlier studies reported that PCR was suitable for mycoplasma detection with various advantages, including sensitivity, specificity, accuracy, low cost, and speed\(^{[28]}\). Dai et al\(^{[29]}\) compared the diagnostic value of the traditional culture method and the PCR method for detecting M. fermentans among females, and found that the sensitivity of the PCR method was superior to that of the traditional method. The present study determined that the pooled OR of seven studies using PCR method was 2.80 (95%CI 0.72–10.96), which indicated that the M. fermentans infection could not increase the risk of HIV-1 infection. However, the pooled OR of four studies using other detection methods (ELISA, metabolism inhibition, HPTLC+ELISA, and modified immunoblotting technique) was 5.54 (95%CI 1.21–25.28), which indicated that the M. fermentans infection could increase the risk of HIV-1 infection. Due to the variety of detection methods and lack of uniform testing standards, the accuracy of the detection results varied greatly. Thus, we suggest that performing the detection by combining several detection methods may improve the detection rate for M. fermentans.

Katseni et al\(^{[10]}\) assessed the prevalence of M. fermentans in 117 HIV-1-seropositive patients and 73 HIV-1-seronegative subjects in blood, throat swab, and urine specimens, and found the detection rate of M. fermentans varied depending on the source of the samples. The results revealed that the prevalence of M. fermentans in blood, throat swab, and urine was 10%, 23%, and 8%, respectively, among HIV-1-seropositive patients, and 9%, 20%, and 6%, respectively, among HIV-1-seronegative subjects. In the current meta-analysis, we found varied prevalence of M. fermentans among subjects. Indeed, we found inconsistent results when the risk of HIV-1 infection was assessed only by analyzing blood samples or urine samples. Therefore, to obtain a comprehensive detection result, it is necessary to collect samples from different tissue sources.

Other factors could also confound the accuracy of our results of this study, for example the choice of control group. We found that compared with the “health” individuals, M. fermentans could significant increase the risk of HIV-1 infection, and the OR value was 8.25. However, this finding did not obvious when compared with the STD people. This interesting result may be related to the similar prevalence of M. fermentans infection in HIV-1 individuals or in STD individuals\(^{[10]}\). At the same time, this result also reminded us that STD individuals should beware of the M. fermentans invasion, for the co-infection of the sexually transmitted infection and HIV\(^{[10,31]}\).

This meta-analysis had several drawbacks, which should be taken into account in future research. First, M. fermentans infection might promote the progression of HIV-1 infection to AIDS\(^{[30]}\). However, most of the subjects in the included studies were not divided into HIV-1 positive (without AIDS) patients and AIDS patients. Thus, the subjects included in this meta-analysis were collectively referred to as HIV-1-positive patients, which resulted in insufficient information to evaluate the M. fermentans infection for the risk of HIV-1 without AIDS or for the risk of AIDS. Second, HIV-1 infection has been characterized by a decrease in CD4+ T-cell counts\(^{[29]}\). However, due to the lack of sufficient data on the CD4+ T-cell counts of the patients in the included studies, in this study we did not analyze the influence of CD4+ T-cell counts on the results of the association between M. fermentans infection and the risk of HIV-1.

In conclusion, this meta-analysis showed that M. fermentans infection could increase the risk of HIV-1 infection, which could provide a basis for future research and policy development towards M. fermentans prevention and control of HIV-1 infection. However, concerning the heterogeneity of our meta-analysis, more studies with larger samples are necessary in the future.

Author contributions

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