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Oropharyngeal Candidiasis, *Candida Albicans* Infections, and Oral Immune Mediators Associated with Oral Human Immunodeficiency Virus: A Literature Review

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Abstract

Introduction: While *Candida albicans* are usually commensal and present in low density in the oral cavity of healthy individuals, an immunocompromised immune system can lead to the overgrowth of this fungal species, leading to oral microbiome "dysbiosis" and activation of immune responses. In severe cases, *C. albicans* overgrowth can lead to an oral infection called oropharyngeal candidiasis (OPC), which is associated with inflammation, lesions, and sores of the oral cavity. While human immunodeficiency virus (HIV) infection has been linked to an increased risk of OPC, few studies have associated OPC and *C. albicans* infection with subsequent risk for oral HIV acquisition. Evidence on the oral microbiome and how it can alter HIV risk is also lacking.

Methods: A literature search was performed on PubMed, Google Scholar, and the University of Alberta Library Database from inception to November 2023.

Results and Discussion: The risk of oral HIV transmission is low. OPC and *C. albicans* fungal infection can increase HIV susceptibility by activating immune responses associated with the clearance of microbial pathogens, inducing inflammation and elevations in cytokines related to HIV risk including IL-17, IL-6 and IL-1ß. Persistent *C. albicans* infections also promote the recruitment of T-helper 17 cells, which is a common HIV target cell, and neutrophils, which releases neutrophil proteases upon inflammation and mediates the cleavage of tight junction proteins, ultimately disrupting the oral microbiome.

Conclusion: Increased immune cell recruitment to the mucosa and increased epithelial breakdown may facilitate the diffusion and access of HIV virions across the epithelium to immune target cells, suggesting that OPC and *C.albicans* infections has the potential to increase risk for oral HIV acquisition. Limited evidence of the relationship between *C. albicans* density, OPC, and oral HIV risk, warrants high-quality cross-sectional studies in the future.

Keywords: oropharyngeal candidiasis; human immunodeficiency virus; epithelial damage, oral HIV transmission; microbial dysbiosis; inflammation

Introduction

There were 1.33 million new Human Immunodeficiency Virus (HIV) infections globally in 2022 [1]. HIV is a retrovirus which can be transmitted through bodily fluids such as semen, blood, or cervicovaginal secretions [2]. Primary HIV target cells include CD4+ T cells, particularly those harboring the CCR5 HIV-coreceptor, and T-helper 17 (Th17) cells [3]. Chronic HIV infections can lead to acquired immunodeficiency syndrome (AIDS), characterized by the depletion of serum CD4+ T cells [3]. HIV transmission between men who have sex with men are most common via penile-anal sex, while penile-vaginal sex is the most common route of transmission in females [2]. Despite the chance of penile-vaginal HIV transmission being extremely low (1/500-1/1000 chances), HIV infections each year remain high. Elevations in pro-inflammatory cytokines and chemokines in the female genital tract have been associated with an increased risk of HIV acquisition, leading to the recruitment of HIV target immune cell subsets such as CD4+ T cells [4–7]. Inflammation is also associated with tissue damage and epithelial disruption to facilitate viral access to immune cells in the mucosa [4,8]. This inflammation is closely linked to genital inflammation, where decreased levels of common "protective" vaginal bacteria is associated with increased risk for sexually transmitted infections (STIs), HIV infections, and obstetric complications [8–10].

In contrast, the rates of oral HIV transmission are comparatively low, and the mechanisms that elevate the risk of oral HIV infection are less studied. HIV can be transmitted orally via two main routes: mother-to-child transmission and adult sexual transmission, with the former harboring higher risk of acquisition than adult transmission [11]. Although mother-to-child transmission most commonly occurs through the transfer of virions through

breast milk, adult transmission occurs primarily through the exchange of pre-ejaculate, seminal fluid, vaginal fluids, the mucous found in the rectum, and blood [5]. As such, adult transmission occurs predominantly through oral-genital sex, and those at high risk of infection include men who have sex with men, and individuals with oral sores, lesions, and immunocompromised immune systems [11,12].

Similarly, a normally "optimal" oral microbiome can be perturbed by imbalances in microbiome composition, leading to opportunistic bacterial infections [13]. When opportunistic pathogens establish oral infections, they can cause a positive feedback effect that amplifies mucosal inflammation and epithelial damage [14]. However, this aspect has seldom been studied in the context of oral HIV transmission [14,15].

Candida albicans, a commensal yeast found in the oral cavity, gut, and genital tracts of healthy individuals, has the potential to cause an opportunistic infection, oropharyngeal candidiasis (OPC), in immunosuppressed individuals [16,17]. Symptoms of OPC include swelling and redness of the mouth, a persistent cottony feeling, and altered taste perception [16]. While vaginal Candida infections in heterosexual women are associated with an increase in HIV risk, OPC is mostly understood as the initial manifestation of HIV infection [18,19]. Upon *C. albicans* infection, toxins released by yeast cells induce inflammation and the recruitment of Th17 cells, common HIV target cells, to the underlying epithelium [20]. The natural inflammatory response against opportunistic infections also triggers the recruitment of neutrophils, which has the potential to mediate tissue damage and increase the access of HIV virions to target cells [4,7,20]. Altogether, components of OPC infection seem related to risk factors for HIV, but few studies have directly linked oral Candida density to subsequent risk for HIV. The goal of this review is to understand immune risk factors of adult oral HIV acquisition and how opportunistic *C. albicans* infections can influence oral HIV susceptibility.

Methods

A literature search was performed by CK on PubMed, Google scholar and the University of Alberta Library Database using these key words: "HIV Transmission", *Candida albicans* infections", "Oropharyngeal candidiasis" "Oral immunity", "Oral HIV transmission", and "Microbiome-immune axis". Literature from inception to November 2023 was used as to not limit the scope of potential results given the scarcity of study in this area.

Results and Discussions

The Impact of Oral Epithelial Structure During Oral Transmission of HIV

Adult HIV oral transmission primarily occurs through receptive oral intercourse (ROI) with a reported rate of 0.04% per oral-genital HIV exposure in studies of men who have sex with men [11]. Studies in rhesus macaques infected with simian immunodeficiency virus (SIV), a lentivirus closely related to HIV, provided insights into the role of the innate immune system after oral exposure to the virus [5,11]. Similar to humans, rhesus macaques experience an AIDS-like disease following infection by SIV, which is characterized by CD4+ T cell depletion [21–23]. Although oral transmission rate is low, SIV in the oral cavity rapidly penetrated through the oral mucosa and epithelium, subsequently spreading to lymphoid tissues within two days after exposure [11]. In contrast, vaginal SIV established a localized infection at the mucosa three to four days after exposure, infecting only a few CD4+ T cells [11]. Differences in SIV and HIV penetration may be attributed to the differences in the epithelial structure between the oral and vaginal epithelium [11]. Both epitheliums are composed of a keratinized stratified squamous epithelium, which acts as a physical barrier against HIV penetration compared to the anal epithelium, largely made of a simple columnar epithelium and harboring the greatest HIV risk [5,20,24–26]. The vaginal epithelium has more cornified cells than the oral epithelium, forming an insoluble and tough layer beneath epithelial cell membranes [27,28]. This may offer greater physical protection against HIV-1 infection, which enters epithelial layers via diffusion, where the rate of virion diffusion is highly dependent on the presence of tight junction proteins and an intact epithelial layer [29,30]. While macaque SIV infection models limit direct comparisons to human HIV infections due to differences in the surface epitopes of each virus, the Rhesus macaque remains a strong model for HIV transmission [22,31,32].

Although stratified squamous epithelium is the most predominant throughout the oral cavity, columnar epithelial cells can be found in the salivary glands [11]. Studies investigating the oral mucosa as a primary site of HIV infection focused on the tonsils, given that they are easily inflamed by infections, allergies, or exposure to environmental irritants, and serve as an easy entry site for HIV [11,33–37]. Despite various studies, understanding specific sites of HIV entry in macaque models are limited, and more evidence is needed to understand how inflammation and infections in the oral cavity are associated with HIV risk [11].

Immune Responses Associated with HIV Infection in the Oral Cavity

Despite various risk factors, oral transmission is considered relatively low risk, which may be attributed to the "protective" nature of saliva in the oral cavity [5,11]. Saliva contains several anti-HIV soluble factors, such as salivary agglutinin 340 (gp340), which binds to gp120 to block the binding of HIV to T cells, monocytes, macrophages, and dendritic cells [38,39]. Saliva also contains secretory leukocyte protease inhibitors (SLPI), which binds to annexin II on macrophages to reduce the rate of macrophage HIV infection *in vivo* [40]. Moreover,

the risk of oral HIV transmission is associated with higher plasma viral load, and decreased oral HIV transmission risk is associated with soluble factors in saliva inactivating virions upon exposure [11,41]. While offering protection from HIV, saliva may also indirectly enhance HIV infections. For example, saliva can induce NETosis, a process by which neutrophils release neutrophil extracellular traps (NETs) composed of unwound genomic DNA complexed with antimicrobial proteins to kill and inactivate pathogens [42,43]. Although effective against some viruses and bacterial infections, HIV can evade NETs by inducing the release of IL-10, an anti-inflammatory cytokine involved in the inhibition of reactive oxygen species (ROS) formation, from dendritic cells [42,44]. Since ROS formation is required in NETosis, HIV has the potential to avoid NETs during oral infection and increase the chances of HIV penetration [42]. Despite these considerations, oral transmission of HIV remains low risk, underscoring the importance of discussing factors that contribute to increased susceptibility.

Oral Immune Activation during C. albicans and Oropharyngeal Candidiasis Infection

OPC, caused by opportunistic *C. albicans* infections, commonly occurs in individuals who are immunocompromised, often due to prolonged stays in sterile environments such as hospital intensive care units or using immunosuppressive therapies [45]. High-risk groups for OPC include patients with cancer, asthma, diabetes, and HIV [45]. The two groups most frequently affected by OPC are patients undergoing leukemia treatment and advanced HIV patients with CD4+ T cell counts below 350 CFU/mL, where 95% of advanced HIV patients experience OPC [18,46]. Hallmarks of both HIV and leukemia include the depletion of blood T cell counts, which is associated with patients experiencing OPC [46].

During OPC, the weakened immune system fails to maintain a healthy commensal relationship with *Candida* species [47]. An “optimal” oral microbiome consists of approximately 700 different prokaryotic species and 85 fungal genera, which facilitates fungal colonization to prevent fungal overgrowth [48]. Commensal colonization of *C. albicans* involves low rates of *C. albicans* adhesion to the oral epithelium and is associated with a low rate of hyphal growth [49]. *Candida* species exhibit three distinct morphologies: ovoid-shaped budding yeast cells, branching filamentous cells known as Pseudo-hyphae, and structures with true septa, parallel walls in between each cell, called hyphae [50]. In immunocompromised individuals, the optimal oral microbiota is not maintained, leading to oral "dysbiosis” [51]. This results in the flourish of *C. albicans* colonies, displacing protective microbes and adhering to the epithelium in large numbers [52]. Subsequent adhesion to the epithelium promotes a switch in morphology from yeast to hyphae resulting in the growth of long, filamentous appendages, allowing *C. albicans* to express hyphae-specific cell wall proteins, such as the hyphal wall protein 1, which aids in adhesion and invasion of the oral epithelium [17,50,53,54]. *C. albicans* invades the host epithelium in two ways: induced endocytosis and active penetration, which acts through the hyphal-associated adhesin Als3 and the physical forces from the hyphae. Als3 binds to E-cadherin, a tight junction protein between epithelial cells to facilitate uptake of the fungal cells by host cells [49,50,54,55]. In addition to invasins, hyphae cells secrete hydrolases such as aspartyl proteases (SAPs), which are associated with increased fungal virulence by promoting adhesion and hyphae formation *in vitro* [50,56,57]. OPC-causing *C. albicans* isolated from symptomatic individuals also produced greater levels of SAPs than those isolated from asymptomatic individuals, pointing to *C. albicans*-mediated epithelial disruption possibly elevating oral HIV susceptibility [4,56,58]. Thereafter, excessive *C. albicans* adhesion exacerbates epithelial damage by inducing inflammation through immune activation, physical penetration of the mucosa, and the release of hyphae-associated toxins such as candidalysin [50]. Physical penetration and receptor mediated endocytosis by hyphae causes the invagination of the epithelium, forming an “invasion pocket, where candidalysin accumulates, forms pores in the host epithelium, and triggers cytokine release [20,59,60]. Elevated cytokines, including IL-1α, IL-1β, IL-6, GM-CSF, and G-CSF, activate and recruit innate immune cells such as macrophages, neutrophils, and Th17 cells [20]. Normal immune responses against *C. albicans* include the activation of Th17 cells, which mediate antimicrobial peptide release, while recruiting and activating neutrophils in response to epithelial damage [49,61]. Subsequently, recruited neutrophils phagocytose *C. albicans* cells, followed by releasing ROS and NETs to clear *C. albicans* cells [43]. In contrast, resistant strains of *C. albicans* can curb the immune response to favor fungal persistence, leading to prolonged induction of Th17 cells and neutrophils, which are important HIV target cells [62]. Persistent recruitment and activation of common HIV immune cell subsets to the epithelium suggests a potential mechanism which *C. albicans* infection increases oral HIV risk.

Implications of Epithelial Disruption and C. albicans Infections

HIV and Oral Lesions

HIV is associated with several different oral manifestations, such as oral hairy leukoplakia and Kaposi sarcoma, that present with oral lesions [63]. Oral lesions are often considered an early sign of HIV infection, due to their association with lower CD4+ T cell counts and high plasma viral loads [64–66]. The risk of oral HIV acquisition upon exposure is also associated with the presence of oral lesions possibly by providing virions direct access to immune target cells within inflamed epithelium [11,67]. Oral lesions and

sores are amongst the most common symptoms of OPC, likely caused by the epithelial damage associated with *C. albicans* overgrowth and secretion of candidalysin [46]. Epithelial damage as a result of harboring lesions and sores may lead to increased inflammation that could be associated with increased presence of HIV target cells and further epithelial damage [3,5,20,62]. Therefore, the presence of oral candidiasis infections and increased risk of oral HIV transmission demands a more in depth understanding of the immune implications of *C. albicans* infection.

Epithelial Disruption by the Immune Response

Levels of MMP-9, a neutrophil associated protease, are associated with increased levels of the inflammatory cytokines IL-1ß, IL-8, IL-17, and MIP-1β in the female genital tract (FGT) [4]. Proteases mediate the cleavage of tight junctions, such as E-cadherin, between epithelial cells into its soluble form, which can be used as a biomarker of epithelial damage [20,68]. Notably, MIP-1β and IL-8 were linked to HIV risk in the genital tracts of South African females [7]. Persistent recruitment of neutrophils, especially by resistant strains of *C. albicans*, can result in increased tissue damage mediated by proteases and pro-inflammatory cytokines that may also influence oral HIV risk [4,7]. The breakdown of epithelial barriers and the recruitment of immune cells to a non-intact epithelium likely facilitates HIV access to target cells at the epithelium, heightening the risk of HIV infection [4]. Likewise, the breakdown of tight junctions, complexes of proteins that hold epithelial cells together to prevent passive diffusion of large molecules between epithelial cells, during an OPC infection could result in increased levels of pro-inflammatory cytokines such as IL-1α, IL-1β, and IL-6 [50,58]. Release of these cytokines aids in the recruitment of HIV target cells such as Th17 cells, neutrophils and macrophages [20]. Therefore, a possible synergistic relationship between the epithelial disruption and increased inflammation may increase risk of oral HIV transmission.

While the FGT and oral cavity environments differ, similarities in the structure of their epithelial layers may impact immune responses against mucosal infections in similar ways. Similarities also lie in its mechanism of infection, where Als3 is released by *C. albicans* during both OPC and vulvovaginal candidiasis infections [50,69]. Despite structural similarities, interactions between C. albicans and host epithelium do not explain all factors affecting OPC infection.

Oropharyngeal Candidiasis and the Oral Microbiome

Candida species, specifically *C. albicans*, is the most prevalent fungi species in the oral cavity [70]. Dysbiosis in the oral microbiome can contribute to the overgrowth of *C. albicans*, a condition often triggered by factors such as antibiotic use, immunosuppression from cytotoxic chemotherapy, and corticosteroid inhalers [52]. In addition to immune deficiency, collaborative interactions between *C. albicans* and mucosal bacteria can elevate the risk of infection [43]. For instance, *Streptococcus mutans* and *C. albicans* display synergy in colonizing the teeth in children via formation of inter-species biofilms [71,72]. These biofilms provide a structural shield, promoting cell adhesion, enhanced growth, and shared resource utilization, creating a cooperative environment that contributes to increased virulence and persistence [73–75]. Moreover, inter-kingdom biofilms enhance the ability for *C. albicans* to metabolize sucrose in the oral cavity, and the high intake of fermentable sugars provides significant advantages for fungal replication and toxin production [71,76,77].

Likewise, interactions between *C. albicans* and *S. oralis* can promote invasiveness and hyphae growth, while co-culture of *C. albicans* with *S. gordonii* increases biofilm resistance to antibiotics and antifungals, increasing the overall virulence of *C. albicans* through the up regulation of bacterial and fungal genes for carbohydrate and amino acid metabolism [70,78–80]. An increase in metabolic flexibility allows for better adaptation to host responses and changes in the environment during infection [50]. An example of metabolic flexibility being advantageous for a pathogen would be *C. albicans* upregulating genes involved in gluconeogenesis (pathway that produces glucose) when inside a macrophage [50,81,82]. Macrophages are a subset of immune cells that patrol the blood and many tissues that phagocytose damaged cells or foreign substances such as pathogens to kill them [50]. A macrophage kills the pathogens it swallows by exposing them to ROS as well as nutrient limiting conditions [50]. *C. albicans* can circumvent nutrient-limiting conditions by upregulating gluconeogenesis to provide energy for growth [50,81]. A flexible metabolism could allow for more persistent infection by allowing survival inside host macrophages [50]. However, not all oral microbes have a mutualistic relationship with *C. albicans*. For instance, *Lactobacillus johnsonii* inhibits the growth of *C. albicans in vitro*, suggesting that a higher presence of *L. johnsonii* in the oral cavity will likely lower the risk of developing OPC [74,83]. Nevertheless, interactions between different species of bacteria and fungi are more likely to occur only during immunosuppression [70].

Cross-kingdom biofilms are associated with an overall decrease in microbial diversity, and oral bacteria in the microbiome play a role in regulating production of type-1 interferon (IFN-1) signaling in dendritic cells to mediate viral infections [15,70,84]. A lower microbiome diversity is associated with a weaker IFN-1 response suggests that the diversity and composition of the oral microbiota might affect susceptibility to HIV through regulation of host immune responses [58,85,86].

The microbiome plays a pivotal role in modulating the immune system's activation [75]. Consequently, microbial dysbiosis induced by the overgrowth of opportunistic pathogens is believed to compromise the immune response against bacterial-Candida biofilms, potentially resulting in chronic inflammation [70,75,87]. However, the intricacies

of host interactions with bacterial-Candida biofilms vary across specific niches, presenting challenges in studying host defenses against these biofilms [70].

Co-infection by *C. albicans* and *S. oralis* results in an increased release of neutrophil activating cytokines, including IL-17, TNF, IL-1a and IL-1ß [70,72]. In general, polymicrobial biofilms are considered to elicit a more robust immune response than an infection caused by *C. albicans* alone [87]. This heightened immune response is attributed to the greater number of microbial species interacting with host immune cells, potentially leading to an increased presence of immune cells in the oral epithelium during infection, which could enhance susceptibility to HIV [70,88].

Overall, the impact of microbial commensals on OPC infections can vary depending on the composition of the microbiota [70]. The presence of diverse bacterial commensals can result in inter-kingdom biofilms that synergistically improve the growth of both microbial colonies, leading to oral dysbiosis and disruption of the immune response [70]. Subsequently, Candida species may gain increased resistance to anti-fungal medications, increased penetration and growth of hyphae and improved metabolism [70,80,89]. Additionally, presence of additional microbial species induces a greater inflammatory response, potentially increasing HIV risk by allowing for easier penetration of HIV virions into the epithelial layer [70,87].

Limitations and Future Perspectives

OPC infections have been linked to an increased risk of oral HIV transmission. However, the scarcity of studies investigating the association between OPC and HIV transmission impedes the establishment of direct causal relationships. The relatively infrequent incidence of oral HIV transmission has led to a lack of comprehensive research in this area. Consequently, the limited body of evidence impedes the formation of definitive conclusions regarding the precise mechanisms of infection. Additionally, the paucity of reports detailing the impact of inflammation on the integrity of the oral epithelium further constrains the depth of conclusions that can be drawn. Despite these challenges, the significance of understanding how OPC infections may influence HIV transmission should not be overlooked.

Conclusions

OPC typically emerges as an opportunistic pathogen during periods of immunosuppression, immunodeficiency, or microbial dysbiosis. This review suggests that OPC could heighten susceptibility to HIV by augmenting the presence of target cells at the epithelium, compromising epithelial integrity, and reducing oral bacterial diversity. In essence, OPC has been associated with various factors that might increase vulnerability to oral HIV transmission. Despite this correlation, limited research has ventured into this domain. This review calls for future studies that strives to elucidate the immune mediators specific to increased risk for oral HIV acquisition, highlights the crucial roles of the innate defense offered by the epithelial barrier, and provides further understanding of the oral microbiome in the context of transmissible diseases. These topics can be further explored by comparing the rate of oral HIV transmission in two individuals: one with wild type virulent *C. albicans* and the other with key adhesins or invasins knocked out. Additionally, oral HIV transmission can be compared between individuals with OPC infections and co-infections with some *Streptococcus* species. Therefore, it will be important to keep in mind the relationship between OPC and the innate immune barrier and microbiome in the oral cavity.

List of Abbreviations Used

FGT: female genital tract
G-CSF: granulocyte colony stimulating factor
GM-CSF: granulocyte macrophage colony stimulating factor
Gp340: salivary agglutinin 340
HIV: human immunodeficiency virus
IFN: interferon
IL: interleukin
MIP-1β: macrophage inflammatory protein 1 beta
NETs: neutrophil extracellular traps
OPC: oropharyngeal candidiasis
ROI: receptive oral intercourse
ROS: reactive oxygen species
SIV: simian immunodeficiency virus
SLPI: secretory leukocyte protease inhibitors
STIs: sexually transmitted infections
Th17 cells: T helper 17 cells
TNF: tumor necrosis factor

Conflicts of Interest

The authors declare that they have no conflict of interests.

Ethics Approval and/or Participant Consent

This review article did not require ethics approval, and no participants were used to synthesize findings.

Authors' Contributions

CK: Made substantial contributions to the concept and design of the study, acquisition, analysis, and interpretation of data, drafting and revised critically for important intellectual property, final approval of the version to be published, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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