Microbiological study of periodontal disease in populations with HIV: a systematic review and meta-analysis

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Abstract

Background: No systematic review/meta-analysis has been conducted on the microbiological profile associated with the occurrence of periodontitis in patients with HIV. The aim of this study was to evaluate the prevalence of identified bacteria in HIV-infected patients with periodontal disease.

Methods: Three English electronic databases (MEDLINE (via PubMed), SCOPUS, and Web of Science) were searched systematically from the beginning to 13 February 2021. The frequency of each identified bacteria in HIV-infected patients with periodontal disease was extracted. All meta-analysis methods were performed using STATA software.

Results: Twenty-two articles met inclusion criteria and enrolled into the systematic review. This review analyzed a total of 965 HIV-infected patients with periodontitis. The prevalence of periodontitis was higher in HIV-infected male patients (83% (CI95%: 76-88%)) compared to females (28% (CI95%: 17-39%)). In our study, the pooled prevalence of necrotizing ulcerative periodontitis and necrotizing ulcerative gingivitis in patients with HIV infection was 67% (CI95%: 52-82%) and 60% (CI95%: 45-74%), while a lower prevalence of linear gingivitis erythema was reported (11% (CI95%: 5-18%)). More than 140 bacterial species were identified from HIV-infected patients with periodontal disease. High prevalence of *Tannerella forsythia* (51% (CI95%: 5-96%)), *Fusobacterium nucleatum* (50% (CI95%: 21-78%)), *Prevotella intermedia* (50% (CI95%: 32-68%)), *Peptostreptococcus micros* (44% (CI95%: 25-65%)), *Campylobacter rectus* (35% (CI95%: 25-45%)), and Fusobacterium spp. (35% (CI95%: 3-78%)) in HIV-infected patients with periodontal disease was found.

Conclusion: Our study demonstrated that the prevalence of red and orange complex of bacteria in HIV patients with periodontal disease is relatively high.

Background

Globally, the number of individuals infected with the human immunodeficiency virus (HIV) continues to rise. At the end of 2019, nearly 38.0 million people worldwide were diagnosed with HIV, with 1.7 million being newly infected (http://www.who.int/news-room/fact-sheets/detail/hiv-aids) [1].

HIV periodontal manifestations were first identified in 1987 [2]. At least 24 distinct oral lesions have been identified in the HIV literature, but only ten of these are observed consistently. In decreasing order of prevalence, they are oral candidiasis, oral hairy leucoplakia, herpes simplex virus infection, Kaposi's sarcoma, nonspecific ulceration, aphthous ulcers, periodontal disease, and salivary gland disease, oral melanotic hyperpigmentation, and oral warts [3].

Periodontal disease is closely linked to HIV infection and refers to a group of inflammatory-based diseases that include gingivitis and periodontitis [4]; however, it is unclear if the combination of HIV infection and periodontitis raises the risk of aggravation of their periodontitis [5, 6].

Severe periodontitis, which can lead to tooth loss, threatens 5–20 percent of the world's adult population. [7]. The prevalence of HIV periodontitis and gingivitis was reported to be 14%, 9.3%, 8%, and 4.4%, respectively, in Asia, Europe, Africa, and America [3].

Numbers of scientific research has been dedicated to the study of periodontal-disease-associated microflora, ranging from traditional cultural techniques to new genetic, whole-genome, and proteomic approaches [8].

Bacteria that cause periodontal disease can be categorized based on how they interact with each other when colonizing the gingival sulcus [9]. There is a balance between microbial challenge and host immune response; any change to that with the presence of other modifying factors is responsible for periodontal infection clinical manifestation. [10].

For several years, scientists have recognized that studying oral health and disease requires recognizing and comprehending the pathogenic potential of all bacteria that colonize the oral cavity [11]. More than 700 bacterial species have been identified in the subgingival plaque, and some of these microorganisms have been linked to the initiation /progression of periodontal diseases. *Porphyromonas gingivalis*, *Tannerella forsythia* (previously known as *Bacteroides forsythia*), and *Actinobacillus actinomycetemcomitans* were classified as key pathogens. In 1998, Socransky *et al.* proposed that understanding oral diseases could be enhanced by concentrating on consortia of species rather than individual pathogens. They discovered five groups of bacteria, or complexes, that were present together in periodontitis on several occasions. They hypothesized that the most pathogenic complex included *P. gingivalis*, *T. forsythia*, and *Treponema denticola* (the red complex) and was dependent on earlier colonization of the pocket by the orange complex, a group of less pathogenic species [11, 12].

There are several unanswered questions in dental science [13], especially in the microbiology, immunology, inflammatory host response, and epidemiological developments of periodontal disease in HIV-infected populations. No systematic review/meta-analysis has been conducted on the microbiological profile associated with the occurrence of periodontitis in patients with HIV. The aim of this study was to evaluate the prevalence of identified bacteria in HIV-infected patients with periodontal disease.

Methods

Search method and selection criteria

Three English electronic databases (MEDLINE (via PubMed), SCOPUS, and Web of Science) were searched systematically from the beginning to 13 February 2021. Publication searches were performed by various combinations of the following terms: “Immunodeficiency” or “Human immunodeficiency virus” AND “Periodontitis” AND “Bacteria” or “Oral microbiota” or “Oral microbial” or “*Aggregatibacter actinomycetemcomitans*” or “*Porphyromonas gingivalis*” or “*Tannerella forsythia*” or “*Prevotella intermedia*” or “*Treponema denticola*” or “*Fusobacterium nucleatum*” or “*Campylobacter rectus*” or “*Eikenella corrodens*” or “*Eikenella corrodens*” or “*Peptostreptococcus micros*”. The reference lists of selected articles were also screened manually and applicable articles were

included. Abstracts of papers presented at conferences were not reviewed because they lacked sufficient details data. Dissertations and thesis were not included. The study was conducted according to the guidelines of PRISMA (the preferred reporting items for systematic reviews and meta-analyses.

Inclusion criteria

Titles and abstracts of all articles were screened by one reviewer, and eligibility of the screened articles was assessed by two independent investigators using the following criteria: titles, abstracts, and full texts. When necessary, authors were contacted for additional information. Studies were excluded if they had insufficient data.

Periodontal diseases

A periodontal diseases related to HIV was categorized as necrotizing ulcerative periodontitis, necrotizing ulcerative gingivitis, and linear gingivitis erythema [14].

Bacterial complex definition

Six closely related classes of bacterial species were included for meta-analysis. Colors ranging from red to yellow have distinct connotations. The most pathogenic color is red, while yellow represents commensales. A red complex composed of *P. gingivalis, T. denticola*, and *T. forsythia* that is highly correlated with the clinical progression of chronic periodontitis [15]*, an* orange complex included anaerobic gram-negative species such as *Prevotella intermedia, Prevotella nigrescens, Prevotella micros*, and *Fusobacterium* nucleatum, a yellow complex consisting of members of the genus *Streptococcus*, a green complex included *Capnocytophaga* species, *A. actinomycetemcomitans serotype A, Eikenella corrodens* and *Campylobacter* and a purple complex containing of *Veillonella parvula* and *Actinomyces odontolyticus* [16].

Exclusion criteria

Investigations with not-relevant topics, review and case report articles, books, non-english articles or the ones worked on non-human subjects were excluded. The articles, in which bacterial information was given in a graph/phylogenetic tree or as mean value or relative distribution, were deleted. The articles, in which bacterial frequency data was reported among the sites or isolates studied, were also omitted.

Data extraction

Data from eligible studies was extracted independently by 2 reviewers and checked by a third reviewer. Disagreements among the reviewers were resolved through discussion. The following data were extracted from included studies; first author and publication year, country region, sample size, sex and age of patients, number of HIV-positive patients diagnosed with periodontal diseases, type of sampling, type of the periodontal diseases, diagnostic methods used, and the frequency of each type of microorganisms. If the data was reported as a percentage, the number was calculated through the use of proportions. The frequency of each identified bacteria in HIV-infected patients with periodontal disease was extracted.

Data analysis

All meta-analysis methods were performed using STATA (Release 12. statistical software. College Station, Texas: STATA Corp LP). Results of the meta-analysis were illustrated by a forest plot diagram, which demonstrated the pooled prevalence of each microorganism and their relevant 95% confidence interval (CI).

The Cochrane Q-test and the inverse variance index (I^2) were used to evaluate the heterogeneity in this study. The I^2 values of 25%, 50%, and 75% were representatives of low, moderate and high heterogeneity, respectively [17].

Publication bias was estimated by a funnel plot diagram based on Egger's regression test [18].

Quality assessment

The quality of the studies included in this study was independently evaluated by two reviewers using the Joanna Briggs Institute's updated Critical Appraisal Checklist for Prevalence Studies, which includes nine questions that the reviewers answered for each of the qualifying studies. Any dispute was resolved through discussion [19].

Results

Of the 2075 records identified in the mentioned electronic databases, 559 and 252 articles remained after duplicates removal and title-based screening. By screening of full-texts, 230 records were excluded for various reasons including reported bacterial data in graph/phylogenetic tree or as mean value or relative distribution. Twenty-two articles met inclusion criteria and enrolled into the systematic review (Fig. 1).

This review analyzed a total of 965 HIV-infected patients with periodontitis. Demographic and clinical information is presented in Table 1.

Table 1
Summary of the studies included in systematic review

First author	Date	Country	Age range	Male	Female	Sample size	HIV periodontal	Gingivitis	Periodontitis	Microbial samples	Identifica microorg
Zambón J. J. [36]	1990	USA	27–51	45	5	50	-	18	32	-	Immuno microsc
Rams T. E. [21]	1991	USA	25–50	13	1	14	-	-	14	Subgingival plaque	Culture
Lucht E. [20]	1991	Sweden	-	28	2	30	-	-	-	Subgingival plaque	Culture
Rosenstein D. I. [37]	1993	USA	21–55	-	-	11	11	-	-	Subgingival plaque	Staining
Moore L. V. H. [23]	1993	USA	28–51	37	2	39	39	22	17	Subgingival plaque	Culture/ detectio
Brady L. J. [22]	1996	USA	33–46	-	25	25	-	21	13	plaque samples	Analysis microsc Mycosel
Brady L. J. [22]	1996	USA	33–46	-	25	25	-	21	13	Subgingival plaque	Analysis microsc Mycosel
Hofer D. [24]	1996	Switzerland	27–43	6	1	7	-	7	-	Biofilm	Culture
Mellanen L. [40]	1996	Finland	23–68	46	10	56	-	-	-	Subgingival plaque	-
Nakou M. [25]	1997	Greece	34.3–41.1	32	28	60	60	-	-	Periodontal pocket	Culture
Lucht E. [39]	1998	Sweden	-	33	12	45	13	-	-	Periodontal pocket	Microsc
Chattin B. R. [26]	1999	Japan	15–65	61	6	67	67	-	-	Gingival papilla and contiguous Supragingival plaque	Culture/
Teanpaisan R. [27]	2001	Thailand	-	40	10	50	-	-	-	Subgingival plaque	Culture/
Tsang C. S. [29]	2001	China	20–50	21	-	21	-	-	-	Subgingival plaque	staining/
Cobb C. M. [38]	2003	USA	18–35	10	6	16	16	-	-	Saliva	TEM/SE
Botero J. E. [28]	2007	Colombia	-	26	5	31	31	-	31	Plaque	Culture
Brito A. [34]	2008	Venezuela	-	27	5	32	32	-	-	Plaque	PCR
Júnior E. G. [30]	2008	Brazil	20–43	59	21	80	80	40	40	Saliva/Subgingival plaque	Culture
Grande S. R. [35]	2009–2010	Brazil	-	36	14	50	50	23	27	Subgingival plaque	PCR
Gušić, I. [31]	2010–2011	Serbia	-	51	9	60	60	-	-	Subgingival plaque	Culture
Cembranelli S. B. S. [32]	2013	Brazil	-	51	31	82	82	-	-	Gingival pockets	PCR/fres examina
Jordan R. A. [41]	2016	Germany	-	11	-	11	11	-	-	Saliva/plaque/feces	DNA chi
Dai L. [33]	2020	USA	21–67	32	21	53	-	-	-	Periodontal pocket	PCR/ELI

PCR: Polymerase chain reaction

ELISA: enzyme-linked immunosorbent assay

TEM: transmission electron microscope

SEM: Scanning Electron Microscopy

Sample sizes of the HIV-infected group with periodontitis ranged from 7 to 82. With regard to the applied method for organism identification, the majority of the studies used the culture method [20–31], while five studies used the polymerase chain reaction (PCR) method [26, 32–35]. No study considered children exclusively. The age groups of the investigated patients were > 15 years in 13 papers, respectively. However, the age group of the study population was not mentioned in the remaining 9 studies. Regarding sampling, in the majority of the studies (n = 11), subgingival plaque was used as the specimen for analysis. However, the periodontal pocket (n = 3), saliva (n = 3), gingival papilla and contiguous supragingival plaque (n = 1), gingival pockets (n = 1), biofilm samples (n = 1), and plaque (n = 2), and feces (n = 1) were also applied in other studies.

The prevalence of periodontitis was higher in HIV-infected male patients (83% (CI95%: 76–88%)) compared to females (28% (CI95%: 17–39%)).

Seven studies were from the USA [21–23, 33, 36–38], three from Brazil [30, 32, 35], two from Sweden [20, 39], one from Switzerland [24], one from Finland [40], one from Greece [25], one from Japan [26], one from Thailand [27], one from China [29], one from Colombia [28], one from Venezuela [34], one from Serbia [31], and one from Germany [41].

In our study, the pooled prevalence of necrotizing ulcerative periodontitis and necrotizing ulcerative gingivitis in patients with HIV infection was 67% (CI95%: 52–82%) and 60% (CI95%: 45–74%), while a lower prevalence of linear gingivitis erythema was reported (11% (CI95%: 5–18%)) (Table 2).

Table 2
The pooled estimate of HIV related oral lesions and bacteria identified from clinical samples of HIV-infected cases with periodontal disease

	Pooled estimate	95% CI	I^2	Chi^2	P value
HIV related oral lesions					
Necrotizing ulcerative gingivitis	60	45–74	84.36	44.68	< 0.001
Necrotizing ulcerative periodontitis	67	52–82	88.87	71.88	< 0.001
Linear gingivitis erythema	11	5–18			< 0.001
Bacteria					
T. forsythia	51	5–96	96.9	96.7	< 0.001
F. nucleatum	50	21–78	93.29	59.63	< 0.001
P. intermedia	50	32–68	92.19	115.3	< 0.001
P. micros	44	25–65	89.49	57.08	< 0.001
C. rectus	35	25–45	49	7.84	0.1
Fusobacterium spp.	35	3–78	95.13	61.63	< 0.001
S. sanginosus	27	7–53	91.87	49.18	< 0.001
S. intermedius	25	3–57	92.6	40.54	< 0.001
P. gingivalis	23	11–39	90.34	93.13	< 0.001
B. gracilis	22	6–44	88.91	27.04	< 0.001
A. naeslundii	22	11–35	70.78	13.69	0.01
A. viscosus	19	13–25	0	2.93	0.57
A. israelii	16	2–40	88.45	25.97	< 0.001
E. corrodens	16	7–27	67.88	15.57	0.01
A. actinomycetemcomitans	15	8–24	79.13	57.51	< 0.001

In this systematic review, more than 140 bacterial species were identified (supplementary file).

To calculate the pooled prevalence of associated groups of bacterial species of each complex (if the number of studies were more than 3), the cumulative meta-analysis was performed and the forest plots indicated separately.

In the red complex group, the pooled prevalence of *Tannerella forsythia* and *Porphyromonas gingivalis* was 51% (CI95%: 5–96%) and 23% (CI95%: 11–39%), respectively (Fig. 2).

In the green complex group, the pooled prevalence of *A. actinomycetemcomitans* and *E. corrodens* was 15% (CI95%: 8–24%) and 16% (CI95%: 7–27%), and the heterogeneity was very high, with I^2 equal to 79.13% (*p*-value < 0.001), and 67.88% (*p*-value = 0.01), respectively (Fig. 3).

In the orange complex group, the pooled prevalence of *F. nucleatum* and *P. intermedia* was 50% (CI95%: 21–78%) and 50% (CI95%: 32–68%), and the heterogeneity was very high, with I^2 equal to 93.29% and 92.19%, (*p*-value < 0.001), respectively. *P. micros* and *C. gracilis* showed a pooled prevalence of 44%

(CI95%: 25–65%) and 22% (CI95%: 6–44%), respectively. Moreover, the cumulative meta-analysis presents an overall (I^2 = 49%; *p*-value = 0.1) of 35% (CI95%: 25–45) for *C. rectus* (Fig. 4).

In the yellow complex group, the cumulative meta-analysis presents an overall (I^2 = 91.87%; *p*-value < 0.001) of 27% (CI95%: 7–53%) for *S. sanguinis* and an overall (I^2 = 92.6%; *p*-value < 0.001) of 25% (CI95%: 3–57) for *S. intermedius*, respectively (Fig. 5).

In the purple complex group, the pooled prevalence of *A. naeslundii*, *A. viscosus*, and *A. israelii* was 22% (CI95%: 11–35%),19% (CI95%: 13–25%), and 16% (CI95%: 2–40%), respectively (Fig. 6).

Based on the results of Egger's regression test, the publication bias among included studies could not be ignored (*p*-value < 0.0001).

Discussion

To our knowledge, this is the first systematic review and meta-analysis to determine the periodontal conditions and the distribution of associated groups of bacterial species in HIV-infected patients with periodontal disease.

In this study, high prevalence of *T. forsythia* (51% (CI95%: 5–96%)), *F. nucleatum* (50% (CI95%: 21–78%)), *P. intermedia* (50% (CI95%: 32–68%)), *P. micros* (44% (CI95%: 25–65%)), *C. rectus* (35% (CI95%: 25–45%)), and Fusobacterium spp. (35% (CI95%: 3–78%)) in HIV-infected patients with periodontal disease was found. Therefore, periodontal disease may be regarded as a polymicrobial infection.

We found a high prevalence of red complex bacteria, particularly *T. forsythia* in HIV-infected patients with periodontal disease, which is basically in agreement with some previous studies [41, 42].

Periodontal infections have been linked to an increased risk of HIV-1 reactivation in infected people, as well as the progression of acquired immunodeficiency syndrome (AIDS). Furthermore, it would suggest that preventing and treating periodontitis induced by red complex infection could effectively inhibit further clinical progression of AIDS [43].

The periodontal clinical parameters are closely linked to the occurrence of the red complex [44]. *T. forsythia*, *P. gingivalis*, and *A. actinomycetemcomitans* are strongly related to the onset of periodontal infection, disease development, and failed periodontal therapy [42, 45]. However, in this study, the pooled prevalence of *T. forsythia* was higher than *P. gingivalis* (23% (CI95%: 11–39%)) and *A. actinomycetemcomitans* (15% (CI95%: 8–24%)), respectively. Despite the fact that P. gingivalis is one of the most common microbial diseases in humans [43], it was found to have a lower prevalence in HIV-infected patients with periodontal disease (23% (CI95%: 11–39%)). Moreover, *P. gingivalis* can be present even though there is no disease, ruling out its position as an exogenous pathogen [46].

F. nucleatum has been shown to be a major marker for destructive periodontal disease in adult subjects. It is also likely to play a role in biofilm colonization and lead to the reducing conditions required for the emergence of oxygen-intolerant anaerobes [46]. It has also been mentioned that *F. nucleatum* promotes *P. gingivalis* invasion of host cells [47].

Moderately strong evidence has been accumulated for other bacteria isolated from subgingival microbiota, including *P. intermedia*, *C. rectus*, *P. micros*, *F. nucleatum*, and *Eubacterium nodatum* (14).

Bacterial organisms should be able to colonize the subgingival region and develop virulence factors that either directly (enzymes and toxins) or indirectly (antigens and activators) cause an individual's destructive inflammatory response and periodontal tissue injury. Proteases, alkali and acid phosphatases produced by microorganisms, fatty and organic acids, IgG- and IgA-proteases, chondroitinsulfatase, and toxic products including endotoxins, leukotoxin, mucopeptides of the bacterial wall, and end-products of metabolism are types of agents that directly damage periodontal tissues [42].

On the other hand, certain variations in cellular immunity can also promote the proliferation of virulent commensals or combinations of bacterial species, and possible symbiotic relationship between the species [48]. The role of all recognized periodontal bacteria in various periodontal diseases is unknown, but it is known that these bacteria can function in a variety of ways, including passively occupying niches, restricting a periodontal pathogen's ability to bind to suitable tissue surfaces, improving a pathogen's vitality and growth, and enhancing a pathogen's ability to produce virulence factors [42].

The pooled prevalence of *S. sanguis* was 27% (CI95%: 7–53%) and *S. intermedius* was 25% (CI95%: 3–57), which was higher than the pooled estimate of *A. actinomycetemcomitans* (15% (CI95%: 8–24). It has been reported that *S. sanguis* develops hydrogen peroxide, which can destroy *A. actinomycetemcomitans* either directly or by host-enzyme amplification; therefore, some of the beneficial microorganisms which can produce anti-periodontal pathogen factors should not be ignored [45].

Increased oral health knowledge and the discovery of different disease-causing pathogens contribute in the reduction of risk factors for oral diseases. Certain treatments have demonstrated promising results, and could be investigated further in prospective clinical trials [16].

Poor oral hygiene is a typical clinical finding in HIV patients. Despite the obvious need for oral health services, these patients are not provided with proper dental care due to the HIV-related stigma that exists in many settings, putting them at a greater risk for developing oral and systemic diseases [49, 50]. Therefore, designing and implementing of low-cost and easily available diagnostic and therapeutic methods for periodontal diseases is highly recommended [51].

This study has several limitations. The stage of HIV infection and its progression was not mentioned in the studies and this can affect the final evaluation. There are evident gaps in knowledge in relation to periodontal diseases in patients with HIV in some countries in Africa, Asia and Europe. Data heterogeneity within these studies can be explained by differences in detection strategies, genetic history, behavioral and/or environmental factors.

Conclusion

In conclusion, our study demonstrated that the prevalence of red and orange complex of bacteria in HIV patients with periodontal disease is relatively high. This information will eventually lead to the implementation of innovative and/or more effective preventive and therapeutic methods, as well as diagnostic applications in periodontics. Early diagnosis, efficient periodontal management, proper oral hygiene maintenance is the key for the treatment of periodontal manifestation of HIV.

Abbreviations

HIV: human immunodeficiency virus

PCR: polymerase chain reaction

AIDS: acquired immunodeficiency syndrome

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data obtained

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SM: involved in designing, interpretations and writing of the manuscript. NKV: involved in gathering and grouping the articles. BH and MTA revised the manuscript. All authors read and approved the final manuscript.

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Figures

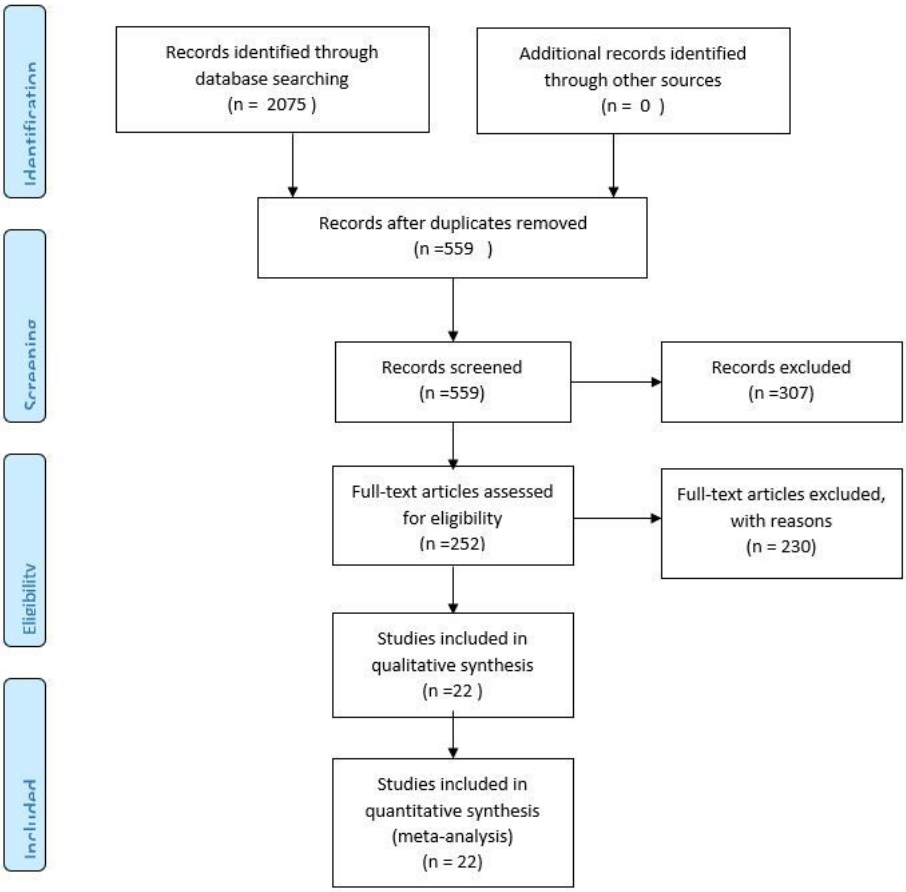

Figure 1

Summary of the literature search and study selection

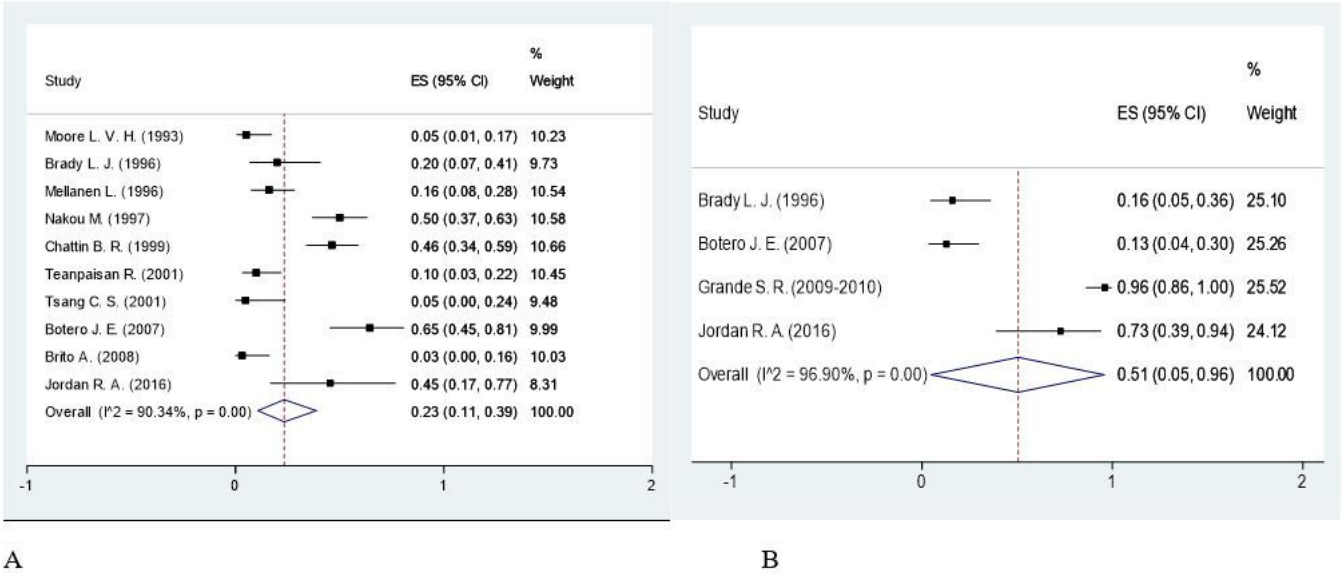

Figure 2

Forest plot analysis of the prevalence of bacterial species of red complex group in HIV-infected cases with periodontal disease (A= P. gingivalis, B= T. forsythia)

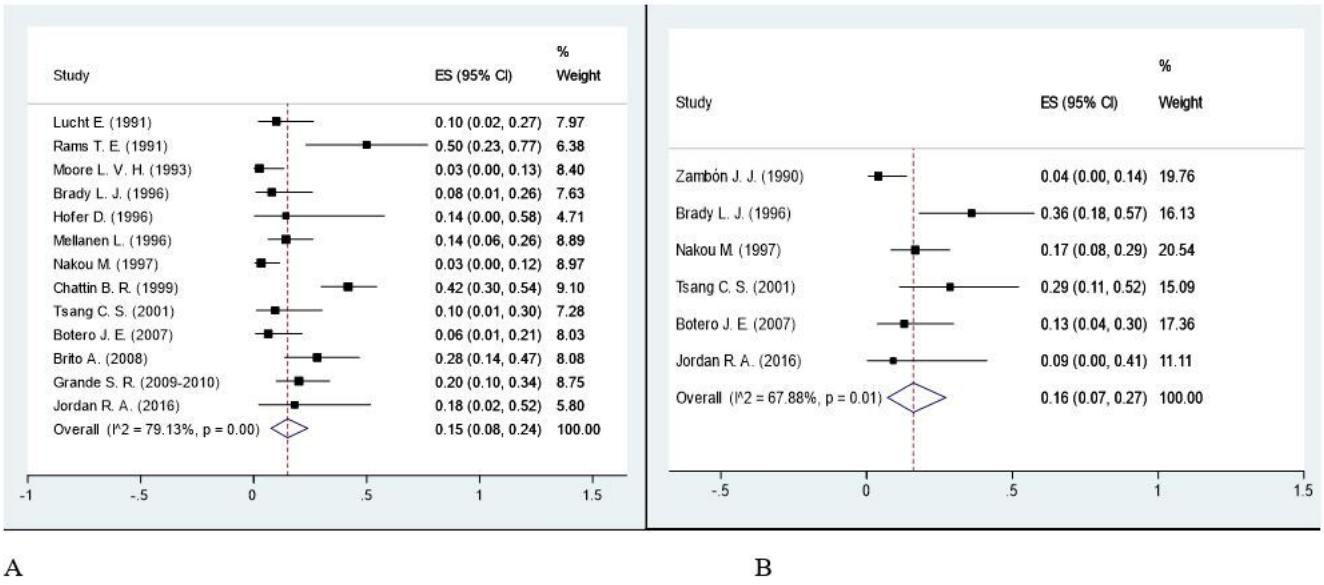

Figure 3

Forest plot analysis of the prevalence of bacterial species of green complex group in HIV-infected cases with periodontal disease (A= Actinobacillus actinomycetemcomitans, B= Eikenella corrodens)

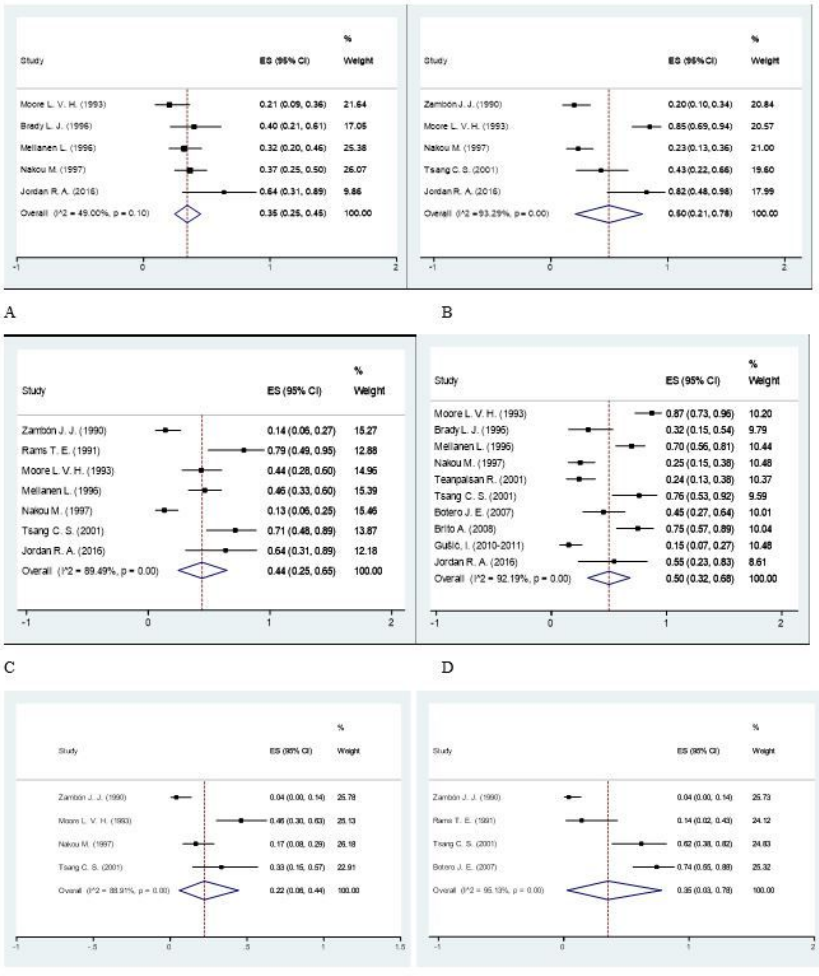

Figure 4

Forest plot analysis of the prevalence of bacterial species of orange complex group in HIV-infected cases with periodontal disease (A= Campylobacter rectus, B= Fusobacterium nucleatum, C= Peptostreptococcus micros, D= Prevotella intermedia, E= Campylobacter gracilis, F= Fusobacterium spp.)

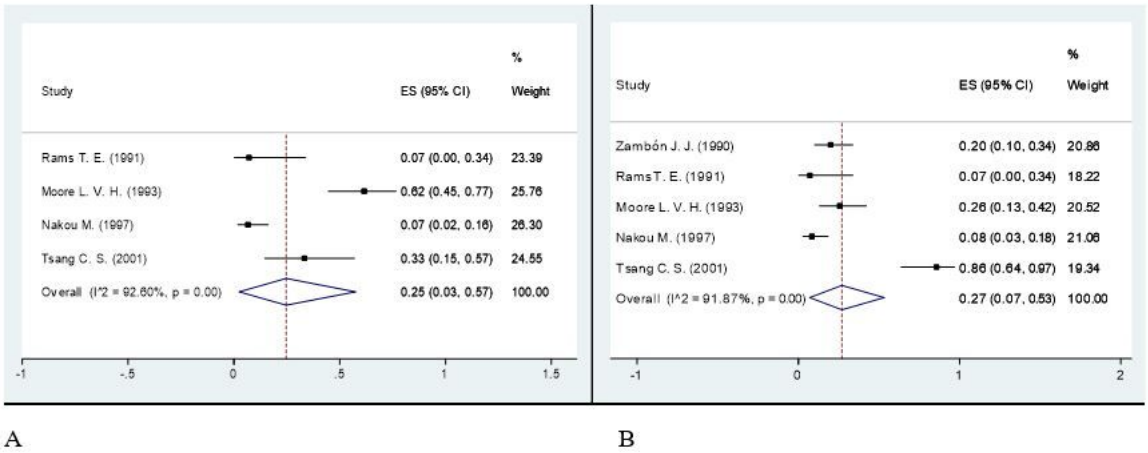

Figure 5

Forest plot analysis of the prevalence of bacterial species of yellow complex group in HIV-infected cases with periodontal disease (A= Streptococcus intermedius, B= Streptococcus sanguinis)

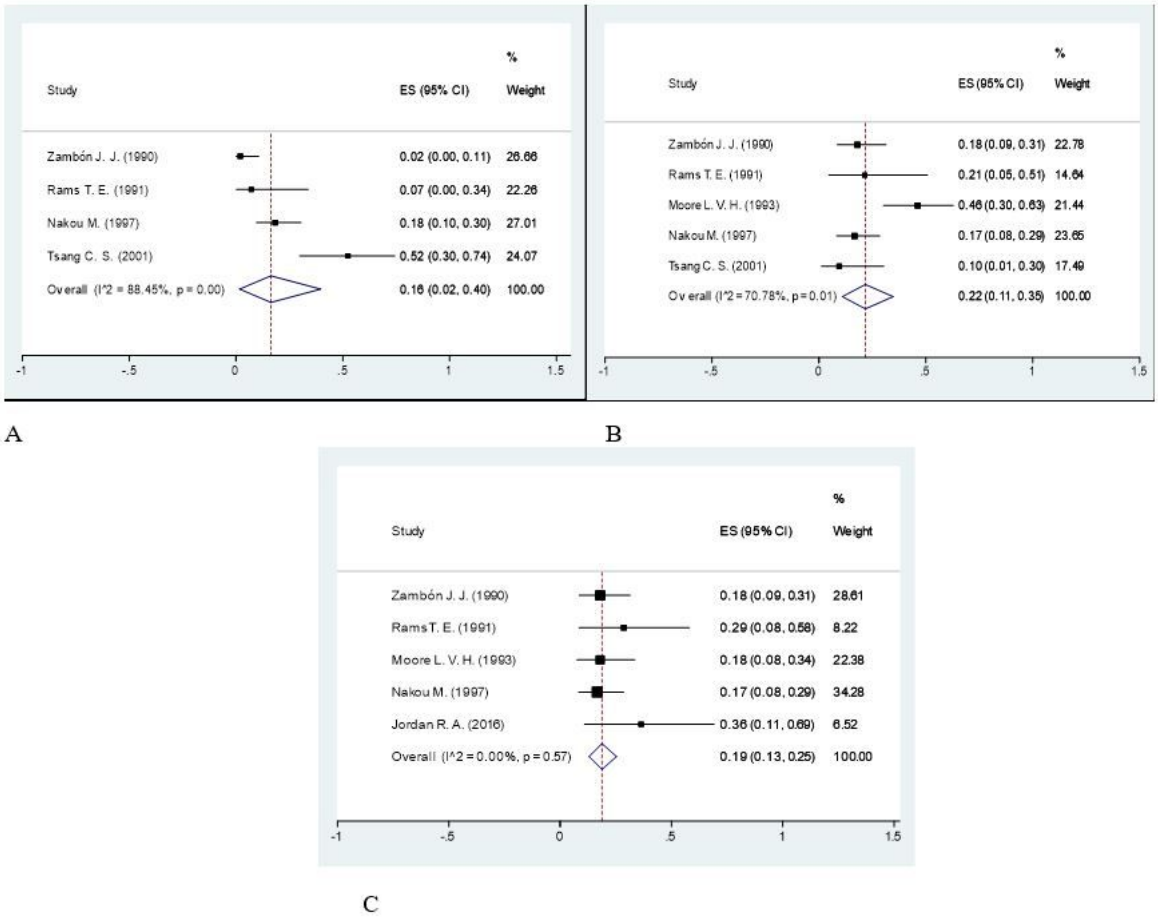

Figure 6

Forest plot analysis of the prevalence of bacterial species of blue complex group in HIV-infected cases with periodontal disease (A= Actinomyces israelii, B= Actinomyces naeslundii, C= Actinomyces viscosus)

Supplementary Files

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- Supplementarytable.docx