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Independent Reading Assignment
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Spring 2012

HIV/AIDS Impact on the Oral Cavity

Abstract

Examining the connection between HIV/AIDS, the oral cavity microflora, and overall oral health will help in understanding the role of the microbiome in HIV/AIDS infected individuals. The microflora of the oral cavity is influenced by HIV/AIDS, impacting the colonization of microorganisms by preventing the commensal bacterial from being able to fight the pathogenic microbes(2). HIV, or the Human Immunodeficiency Virus, is a retrovirus that disrupts the immune system's ability to protect the body, in time causes Acquired Immune Deficiency Syndrome, or AIDS. The viruses break down the immune system by attacking helper T cells preventing them from protecting the body by breaking down infected cells (7). Overall health of the immune system is affected by oral, gut, penile, vaginal mucosal bacteria that are in symbiotic relationship, in which one species is benefited while the other is unaffected. (12) The impact that HIV/AIDS has on the microflora of the oral cavity has been observed in levels of *S. mutans*, total *Lactobacillus species*, and total *Candida* species in saliva to be higher in HIV infected then HIV negative individuals (12). Increase the risk for common dental conditions including dental caries, and gingivitis, along with HIV-related infections including hairy leukoplakia and varying oral lesions (6).

Human Microflora

The human microbiome involves all the microbes, their genomes, and environmental interactions in a defined environment (2). The microbiota is the microorganisms in region of the body (2). The oral microflora is the bacterial population in the oral cavity (2).While there is generous amounts of information on human cells, microbes, which are more plentiful in the human body, are less understood (2). Characterized as anaerobic bacteria, they live in areas with little or no oxygen and are able to be either pathogenic or opportunistic depending on the environmental state of the immune system (12)(10). Recognized as bacterium, fungi, protozoan or virus, microbe origins are microscopic life forms (12). That are found throughout varying interior and exterior environments of the body which include the oral and nasal cavities, stomach, intestines, urinary tract and skin. For a healthy individual, all organisms work in a harmonized environment, but when there is a decrease in an individuals' immunity, pathogenic organisms thrive (12). HIV/ AIDS infections and their influence on an individuals' immunity brings interest in observing why and how they have an impact on the human microbiome.

To further understand HIV/AIDS infections and its impact on the human microbiome, the field of metagenomics was developed. In recent years, metagenomics research indicated, with the use of molecular methods that there is over 400 species of bacteria in the oral cavity but so fare only 150 of them have been able to be cultured in a lab and been cataloged with scientific names. Metagenomics looks at samples of microbial communities obtained from varying environments to analyze sequencing, along with obtaining data to further study the influence HIV/AIDS has on the human body (2) (4). A clearer knowledge of microbial community genetic

material will providing more information regarding microbial characteristics. Advances in DNA sequencing technology has allowed for the development of metagenomics to characterize and better understand the microbial communities' locations and impact on the oral and nasal cavity, intestinal tract, excretory system, skin, and throughout the body (2). Several organizations worldwide, similar to that of the Human Genome Project, are working on this mission (2). This ongoing process of analyzing and creating a clearer understanding of the human genetic material is the goal of organizations like the HGP and other groups (12). As research obtains more information regarding the influences that microorganisms have on the health and presence of disease, clearer understanding of the impact microorganisms have on the composition of the microflora will be achieved.

Oral Cavity Characteristics

The oral cavity is the initial area where the exterior environment is able to interact with the inner environments of the body, allowing for microorganisms found in the oral cavity to be introduced in other areas of the body. This occurs due to the oral cavity's connection to the rest of the body, allowing air to travel through the mouth and nose to the lungs (2). Nutrition and water are introduced to saliva, and these microorganisms aid in nutritional breakdown and absorption, continuing to travel down for further digestion (4). Bacteria that colonizes the oral cavity has a wide range of environments consisting of the tongue, cheeks, hard/ soft palates, teeth, gums, lips and tonsils, which are all environments that harbor varying microbial organisms (2). These habitats and their varying colonization of the microorganisms, makes up the

microflora of the oral cavity. Evaluating different habitats in the oral cavity has made it clear that there is a link between the colonized communities of microorganisms and how they are influenced by the variation in the tissue structures (5). This allows for a wide amount of organisms to colonize, causing common dental infections like dental caries and gingivitis because of the bacteria that colonizes those areas. Not only can there be an increase in the prevalence of common dental problems, but it has been observed that individuals with HIV/AIDS have developed infections like oral hairy leukoplasia, and various oral lesions. There is a correlation between individuals that have an inability to maintain proper oral hygiene, and negative health implications such as heart attacks and suppressed immune system (6). Understanding the organisms found in the oral cavity and their relationship to various diseases, can aid in the further understanding of what influences the ability for infections to occur in the oral cavity.

Oral Microbiota/ Biofilms

Within the oral microbiota, there are a range of environmental conditions that contribute to species composition of biofilms present at each area. These varying conditions including pH, temperature, redox poetical, salinity, atmospheric conditions, and water involvement with saliva (18). Biofilms are a thin film of bacteria that is attached to the surfaces of the oral cavity (2). Dental plaque has many types of biofilms which include biofilms that form on the surface of the teeth and above the gingival where the gum meets the tooth. Other locations that have varying oral microbiotas are the subgingival plaque, tongue, fillings, and mucosal surfaces (17). Different

species of microorganism find surfaces in each of these microenvironments (18). The classification of the different microorganisms is based on their oxygen requirements, these groups include obligate anaerobes, needs no oxygen to grow, obligate aerobes, needs oxygen to grow, facultative anaerobes, little oxygen to grow examples incude streptocci and Actinomyces, microaerophiles, species that grow best at low O2 conectrations, and capnophiles, species that grow best at high CO2 concnetrations (18). Environmental conditions impact the amount of biofilms, for example saliva flow in the oral cavity. Formation of biofilms occurs by initial surface attachment to the primary colonizer, which results in accumulation of microbial, that is one molecule think (18). Following this, migration of early colonizers form multilayered microcolonies (2). The primary colonizers in the oral microbiota for both tooth surface and mucosal are usually streptococci, which account for 80% of early biofilm (18). Salivas is important because it is used by the oral biofilms as a way for delivery, bringing nutrition, partially dissolved carbohydrates and peptides (18). Other functions that saliva does includes, lubrication for digestion, regulation of temperature and defending the host (18). The oral microbiota also has other challenges that other microbiota do not have, which involves the host taking good personal hygiene. In response to eating, tooth brushing, salivating, flossing, and tongue movement the oral microbial communities have evolved so that they can survive (18).

Immune Cells in the Oral Cavity

The oral cavity is made up of an array of immune cells that are both intraepithelial, inside the layer of cells that makeup the lining of the oral cavity, and submucosal, connective tissue underneath the mucous membrane. These immune cells have CD4 and CCR5 chemokine

receptors, which are on the surface of the immune cells and help to mediate entry of HIV into the cell. CD4, helper T cells with CD4 receptors and CD8, killer T cells with CD8 receptors are present intraepithelial cells (15). Intraepithelial Langerahans cells are CD4 and CCR5 positive, and in the oral mucous membranes lining of the inside of the mouth, in large amounts (15). The cellular mechanisms by HIV has been closely studied, but these interaction are complex and not fully clear (15). Current knowledge is very basic but it has been understood that the mode of transmission of AIDS in humans is by exposure of HIV and HIV infected cells to mucosal surfaces (16). When epithelial barriers are harmed it is possible for virus entry across any mucosal surface (16). Although HIV can use different strategies when infecting the human host via mucosal surfaces, HIV transmission at muscosal surfaces will have common actions, including survival of HIV or HIV infected cells in mucosal secretions, interaction of HIV or HIV infected cells with epithelial cells, transport of virus across epithelium, and initial infection of CD4+/chemokine receptors+ target cells in the submucose (15).

HIV Effects Immune Cells

There is limited information regarding the effect that HIV infection and contact has on epithelial cells. Whether or not oral epithelial cells can be infected by HIV continues to be explored in several studies (15). Oral epithelial cells that have been studied in vitro, have shown that they do not express CD4, but instead express galactosylceramide (GalCer), which is a sphingolipid, along with expressing HIV co-receptor CCR5 and/or CXCR4 (15). Other studies have shown that there is no evidence of HIV infection in oral epithelial cells. It has also been shown that primary epithelial cells isolated from adenoids were susceptible to both cell-free and

cell-associated virus (15). These along with other studies have only uncovered limited information but demonstrate that epithelial cells of the oral cavity can influenced by HIV by cell-borne virus in the absence of CD4 (16). Along with understanding that the mechanisms of infection must be from GalCer and the CXCR4 co-receptor receptor and not by CD4 or CCR5 receptors (15).

Immune deterioration with the decrease of CD4 cell count has been inked to the presence of HIV associated oral lesions (4). An increase of the present of human papilloma virus, salivary gland disorder, and xerostomia has been seen with the use of HAART. It has been observed that there is a decrease in oral candidiasis, oral hairy leukoplakia, and HIV associated periodontal diseases after HAART (4)(2). This observation have possibly associated with the difference in oral health care, social and demographic, mode of transmission of HIV, immune state, and the oral microbiome formation. The stage and influence of HIV has been indicated by the presences of oral infections (4).

Saliva

The oral cavity has a low presence of HIV-1 in saliva, making it less common for HIV transmissions in the mouth. Whole saliva has been thought to be a factor in causing of the breakdown of the HIV infected cells by distorting the cell membrane (10). Saliva is produced mainly from salivary glands, by the parotid glands, and submandibular glands and consists mostly of electrolytes, water, enzymes, and glycoproteins (4). Two types of protein secretions are present in saliva. These include a mucus secretion, which lubricates mucosal surfaces,

consisting of mucins and a serous secretion, containing digesting starch enzymes (9). The most important source of IgA antibodies is from the salivary glands located in the upper respiratory and gastrointestinal tracts (10). Iga is the main mechanism for providing local immunity against infections and acts by reducing the binding between an Iga coasted micro organism and a host epithelial cell (15). Mucosal Iga is possibly thought to act agains HIV in many ways including, direct neutrolization of HIV, inhibition of HIV enzyme activity, inhibition of attachment of HIV to its epithelial or other cell receptor, or occurring through or across an epithelium movement of HIV(15). It is now understood that salivary Iga can block epithelial transcytosis of HIV across epithial cells (15). IgA antibodies are also found in the nose, ears, eyes, digestive tract, tears and saliva that protect the surface of the body that is exposed to foreign substances (9). Additionally, other glands located on the tongue and in the mucosa of the tongue, palate and lips as well as other areas of the oral cavity help to generate saliva (8).

Types of saliva produced are whole and parotid saliva. Whole saliva is the saliva produced from the major and minor salivary glands along with oral mucosa, periodontium and oral microflora that represents the composition of whole saliva (9). Parotid saliva is produced from the parotid glands and does not contain mucinis making it less viscous then other saliva (8)(9). Whole saliva consists mainly of IgA and there are higher amounts of IgA, IgG, and IgM in whole saliva than found in parotid saliva (9). Igs in whole saliva must not be produced from parotid salivary glands but from another gland. Individuals with HIV/AIDS have a decrease in the rate of antibody secretion which is caused by lower levels of anti-fungal antibodies in saliva (9). Several factors that have anti-HIV activity have now been reported in saliva but not fully clear if they have activity in vivo. The factors include mucins, SLPI, lactoferrin, proline-rich

proteins, and cystatins, as well as specific antiviral activity residing in secretory Iga. Saliva composition is important when evaluating HIV/AIDS infected patients because its production helps prevent virus, pathogenic bacteria and food particles from forming on the surfaces in the oral cavity.

HIV Salivary Glands

Patients that have HIV are commonly observed to have dry mouth, which is normally demonstrated in early stages of HIV infection with the decrease of salivary flow (10). Dry mouth is reported in HIV infected individuals that have more than 100,000/mm3 load of viral mRNA load (9). Individuals that have dry mouth, or xerostomia, are encouraged to be evaluated for HIV infection because of the connection. Evaluating the relationship between HIV and dry mouth, HIV positive patients who exhibit dry mouth and taking immunosuppressive drugs, needs to be further observed to determine if the infection, treatment or both are causing the dry mouth. (10). The combination of xerostomia and the decrease of saliva production from salivary glands caused by the use of immunosuppresive drug has been evaluated in women, which showed that the CD4+ cell count is much higher in women positive for HIV-1 than women at risk for HIV infection (9).

When saliva production is compromised, it is common to see enlargement of the salivary glands, and a change in saliva composition. When salivary glands become swollen in either one or both parotid glands, an individual is considered to have HIV-Associated salivary gland disease

(8). Enlargement of the salivary glands can be one of the first indications of an HIV infection, followed by inflammatory conditions, and lastly by neoplastic lesions (abnormal cell growth) (9). The parotid gland is affected by swelling on either slide along with lymph nodes disease, and diffuse infiltration lyphocytosis syndrome, which is a condition when there is a low CD4 count along with presences of CD8+ lymphocytosis and lymphocytic infiltration (8)(9). Infection and inflammation of salivary glands are the second common disorder next to neoplastic lesions in individuals infected by HIV (9).

Oral Lesions

Oral infections, along with the concentration of T cells, help to determine immune system health. They are both an important tool in understanding the impact that HIV and other infections have on the microbiome. Early signs of HIV infection have been seen in the oral cavity as oral candidiasis, which is a fungal infection on the mucous membrane, mostly seen in younger patients (8). Oral hairy leukoplaskia, is another early indication of HIV found in the oral cavity, which is indicated by a hairy gray or white patches found on the inside of the cheek or on the sides of the tongue (4)(8). Other common oral lesions caused by HIV are Kaposi's sarcoma, herpes virus, and aphthous (3). The microflora diversity of the oral cavity is affected with individuals that have a suppressed immune system. Individuals with oral candidiasis and oral lesions are seen to have a major decrease in their CD4+ whitened cell counts (lymphocyte) along with a lower ratio of CD4/CD8 lymphocyte compared to individuals without lesions (8). A continued decrease of CD4 lymphocyte count increases HIV viral infections in the blood,

making it important for detection and treatment of oral lesions during early stages of HIV infection (8).

Oral HIV Fungal Infection: *Oral Candidiasis*

Oral Candidiasis is a fungal infection commonly involving the oral mucosa caused by Candida albicans, a yeast like fungal organism . The yeast mainly uses the dead cells that are on the surface of the mouth's lining. Oral candidiasis is not like other infections because it is only found on the outer surface of the humans body and does not goes into the body (17). There are three main variation of oral candidiasis, which include pseudomembranous candidiasis, erythematous candidiasis and angular cheilitis (17). Pseudomembranous candidiasis causes a creamy white patches on any mucosal surface of the oral cavity, is easily rubbed off leaving bleeding or redness (17). Erthematous candidiasis is commonly present as multiple flat, red pates on the palate, dorsum of the tongue, and sometimes seen on other intraoral mucosal areas. These lesions at times can be hard to identify from other red lesions (17). Angular cheilitis apears as cracks or diffuse redness at the corners of the lips. All variation of oral candidiasis many occur at the same time.

Oral candidiasis has been reported to be one of the most common oral lesions in all stages of HIV-1 infected individuals (8). In children who are identified as HIV positive, and have a high level of gingival inflammation as well as a high concentration of plaque and developed caries are frequently seen to also have oral candidiasis (8). Among older populations

of patients with AIDS, around half of them have been seen to have three times more of one or more oral lesions, especially with denture use (8). Early HIV infected individuals are more likely to have oral candidiasis, a fungal infection of the oral cavity primarily colonized by *candida albicans* yeast in HIV infected and healthy individuals throughout the world (8). Oral pseudomembranous candida, normally seen in more developed HIV/AIDS individuals has been used as a way to define the severity of HIV infection, leading to Erythematous candidiasis and progressive oral candidiasis. When observing the relationship between the varying types of oral candidosis and their presence in the oral cavity of children and adults, influencing factors where noticed for each population. Oral candidacies in children around the world varies from 22.5 - 83.3%, with pseudomembraneous candidosis being the most common, followed by erythematous candidosis. In adults, candidal infection ranges from 1.5 - 56%, with a high prevalance in less developed countries (8). The most common oral candidosis in adults is pseudomembraneous candidosis with a 55.8 - 69.7%, erythematous candidosis ranges from 25.7 -50%, leading to hyperplastic candidosis ranging from 0 - 1.7% (8). The range in the prevalence of oral candidoses is thought to be caused by clinical evaluation method, demographic, and clinical variation in study populations.

Oral HIV Viral Infection: *Oral Hairy Leukoplaskia*

Oral hairy leukplaskia lesions are commonly found on the border around the tongue in immuno compromised individuals and patients with advanced untreated HIV disease, which is a clinical identification of the Epstein-Barr virus infection (14). These oral lesions are

found in 0.42% - 34% of HIV infected adults around the world, mainly connected with HIV-1 homosexual male interaction (8). Oral hairy leukoplaskia produces slowly with little to no symptoms, along with not being life threatening; and therefore in some situations is not treated (8) . During the development of hairy leukplaskia, EBV replicates and undergoes genetic recombination and sequence mutation. Leading to a wide range of multiple EBV strains, sub strains and recombinant variations being produced (14). EBV genes that are related to EBV infection are expressed during EBV replication in hairy leukoplakia. Products of EBV gene may cause cellular variations, causing changes in hairy leukoplaskia tissue (14). These variations in hairy leukoplakia are influences by break down of the immune system. Treatment of oral hairy leukoplaskia is not vital but acyclovir and valacyclovir have been used to inhibit DNA replication, preventing the viruses from replicating (8). An increasing of hairy leukplaskia is thought to be caused by higher incidences of EBV, high HIV load, and lower CD4+ count (14). A decrease in the prevalence of hairy leukoplaskia has been seen with the advancement in highly active antiretroviral therapy treatment.

HIV Impact on Common Dental Conditions

HIV has a significantly impacted on the individuals' oral cavities' ability for bacteria to colonize in the saliva, making them more prone to common dental problems including dental caries, and gingivitis (4). A study that looked at the impact of intensified dental care on outcomes in HIV infection evaluated a population of individuals. The study group had an age range from 19 to 45 years and was located in Portland, Oregon. The goal was to evaluate the

effect that standard care or enhanced care dental treatment plan would have on the impact of an individual's oral/dental health on patients infected by HIV (1). Individuals were evaluated that had at least 20 teeth intact, along with a CD4 count between 100 and 500, and are not on any intensive medical treatments (1). This stipulation guaranteed that the microflora of the oral cavity would not be altered by any unknown effects was meant to have the least amount of variability that could have an impact on the oral cavity. Each individual was evaluated with a basic dental examination along with completing a questionnaire providing further information. Chosen at random, each individual was informed if they would be in a standard care or an extensive care study group. There were 376 HIV infected individuals that partook in the study, with 185 in the base care treatment group, and 191 in the extensive care group (1). The basic care treatment group individuals were seen for prophylaxis treatment and normal checkups unless they needed addition treatment time. Individuals in the extensive care treatment group were seen similarly as the standard care groups, and had additional prophylaxis treatment every two months, along with personal hygiene twice daily, and an in home care regiment of chlorhexidine antiseptic mouth rinses (1).

Patients' exams were performed to collect information on the state of the oral cavity by evaluating the presence of dental caries using the DMFS index, which evaluated the surface of the tooth for decay, indication of filling or missing teeth. Other common dental conditions were also evaluated including measuring the amount of inflammation by using the gingivitis index which indicates periodontal disease. Data was also collected regarding the presence of oral lesions including herpes, and hairy leukoplaskia along with other oral conditions including candidiasis a fungi infections and Kaposi's lymphoma, a cancer (1). The most common oral

lesions in this study population was hairy leukoplaskia and candidiasis because of this the data was ranked on a scale of zero indicating that there was not a presence of these types of lesions (1). Besides the patients receiving dental care, they completed questionnaires during the time of initial baseline data collection, and during the six month and twelve month dental visits. This questionnaire was administered to obtain information regarding the patient's social and financial state, general medical history, and indication of HIV/AIDS condition. Once the data was collected, it was understood that the final number of patients in the trial decreased to 262 patients completing the experiment, this was allotted to patients moving or dropping out because of lack of interest in the research (1). Over all, patients who were treated with chlorhexidine mouth rinses were seen to have a decrease in inflammation of gums and reduction of gingivitis. Even though there was better oral health, patients with HIV/AIDS infection had a higher level of dental and periodontal disease. This study indicated that patients with HIV/AIDS can reduce dental and periodontal disease by following more strict dental treatment plans to provide an overall better health.

Current State of HIV Treatment

Treatment of HIV disease has made great advancements, contributing to the decline in the amount of deaths related to AIDS, but at the same time an increasing number of individuals living with HIV (12). Antiretroviral therapy treatment or highly active antiretroviral therapy is used for an HIV positive person to maintain health and extends the individuals' best quality of life (4). It does this by inhibiting the replication of the HIV managing and hindering possible

infections (12). There are four classes of antiretroviral agents, non0nucleoside analog reverse transcriptase inhibitors, entry inhibitors, nucleoside analog reverse transcriptase and protease inhibitors. Entry inhibitors, the newest agent, blocks HIV entry into the host cells which includes corrector inhibitors, attachment inhibitors, and fusion inhibitors (12). Combination treatments are indicated when there is the use three or more drugs, which are meant to decrease the level of HIV to a less harmful and more manageable level, leading prolonged life expectancy (12). Even though Antiretroviral therapy is an effective method for reducing viral replication, there is still incidences of recurrences of viral replication (4). The main reason for viral resistance is caused by drug toxicity and an ineffective drug.

Conclusion

The pathogeneses of HIV infection in the cellular and molecular functions of the salivary glans, and oral mucosa requirer continues studying. The immune system of the oral cavity illustrates the primary function in protecting the salivary glans, teeth, gingival and other area of the mouth from pathogenic viral and bacterial infections. Oral indication of HIV infection are visual signs that are observed and are informative of sever immune failure and disease progression. Oral examinations are an essential component for early recognition of diseases progression. A better understand of the oral immune mechanisms should help in slowing down, improving and preventing viral and bacterial infections. Additional studies need to be taken to observe the oral microflora which could lead to development of vaccines that could aid in increasing the other all outcome of oral health.

References

(1) Brown, Jonathan Betz, David Rosenstein, John Mullooly, Maureen O'Keeffe Rosetti, Steven Robinson, and Gary Chiodo. "Impact of Intensified Dental Care on Outcomes in Human Immunodeficiency Virus Infection." *AIDS Patient Care and STDs* 16.10 (2002): 479-86. Web.

(2) Dewhirst, F. E., T. Chen, J. Izard, B. J. Paster, A. C. R. Tanner, W.-H. Yu, A. Lakshmanan, and W. G. Wade. "The Human Oral Microbiome." *Journal of Bacteriology* 192.19 (2010): 5002-017. Web.

(3) Greenspan, John S. "Oral Manifestations of HIV Infection." *Oral Surgery, Oral Medicine, Oral Pathology* 73.2 (1992): 142-4. Web.

(4) Gennaro, Sussan, and Sudeshi Naidoo. "Oral Health & HIV/AIDS." *The American Journal of Maternal/Child Nursing* 33.1 (2008): 50-57. Web.

(5) Herzberg, M. C., A. Vacharaksa, K. H. Gebhard, R. A. Giacaman, and K. F. Ross. "Plausibility of HIV-1 Infection of Oral Mucosal Epithelial Cells." *Adv Dent Res* 32.1 (2011): 38-44. Web.

(6) Jeganathan, Sarangapany, and Marijka Batterham. "Predictors of Oral Health Quality of Life in HIV-1 Infected Patients Attending Routine Care in Australia." *Journal of Public Health Dentistry* 71 (2011). Web.

(7) Kanwar, Bittoo, David Favre, and Joseph M. McCune. "Th17 and Regulatory T Cells: Implications for AIDS Pathogenesis." *Current Opinion in HIV and AIDS* 5.2 (2010): 151-57. Web.

(8) Leao, Jair C., Camila M. B. Ribeiro, Alessandra A. T. Carvalho, Cristina Frezzini, and Stephen Porter. "Oral Complications of HIV Disease." *Clinics* 64.5 (2009). Web.

(9) Lu, F.X., and R.S. Jacobson. "Oral Mucosal Immunity and HIV/SIV Infection." *Journal of Dental Research* 86.3 (2007): 216-26. Web.

(10) Navazesh, M., R. Mulligan, J. Pogoda, D. Greenspan, M. Alves, J. Phelan, J. Greenspan, and J. Slots. "The Effect of HAART on Salivary Microbiota in the Women's Interagency HIV Study (WIHS)." *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology* 100.6 (2005): 701-08. Web.

(11) Mulligan, R., H. Seirawan, M. E. Alves, M. Navazesh, J. A. Phelan, D. Greenspan, J. S. Greenspan, and W. J. Mack. "Oral Health-related Quality of Life among HIV-infected

and At-risk Women." *Community Dentistry and Oral Epidemiology* 36.6 (2008): 549-57. Web.

(12) Saxena, Deepak, Yihong Li, Liying Yang, Zhiheng Pei, Michael Poles, William R. Abrams, and Daniel Malamud. "Human Microbiome and HIV/AIDS." *Curr HIV/AIDS Rep* (2011). Web.

(13) Tami-Maury, Irene, and James Willig. "Contemporary Profile of Oral Manifestations of HIV/AIDS and Associated Risk Factors in a Southeastern US Clinic." *Journal of Public Health Dentistry* (2011). Web.

(14) Walling, Dennis M. "Oral Hairy Leukoplakia: An Epstein-Barr Virus-Associated Disease of Patients with HIV." *The Center for AIDS* (2000). Web.

(15) Challacombe, S.J., and J.R. Naglik. "The Effects of HIV Infection on Oral Mucosal Immunity." *Advances in Dental Research* 19.1 (2006): 29-35. Web.

(16) Glick, M. "Oral Manifestations Associated with HIV-related Disease as Markers for Immune Suppression and AIDS." *Oral Surgery, Oral Medicine, Oral Pathology* 77.4 (1994): 344-49. Web.

(17) Reichart, Peter A. "Oral Manifestations in HIV Infection: Fungal and Bacterial Infections, Kaposi's Sarcoma." *Medical Microbiology and Immunology* 192.3 (2003): 165-69. Web.

(18) Avila, Maria, David M. Ojcius, and Özlem Yilmaz. "The Oral Microbiota: Living with a Permanent Guest." *DNA and Cell Biology* 28.8 (2009): 405-11. Web.