

Alterations in the oral microbiome in HIV infection: causes, effects and potential interventions

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Abstract

A massive depletion of CD4⁺ T lymphocytes has been described in early and acute human immunodeficiency virus (HIV) infection, leading to an imbalance between the human microbiome and immune responses. In recent years, a growing interest in the alterations in gut microbiota in HIV infection has led to many studies; however, only few studies have been conducted to explore the importance of oral microbiome in HIV-infected individuals. Evidence has indicated the dysbiosis of oral microbiota in people living with HIV (PLWH). Potential mechanisms might be related to the immunodeficiency in the oral cavity of HIV-infected individuals, including changes in secretory components such as reduced levels of enzymes and proteins in saliva and altered cellular components involved in the reduction and dysfunction of innate and adaptive immune cells. As a result, disrupted oral immunity in HIV-infected individuals leads to an imbalance between the oral microbiome and local immune responses, which may contribute to the development of HIV-related diseases and HIV-associated non-acquired immunodeficiency syndrome comorbidities. Although the introduction of antiretroviral therapy (ART) has led to a significant decrease in occurrence of the opportunistic oral infections in HIV-infected individuals, the dysbiosis in oral microbiome persists. Furthermore, several studies with the aim to investigate the ability of probiotics to regulate the dysbiosis of oral microbiota in HIV-infected individuals are ongoing. However, the effects of ART and probiotics on oral microbiome in HIV-infected individuals remain unclear. In this article, we review the composition of the oral microbiome in healthy and HIV-infected individuals and the possible effect of oral microbiome on HIV-associated oral diseases. We also discuss how ART and probiotics influence the oral microbiome in HIV infection. We believe that a deeper understanding of composition and function of the oral microbiome is critical for the development of effective preventive and therapeutic strategies for HIV infection.

Keywords: HIV; Oral microbiome; Antiretroviral therapy; Probiotics; Intervention

Introduction

Human immunodeficiency virus (HIV) infection is characterized by severe deficiency of the host immune system through the massive depletion of CD4⁺ T cells. The World Health Organization reported that, in the end of 2019, approximately, 38 million people were living with HIV worldwide, with around 67% of them receiving antiretroviral therapy (ART). Despite effective ART, several oral diseases, such as oropharyngeal candidiasis (OPC)^[1,2] and periodontitis,^[3,4] are frequently reported in all stages of HIV infection. In addition, as the life expectancy in people living with HIV (PLWH) increases, the risk of HIV-associated non-acquired immune deficiency syndrome (AIDS) comorbidities such as cardiovascular disease, neurocognitive disorders, cancer, and liver and kidney disease is increasingly reported.^[5-7] Ryder *et al*^[8] also

found that older HIV-infected individuals who have received ART may present with a higher incidence of age-related oral diseases.

In recent years, several studies have shown that the composition of the gut microbiome in PLWH differs from that of HIV-uninfected individuals, including an increase in the abundance of *Prevotella* and a decrease in the abundance of *Bacteroides*.^[9-12] Alterations in the gut microbiome may promote HIV-associated inflammation and immune activation.^[13,14] Similarly, Annavajhala *et al*^[15] suggested that oral microbiome diversity may also play a critical role in systemic inflammation in HIV-infected individuals. Studies have found that CD4⁺ T lymphocytes in gut-associated lymphoid tissue are greatly reduced in the early stage of HIV infection,^[16] resulting in the loss of T helper (Th) 17 cell subsets.^[17] It is believed that these interleukin-17- and interleukin-22-

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producing cells are essential to maintain intestinal epithelial integrity and gastrointestinal barrier function. Therefore, the loss of Th17 cells may contribute to microbial translocation from the gut mucosa into the systemic circulation, promoting inflammation and immune activation in HIV-infected adults.^[18-20] Studies have indicated that Th17 cells are essential for the control of fungal colonization in the oral mucosa.^[21-24] The structure and network of the oral mucosal immune system have also been described to be similar to those of the gastrointestinal mucosal immune system.^[25] This accumulating evidence suggests that oral microbiota may be similar to gut microbiota, both of which might induce systemic diseases through systemic translocation in HIV infection. In addition, Schmidt *et al*^[26] found that oral species, including opportunistic pathogens, might diffuse from the oral cavity to the gut, which may directly cause inflammation in the gut. Therefore, a focused effort on the effects of the oral microbiome on HIV will be critical.

Culture-dependent methods such as growth on media, microscopic observation, and biochemical analysis have been used to determine the composition of the microbiome. However, the appropriate culture conditions of some species might remain unclear, making them difficult to be cultivated. Currently, with the development of molecular techniques, next-generation sequencing, such as whole-metagenome shotgun sequencing and 16S ribosomal RNA amplicon sequencing, has been widely used for microbiome analysis. These “novel” technical approaches clearly contribute to the monitoring and manipulation of the human microbiome and provide new opportunities for diagnostics and therapeutics of human diseases.^[27] To comprehensively understand the human microbiome and the relationship between the microbiome and human diseases, the National Institutes of Health of the US launched the “Human Microbiome Project” in 2007.^[28] This review discusses alterations in the oral microbiome in HIV infection and the effects of the oral microbiome on HIV-associated oral diseases and evaluates the effects of potential interventions on the oral microbiome in HIV-infected individuals.

The human oral microbiome

The oral microbiome is an important part of the human microbiome and includes different microbes e.g., bacteria, fungi, viruses, mycoplasma, and protozoa.^[29] Bacteria are the predominant group of the oral microbiome, of which approximately 700 bacterial species have been identified. The oral microbiome plays a critical role in human metabolism, physiology, and immunity, including inhibiting pathogenic microorganism colonization, maintaining the acid-base balance, regulating local oral immunity, and participating in salivary nitrate metabolism.^[30]

The Human Oral Microbiome Database (<http://www.homd.org/>) contains records for a total of 775 microbial species. Among them, approximately 57% have been cultivated and named, 13% can be cultivated but not named, and 30% are uncultivated. Many of them have unique living conditions, such as specific temperature, pH, nutrition, and interaction with other species. The inability to fully replicate the ecological conditions in the oral cavity may be the reason why some oral microbiota cannot be

cultivated artificially. The human oral bacterial microbiome consists primarily of six phyla: *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *Actinobacteria*, *Spirochaetes*, and *Fusobacteria*.^[29,31] Bik *et al*^[32] analyzed the bacterial diversity in the oral cavity of ten healthy individuals and found that the most abundant genus was *Streptococcus*, followed by *Haemophilus*, *Neisseria*, *Prevotella*, *Veillonella*, and *Rothia*, similar to other reports on the oral microbiome.^[31,33,34]

In addition to bacterial communities, different fungi are also widely colonized in the human oral cavity.^[35] It is known that in elderly and immunocompromised individuals, oral commensal fungi can also serve as opportunistic pathogens. Ghannoum *et al*^[36] used internal transcribed spacer (ITS) sequencing to characterize the oral mycobiome in healthy individuals. This study demonstrated that the oral mycobiome comprises 74 culturable and 11 nonculturable fungal genera. In the samples from 20 healthy individuals, the most common genera were *Candida* (75%), followed by *Cladosporium* (65%), *Aureobasidium* and *Saccharomyces* (50% for both), *Aspergillus* (35%), *Fusarium* (30%), and *Cryptococcus* (20%).

The alterations in the oral microbiome in HIV infection

The homeostasis of oral microbiota can be affected by multiple factors, including diet, smoking, and drugs. Moreover, changes in secretory components in saliva, innate and adaptive immune responses, and the physiological structure and function of the oral mucosa can also cause the dysbiosis of the oral microbiome.^[37] Indeed, several studies have demonstrated a significant difference in the alterations of the oral microbiome between PLWH and HIV-uninfected healthy controls.^[38-42] However, the potential mechanisms of oral microbiota changes in HIV infection remain unclear.

Alterations in salivary composition and function in HIV infection might play a key role in the dysbiosis of the oral microbiome. Saliva contains a variety of secretory components that are essential for maintaining oral homeostasis.^[43] Studies have shown that secretory components, including immunoglobulin A (IgA), lysozyme, and host defense peptides, such as antimicrobial peptides, defensins, and histones, play an important role in microbial control and oral mucosal immunity.^[44,45]

A recent study indicated the composition and function of saliva change in HIV infection. The impairment of local immunity in HIV infection, including decreased salivary IgA, defensins, and cytokines, might convert commensal microorganisms to microorganisms with increased pathogenicity and lead to the dysbiosis of oral microbiota, which could increase the risk of opportunistic infections.^[46,47] Arirachakaran *et al*^[48] showed that HIV-infected individuals, regardless of whether they are receiving ART, have a higher frequency and load of opportunistic microorganisms than HIV-uninfected controls. Other studies also revealed that the diversity and bacterial load in salivary samples from HIV-infected individuals were significantly higher than those in HIV-uninfected samples.^[49] In addition, a negative correlation between oral lesions and CD4⁺ T-cell counts has

been reported.^[50-52] Therefore, the disruption of oral mucosal immunity in HIV infection might destroy the colonization of commensal bacteria in the oral cavity and lead to an increase in oral microbial diversity, resulting in an increased risk of HIV-associated oral diseases. However, different studies have also shown differing results. They found that the oral bacterial diversity in PLWH was significantly decreased when compared with that in HIV-uninfected individuals.^[38,39,46,53] A possible explanation might be the increased proportion of opportunistic pathogens caused by immunodeficiency in HIV infection.^[46] Furthermore, a variety of salivary proteins, such as lysozyme, defensin, lactoferrin, secretory leukocyte protease inhibitor, and salivary agglutinin, have been confirmed to inhibit HIV infectivity *in vitro*, which also shows the importance of changes in salivary components in the pathogenesis of HIV infection.^[54]

In addition to the secretory components, cellular innate immune components in the oral cavity, e.g., macrophages, natural killer cells, polymorphonuclear leukocytes, and dendritic cells, also have the capacity to protect the oral mucosa from the colonization of pathogenic microorganisms.^[55] These innate immune cells can recognize pathogens such as bacteria, viruses, and fungi through pattern recognition receptors (PRRs). PRRs mainly comprise several families, including Toll-like receptors, C-type lectin receptors, retinoic acid inducible gene-like receptors, and nucleotide-binding oligomerization domain-like receptors.^[56] The binding of these PRRs to the pathogen-associated molecular patterns presented on the

surface of microorganisms will induce the production of cytokines, chemokines, and vasoactive molecules, which might play important roles in regulating the innate immune response to infection and promoting the induction of adaptive immune responses.^[55,57] Therefore, these innate immune cells are essential for the prevention of bacterial infections. However, innate immune responses in the oral cavity are impaired in HIV infection, which may lead to the dysbiosis of the oral microbiome and increase the occurrence of opportunistic infections.^[44]

In addition, immunodeficiency associated with HIV infection might lead to defects in the adaptive immune response, which could also promote oral microbiota dysbiosis. A number of studies have shown that the Th17 immune response is essential for the control of fungal infection and inflammation of the oral mucosa.^[21,58] Dutzan *et al*^[59] found that Th17 cells could maintain oral barrier integrity and aid in fighting oral fungal infections. Furthermore, the critical role of Th17 cells in the fight against *Candida* infection has been described in a previous study.^[60] In addition, Th1 cells might mediate early gingival inflammatory lesions in response to bacterial plaques by producing cytokines such as interferon γ (IFN- γ).^[55,61] Th2 immune responses are also closely related to the progression of periodontal diseases^[62] [Figure 1].

Although previous studies have demonstrated that oral microbiome composition might change in HIV infection, the results obtained from the different studies are not the same [Table 1]. A recent study compared saliva micro-

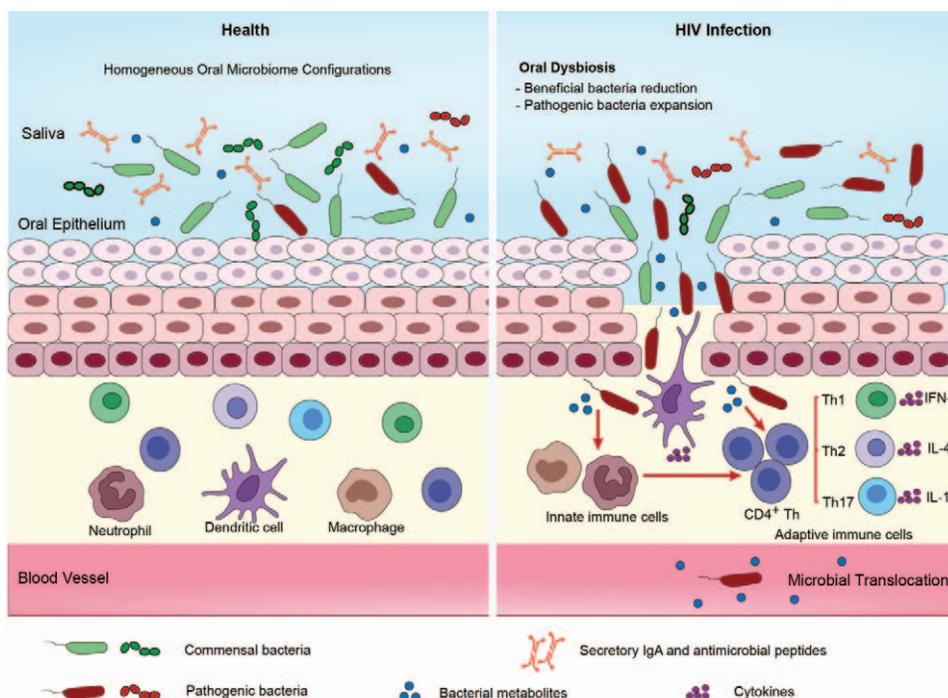


Figure 1: Proposed mechanisms of oral microbiome dysbiosis in HIV infection. In health, oral epithelial cells have the capability to maintain microbial colonization. However, disrupted oral immunity, including changes in secretory components in saliva (sIgA, lysozyme, and antimicrobial peptides), deficiency of innate immune responses (macrophages and dendritic cells), and adaptive immune response (CD4⁺ Th), may cause oral microbiome dysbiosis in HIV infection. Such an imbalance between the oral microbiome and oral immune responses may also contribute to the development of HIV-related oral diseases (periodontal disease) and HIV-associated non-AIDS comorbidities. Periodontal disease is caused by the interplay between pathogenic bacteria and host defense, which can also lead to microbial translocation and an increased risk of systemic conditions. AIDS: Acquired Immune Deficiency Syndrome; HIV: Human immunodeficiency virus; IgA: Immunoglobulin A; IFN- γ : Interferon γ ; IL-4: Interleukin-4; Th: T helper.

Table 1: The oral microbiome in HIV infection.

Study	Cohort	Samples	Design	Major findings
Li <i>et al</i> ^[46]	10 HIV+ subjects prior to and after 6 months of ART 10 HIV- controls	Saliva	Cross-sectional and longitudinal	<ul style="list-style-type: none"> Increased oral <i>streptococci</i>, <i>lactobacilli</i>, <i>Streptococcus mutans</i>, and <i>Candida</i> in HIV Increased <i>Fusobacterium</i>, <i>Campylobacter</i>, <i>Prevotella</i>, <i>Capnocytophaga</i>, <i>Selenomonas</i>, <i>Actinomyces</i>, <i>Granulicatella</i>, and <i>Atopobium</i> and decreased <i>Aggregatibacter</i> after ART
Beck <i>et al</i> ^[99]	18 HIV+ naive 38 HIV+ ART 80 HIV-	Oral wash	Cross-sectional	<ul style="list-style-type: none"> Enrichment of a <i>Streptococcus</i> Operational taxonomic unit (OTU) and two <i>Actinomyces</i> OTUs in HIV+ naive subjects, an <i>Atopobium</i> OTU in HIV+ naive and ART subjects, and a <i>Rothia</i> OTU in ART
Saxena <i>et al</i> ^[47]	46 HIV+ subjects before and after ART and 69 HIV- controls 8 HIV+ subjects and 8 HIV- subjects	Saliva	Cross-sectional and longitudinal	<ul style="list-style-type: none"> Different microbial compositions among HIV+ subjects before and after ART and HIV- controls Differences in <i>Streptococcaceae</i>, <i>Prevotellaceae</i>, <i>Porphyromonadaceae</i>, and <i>Neisseriaceae</i> between HIV+ and HIV- subjects
Arirachakaran <i>et al</i> ^[48]	148 HIV+ ART for >5 years 20 HIV+ untreated 53 vertically transmitted ART HIV+ subjects 30 HIV- controls	Tongue, gingival crevices, and mucosal lesions	Cross-sectional	<ul style="list-style-type: none"> Higher frequency and load of opportunistic microorganisms in the ART group and non-ART group than the HIV- controls Increased <i>Candida</i> spp. on the tongue in HIV+ subjects with CD4+ counts <500 cells/mm³
Presti <i>et al</i> ^[41]	35 HIV+ subjects prior to and after 6 months of ART	Saliva	Longitudinal	<ul style="list-style-type: none"> Higher bacterial richness and diversity in HIV+ subjects with persistently low CD4 counts after 24 weeks of ART Differences in several taxa, including <i>Porphyromonas</i> species discriminated between HIV+ subjects before and after 6 months of ART
Starr <i>et al</i> ^[65]	154 perinatally HIV-infected youth 100 perinatally HIV-exposed, uninfected youth	Subgingival plaque	Cross-sectional	<ul style="list-style-type: none"> Similar microbiomes in the two cohorts Two <i>Corynebacterium</i> species were lower in perinatally HIV-infected youth
Mukherjee <i>et al</i> ^[53]	48 HIV-infected smokers 24 HIV-infected non-smokers 24 HIV-uninfected smokers	Oral wash	Cross-sectional	<ul style="list-style-type: none"> Decreased <i>Firmicutes</i> and increased <i>Proteobacteria</i> in HIV-infected non-smokers compared to HIV-infected smokers and HIV-uninfected smokers No difference in fungal phyla between the three cohorts

(continued)

Table 1
(continued).

Study	Cohort	Samples	Design	Major findings
Gonçalves <i>et al</i> ^[63]	27 HIV+ Brazilian children/teenagers 30 HIV- children/teenagers	Whole saliva, biofilm from the dorsal surface of the tongue, and biofilm from supragingival and subgingival sites	Cross-sectional	<ul style="list-style-type: none"> Higher frequency of the phyla <i>Firmicutes</i> and genus <i>Streptococcus</i> in HIV-infected children/teenagers More complexity in oral microbiome of HIV-infected children/teenagers
Jiménez-Hernández <i>et al</i> ^[49]	12 viremic ART-untreated 18 immunological ART responders 9 immunological ART non-responders 14 HIV-uninfected controls	Saliva	Cross-sectional and longitudinal	<ul style="list-style-type: none"> Higher abundance of potential pathogens as <i>Streptococcus agalactiae</i>, <i>Corynebacterium durum</i>, and OTUs assigned to species of <i>Prevotella</i>, <i>Leptotrichia</i>, <i>Tannerella</i>, and <i>Catonella</i> in HIV+ subjects Increased <i>Actinobacteria</i>, <i>Rothia mucilaginosa</i>, <i>Mogibacterium</i> and decreased <i>Corynebacterium</i>, <i>Fusobacterium</i>, and <i>Prevotella melaninogenica</i> in viremic ART-untreated subjects after prebiotics
Coker <i>et al</i> ^[95]	94 HIV+ children 98 HIV exposed-uninfected children 94 HIV unexposed/uninfected children	Saliva	Cross-sectional	<ul style="list-style-type: none"> Depletion of eight bacterial taxa, including <i>Actinomyces</i> and <i>Neisseria subflava</i> and enrichment of <i>Corynebacterium diphtheriae</i> in HIV+ children when compared to HIV unexposed/uninfected children Low CD4 levels persistently alter the oral microbiota.
Griffen <i>et al</i> ^[40]	252 HIV+ ART 89 HIV-	Oral rinse	Cross-sectional	<ul style="list-style-type: none"> A complex set of clinical features that influenced oral bacterial community composition, including the presence of HIV under ART
Yang <i>et al</i> ^[39]	75 HIV+ ART 93 HIV-	Saliva	Cross-sectional	<ul style="list-style-type: none"> Increased <i>Veillonella</i>, <i>Rothia</i>, and <i>Streptococcus</i> and decreased <i>Neisseria</i>
Annavajhala <i>et al</i> ^[15]	52 HIV+ ART	Saliva and plaque samples	Cross-sectional and longitudinal	<ul style="list-style-type: none"> Bacterial and fungal oral microbiome communities were associated with chronic systemic immune activation in HIV.
Li <i>et al</i> ^[38]	20 HIV+ subjects before and after 6 months ART 20 HIV- controls	Saliva	Cross-sectional and longitudinal	<ul style="list-style-type: none"> Increased <i>Streptococcus</i> and decreased <i>Neisseria</i> in HIV+ subjects <i>Prevotella_7</i>, <i>Neisseria</i>, and <i>Haemophilus</i> negatively correlated with CD4⁺ T cell count, while <i>Neisseria</i> positively correlated with viral load.
Imahashi <i>et al</i> ^[64]	20 HIV+ Japanese with ART 13 HIV- controls	Saliva	Cross-sectional and longitudinal	<ul style="list-style-type: none"> No largely differences in three major genera, <i>Prevotella</i>, <i>Streptococcus</i>, and <i>Veillonella</i> between the HIV+ subjects and controls.

(continued)

Table 1

(continued).

Study	Cohort	Samples	Design	Major findings
Fidel <i>et al</i> ^[68]	149 HIV+ subjects 88 HIV- subjects	Oral rinse	Cross-sectional	<ul style="list-style-type: none"> Limited number of species dominated oral mycobiome Several clinical variables, including HIV positivity and highly active antiretroviral therapy (HAART) affected the oral mycobiome
Li <i>et al</i> ^[42]	15 acute HIV-infected subjects before and after ART 15 chronic HIV-infected subjects before and after ART 15 HIV- controls	Throat swabs	Cross-sectional and longitudinal	<ul style="list-style-type: none"> Increased <i>Prevotella</i> in acute HIV infections and <i>Streptococcus</i> in chronic HIV infections After effective ART, enriched <i>Bradyrhizobium</i> in both acute and chronic HIV infections, enriched <i>Lactobacillus</i>, <i>Rothia</i>, <i>Clostridia</i>, <i>Actinobacteria</i>, and <i>Ruminococcaceae</i> in controls.

ART: Antiretroviral therapy; HIV: human immunodeficiency virus.

biome samples from HIV-infected individuals and HIV-uninfected controls. They found that the abundance of *Streptococcus* was increased in HIV-infected individuals, while the abundance of *Neisseria* was higher in healthy controls.^[38] Another study showed similar results: the abundance of *Veillonella*, *Rothia*, and *Streptococcus* was significantly increased in the oral microbiome of PLWH, whereas the abundance of *Neisseria* was significantly decreased.^[39] The oral microbiome in HIV-infected children and teenagers is also characterized by a higher frequency of the phyla *Firmicutes* and the genus *Streptococcus*.^[63] However, other studies have shown that there are no large differences in the oral microbiome between HIV-treated patients and healthy controls.^[64,65] In addition, alterations in the oral fungal community composition in PLWH have also been noted when compared with those in HIV-uninfected individuals.^[66] A study compared the oral fungal composition of 12 HIV-infected individuals with that of 12 HIV-uninfected individuals. The study showed that *Candida*, *Epicoccum*, and *Alternaria* were the most common, presenting in 92%, 33%, and 25% of HIV-infected individuals, respectively. However, the most abundant fungi in HIV-uninfected controls were *Candida*, *Pichia*, and *Fusarium*, presenting in 58%, 33%, and 33%, respectively.^[67] Fidel *et al*^[68] have also demonstrated the relative abundance of oral fungal communities in 149 HIV-positive and 88 HIV-negative subjects. This study suggested that 168 species can be identified in 12 dominant genera by sequencing of the ITS2 region of the rRNA gene repeat. However, they indicated that the diversity of the oral mycobiome is usually dominated by a small number of species, and HIV and ART might affect the oral mycobiome composition. In addition, many studies have shown increased *Candida* colonization in HIV infection.^[1,35,69,70] These studies support that HIV infection can significantly change the host oral microbiota. However, the effects of an altered

oral microbiome on HIV-associated diseases remain to be shown.

Effects of the oral microbiome on HIV-associated oral diseases

The oral microbiome is known to play an important role in host health and disease. On the one hand, the dysbiosis of the oral microbiome has been found in people with various oral diseases, such as dental caries, periodontal diseases, oral mucosal diseases, and oral cancer.^[71] On the other hand, the dysbiosis of oral microbiota has also been observed in digestive system diseases (inflammatory bowel disease,^[72-74] liver cirrhosis,^[75] pancreatic cancer^[76,77]), nervous system diseases (Alzheimer disease^[78,79]), endocrine system diseases (diabetes^[80]), immune system diseases (rheumatoid arthritis,^[81,82] HIV infection^[39,65]), cardiovascular diseases (arteriosclerosis^[83]), adverse pregnancy outcomes,^[84] and polycystic ovary syndrome.^[85] The potential mechanisms may be that oral microbiota could enter the gastrointestinal tract and respiratory tract through eating and aspiration. Moreover, Han *et al*^[86] reported that oral microbial dysbiosis could promote adverse systemic conditions through bacteremia. Studies have also shown that periodontal disease caused by the interaction between pathogenic microorganisms and host defenses can lead to microbial translocation and an increased risk of inflammatory diseases, such as cardiovascular diseases.^[87,88] Therefore, the systemic translocation of the oral microbiome might also contribute to systemic diseases.

The oral cavity is one of the most common sites for opportunistic infections in PLWH. Several oral diseases often occur in PLWH, including periodontal diseases, OPC, oral warts, oral hairy leukoplakia, and Kaposi sarcoma (KS), even in those receiving ART.^[44] Globally

and throughout the decades, OPC has remained the most common oral manifestation in HIV infection, including among HIV-infected individuals receiving ART (26.2%).^[189] OPC is caused by various *Candida* species, and *Candida albicans* is the most prevalent species isolated from PLWH.^[170,90,91] The incidence of OPC in HIV infection is influenced by a multitude of factors, including immune status,^[92] bacteriome-mycobiome interaction,^[93] antifungal therapy, and ART.^[94] Patil *et al*^[1] showed that oral *Candida* colonization in HIV-infected patients increased, and it was significantly related to a lower CD4⁺ T-cell count. Coker *et al*^[95] also demonstrated that low CD4⁺ T-cell levels in HIV-infected children might persistently alter oral microbiota. In addition, other studies found that the prevalence of dental caries and periodontal diseases in PLWH was increased, which may be related to changes in oral microbiota in HIV-infected patients.^[3,96] Compared with PLWH with mild periodontal disease, *Abiotrophia*, *Rothia*, and unclassified *Pasteurellaceae* were enriched in HIV-infected individuals with moderate and severe periodontal disease, and *Treponema* spp. were enriched in patients with severe periodontal disease.^[4] Moreover, Marion *et al.* found that oral microbiota composition in HIV-infected individuals with oral KS was significantly different from that of HIV-infected individuals without oral KS. They found that at the genus level, the abundances of *Aggregatibacter* and *Lautropia* were decreased, whereas those of *Corynebacterium* and *Shuttleworthia* were increased in HIV-infected individuals with oral KS.^[97] These studies indicated that distinct oral microbiota might affect the development of oral diseases in PLWH.

Effects of potential interventions on the oral microbiome

Although the use of ART can inhibit HIV replication, increase CD4⁺ T lymphocytes, and reduce the occurrence of oral lesions, it cannot completely restore the oral microbiome of PLWH from its dysbiosis to normal.^[38,98] Studies observed that the oral microbiome compositions in HIV-infected individuals with ART became more similar to those in HIV-uninfected controls; however, a difference remained between the groups.^[38,99] Annavajhala *et al*^[15] indicated that the use of specific ART regimens was associated with alterations in both gut and oral bacterial diversity. A study showed that *Fusobacterium*, *Campylobacter*, *Prevotella*, *Capnocytophaga*, *Selenomonas*, *Actinomyces*, *Granulicatella*, and *Atopobium* were increased in HIV-infected individuals after receiving ART, while *Aggregatibacter* was significantly decreased.^[45] Another study collected samples from 35 HIV-infected subjects at baseline and after 24 weeks of ART to compare the differences in oral microbiota. The results showed that the dominant phyla in samples from patients with 24 weeks of ART remained similar to those observed at baseline, and the diversity was not significantly different between samples collected at baseline and those collected after 24 weeks of ART. However, PLWH with persistently low CD4⁺ T-cell counts had significantly increased bacterial richness and Shannon diversity, indicating that shifts in oral microbiota may play an important role in the recovery of CD4⁺ T-cell counts.^[40] A recent study also found that *Prevotella_7*, *Neisseria*, and *Haemophilus* were negatively

correlated with CD4⁺ T-cell count, whereas *Neisseria* was positively correlated with viral load.^[37] Imahashi *et al*^[64] also revealed the effects of long-term ART on gut and oral microbiota in PLWH. They suggested that ART, especially nucleoside reverse transcriptase inhibitor-based ART, has more suppressive effects on the composition and diversity of microbiota in the gut than that in the oral cavity.

Although OPC is still the most common oral opportunistic infection in PLWH, the introduction of ART can reduce its incidence in PLWH.^[1] Interestingly, Maurya *et al*^[100] found that although ART can decrease the risk of OPC in HIV-infected individuals, it does not decrease the colonization of *Candida* in the oral cavity. ART may play a key role in maintaining homeostasis between host immunity and the oral microbiome. However, it can also reduce oral commensal microorganisms that are capable of inhibiting pathogen colonization. Therefore, the potential mechanisms of ART on oral microbiome colonization remain unclear, and the further studies are necessary.

In addition to ART, many studies have demonstrated that probiotics can be used as a new therapeutic approach to improve the quality of life in PLWH.^[101] Probiotics play a beneficial role in human health by regulating the immune system and controlling pathogen colonization.^[102] Studies have shown that probiotics are effective in preventing and treating many disorders, such as acute gastroenteritis,^[103] inflammatory bowel diseases and irritable bowel syndrome,^[104,105] *Clostridium difficile*-associated diarrhea,^[106] allergies,^[107] neonatal sepsis,^[108] and respiratory tract infections.^[109] Hu *et al*^[110] also reported that probiotics might exert their beneficial effects on coronavirus and have a positive effect on host immune functions during severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. In recent years, probiotics have also been used to prevent various oral diseases, such as dental caries,^[111] gingivitis,^[112] and periodontitis.^[113] In addition, the administration of probiotics could have a beneficial effect on OPC.^[114,115] De Barros *et al*^[116] found that *Lactobacillus* could reduce the filamentation of *C. albicans* in *in vitro* and *in vivo* models, presenting the suppressive effect of probiotics on fungal pathogens. Other studies also showed that intake of *Lactobacillus rhamnosus* by immunosuppressed mice might decrease the development of candidiasis.^[117] An *in vitro* study also suggested that *Lactobacillus acidophilus* and *Lactobacillus plantarum* had antifungal effects against different oral *Candida* species isolated from HIV/AIDS patients.^[118] In addition, recent studies also focused on the intervention of prebiotics and found nutritional stimulation of beneficial bacteria by prebiotics might play a crucial role in promoting oral health.^[119,120] Jiménez-Hernández *et al*^[49] conducted a study on the impact of prebiotic intervention on the saliva microbiome of PLWH. A total of 32 HIV-infected subjects completed a 6-week prebiotic intervention, including viremic ART-untreated patients, immunological ART responders, immunological ART nonresponders, and HIV-uninfected controls. The diversity and richness of the saliva microbiome were decreased in the four groups after prebiotic intervention. In viremic ART-untreated individuals, the *Actinobacteria Rothia mucilaginosa* was increased, whereas some potential pathogens, such as

Corynebacterium, *Fusobacterium*, or *Prevotella melaninogenica*, were decreased after the use of prebiotics. These studies have further demonstrated that the probiotics and prebiotics may be beneficial to regulate oral microbiota dysbiosis in HIV infection and prevent and reduce the occurrence of HIV-related oral diseases. However, the oral microbiome could be influenced by multiple factors. It is necessary to identify specific bacteria that are beneficial to preventing and treating HIV-related diseases. Further clinical studies are also needed to determine the efficacy and safety of probiotics in different clinical conditions.

Conclusion

Increasing evidence suggests a significant link of oral microbiome changes to HIV infection. We summarized the recent findings on alterations in oral microbiota of HIV infection and the potential roles of the shifts in oral microbiota in HIV-associated oral diseases. Moreover, we reviewed the effects of ART and probiotics on oral microbiota in HIV-infected individuals. It is evident that the oral microbiome plays an essential role in the pathogenesis of HIV disease, and a better understanding of the oral microbiome might improve the oral health of HIV-infected patients. In addition, further investigations are needed to evaluate the impact of the potential interventions on oral microbiome in HIV infection, which is groundwork for the formidable task of developing novel approaches for the prevention and therapy of HIV/AIDS-associated diseases.

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Conflicts of interest

None.

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