ORAL MANIFESTATIONS IN THE ERA OF HAART

Gail Cherry-Peppers, D.D.S, M.S.
Christine O, Daniels, R.N.
Valli Meeks, D.D.S, MS.
Charles F. Sanders, D.D.S.
David Reznik, D.D.S.

AIDS has reached epidemic proportions in the United States, disproportionately affecting African-Americans and other minorities. As highly active antiretroviral therapy (HAART) have improved the length and quality of life for HIV-infected people, oral health care has made similar strides. It is important that physicians and dentists recognize the earliest signs and symptoms of HIV infection in order that a timely diagnosis and patient referral can be made for early counseling testing, and treatment. At the same time, dentists have seen themselves at considerable risk from HIV infection. Some dentists believe that they may also be more at risk from stigma than other providers if they treat HIV patients.

Key words: HIV/AIDS ♦ dental care ♦ HAART

The 20th year of HIV/AIDS is a milestone in the fight against HIV/AIDS. Since the first acquired immunodeficiency syndrome (AIDS) cases were reported in 1981, AIDS has caused approximately 22 million deaths worldwide. In the United States, approximately 400,000 persons have died, and approximately 1 million persons have been infected[1]. The CDC estimates that 1 in 50 black men and 1 in 160 black women are infected with HIV, meaning that blacks are 10 times more likely to be diagnosed with HIV, and 10 times more likely to die of AIDS[1].

Highly active antiretroviral therapy (HAART) have improved the length and quality of life for the HIV-infected person. The epidemic has affected all aspects of primary care [1,2,3,4] . This report outlines some of the oral health changes of the HIV-infected patient since the advent of HAART and other drug treatment regimen.

Oral manifestations of HIV infection are a fundamental component of disease progression and occur in approximately 30 to 80 percent of the affected patient population.[5,6,7] Factors which predispose expression of oral lesions include CD4 counts less than 200 cells/mm^3, viral load greater than 3,000 copies/mL, xerostomia, poor oral hygiene and smoking.[8,9]

The overall prevalence of oral manifestations in HIV disease has changed since the advent of HAART. One study noted a reduction of oral lesions from 47.6 percent pre-HAART to 37.5 percent during the HAART era[7]. The details of this study included a significant reduction in oral hairy leukoplakia and necrotizing ulcerative periodontitis, yet there was no significant change in the incidence of oral candidiasis, oral ulcers and Kaposi's sarcoma. This population did, however, see an increase in salivary gland disease. Other

published reports show a marked increase in the number of oral warts in the HAART era. [10, 11]

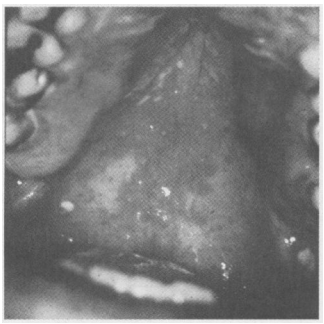
A study of 1,424 adults who participated in the AIDS Cost and Utilization Study revealed that only 9.1 percent reported treatment for oral manifestations. After adjusting for CD4 count and other variables, African-Americans and Hispanics were significantly less likely to receive treatment. Factors which were significant for the receipt of oral health care included more than a high school education, participation in clinical trials and utilization of counseling services.[12] The ability to differentiate one manifestation from another, and to manage some of the more common conditions are fundamental to the overall health care of this patient population. Oral lesions are differentiated as fungal, viral and bacterial infections, neoplasms such as Kaposi's sarcoma and non-specific presentations such as aphthous ulcerations and salivary gland disease.

The following discussion will cover the most commonly seen oral manifestations seen in association with HIV infection (Table 1).

FUNGAL INFECTIONS

The most common fungal infection seen in association with HIV infection is oropharyngeal candidiasis. There are three frequently observed forms of oral candidiasis: erythematous candidiasis, pseudomembranous candidiasis and angular cheilitis.

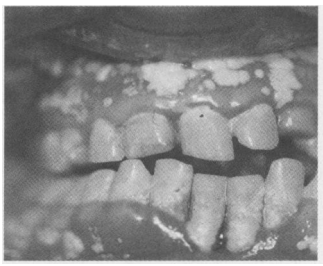
Erythematous candidiasis presents as a red, flat, subtle lesion either on the dorsal surface of the tongue and/or the hard/soft palates.



Erythematous candidiasis on palate with areas of pseudomembranous candidiasis.

Erythematous candidiasis tends to be symptomatic with patients complaining of oral burning, most frequently while eating salty or spicy foods or drinking acidic beverages. Clinical diagnosis is based on appearance, taking into consideration the person's medical history and virologic status. The presence of fungal hyphae or blastospores can be confirmed by performing a potassium hydroxide preparation. Although erythematous candidiasis has been identified as one of the more common oral manifestations seen in association with HIV disease, this presentation is frequently under-diagnosed. [8] Due to the limited nature of this infection, treatment involves the use of topical antifungal therapies.

Pseudomembranous candidiasis appears as creamy white curd-like plaques on the buccal mucosa, tongue and other oral mucosal surfaces that will wipe away, leaving a red or bleeding underlying surface. The most common organism involved with the presentation of candidiasis is Candida albicans, however there are increasing reports of the increased incidence of non-albicans species. [13]



Pseudomembranous candidiasis on alveolar mucosa. Note destruction of soft tissues due to necrotizing ulcerative periodontitis in mandibular anterior.

Like erythematous candidiasis, diagnosis of pseudomembranous candidiasis is based on clinical appearance while taking into consideration the person's medical history. Potassium hydroxide preparation, fungal culture or biopsy, may be useful in obtaining an accurate diagnosis.

There has been a decline in the occurrence of pseudomembranous candidiasis in patients who are on successful highly active retroviral regimens containing protease inhibitors. A review of the literature suggests that immune reconstruction alone does not account for this reduction, but rather the added effect of protease inhibitors on candidal virulence factors such as aspartyl protease.[14]

Whereas there has been a decline in the preva-

Table 1. RECOGNITION AND MANAGEMENT OF THE ORAL MANIFESTATIONS OF HIV/AIDS

Oral Manifestation	Description	Treatment Options
Erythematous Candidiasis	Red, flat subtle lesion, usually found on the dorsal surface of the tongue and/or the hard or soft palate. Lesion tends to be symptomatic with patients complaining of burning or sensitivity.	Topical antifungal therapy: Clotrimazole troches 10mg (dispense 70, Dissolve 1 troche in mouth 5 times a day for 2 weeks); Nystatin oral suspension 500,000u (Hold 1 teaspoonful in mouth for 5 minutes, 4 times/day for 2 weeks)
Pseudomembranous candidiasis	White, off-white or yellow patches which can appear anywhere within the oral cavity. These lesions will wipe away leaving a red and/or bleeding surface. Treatment depends on the extent of disease.	Mild to moderate presentations, see topical antifungal therapy. Moderate to severe presentations: Fluconazole 100mg (dispense 15, 2 tabs on day 1, then 1 tab for the rest of the 2 week treatment time).
Angular cheilitis	Cracking or fissuring at the corner of the mouth.	Ketoconazole 2 percent cream (dispense 30gms, apply to affected area 4 times a day for 2 weeks).
Oral Hairy Leukoplakia	White corrugated lesion normally appearing on the lateral border(s) of the tongue that does not wipe away.	Treatment is not usually required. High dose (4gms/day) acyclovir can be used for temporary relief.
Oral Warts	Published reports indicate increased frequency of oral warts due to Human Papillomavirus in HIV+ patients. This manifestation presents as papillary lesions of normal mucosal color or hyperkeratotic. Recurrence after removal is common.	Cryotherapy or surgical excision. For lesions on the lip (external use only): Podofilox topical solution 0.5 percent (dispense 3.5ml, apply to wart twice a day for 3 days in a row. Do not apply for 4 days, then reapply if necessary.) Imiquimod 5 percent cream (dispense 3gm, apply once a day at bedtime 3 days a week, i.e. MWF or TTS.)
Linear Gingival Erythema (LGE)	Characterized by red bands along the free gingival margin that may present without the presence of dental plaque.	Dental prophylaxis, use of a 0.12 percent chlorhexidine suspension twice a day for 2 weeks, reinforcement of oral hygiene instructions.
Necrotizing Ulcerative Periodontitis (NUP)	Clinical features included ulcerated, cratered, interdental papillae, mobile teeth and a fetid odor. Patients may complain of "deep jaw pain" and spontaneous bleeding. NUP is a sign of severe immune deterioration.	Augmentin® 875mg (dispense 14, 1 tablet PO BID for 7 days or metronidazole 250mg (dispense 28, 1 tablet PO QID for 7 days), plus 0.12 percent chlorhexidine suspension twice a day for 2 weeks plus local debridement.
Oral Ulcer due to HSV	Shallow ulcerations that usually appeared on fixed or keratinized tissues.	Acyclovir 400mg (dispense 30, 1 tablet PO TID for 10 days).
Aphthous ulcerations	These painful ulcerations are characterized by a hallo of inflammation and a gray or yellow pseudomembrane. Aphthous ulcerations present on non-fixed or non-keratinized tissues such as the buccal mucosal, posterior oropharynx and lingual surface of the tongue.	Minor aphthous: Orabase® Soothe-N-Seal™ and if necessary dexamethasone elixir .5mg/5ml (dispense 100mls, swish with 5mls for 1 minute then expectorate, TID until symptoms abate) .Major aphthous may require systemic corticosteroid, nutritional supplements and pain management.

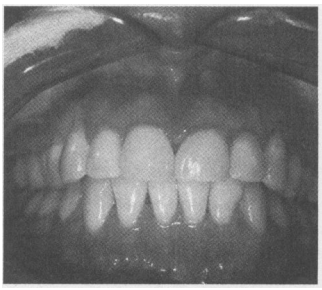
The above treatment options are intended as guidelines only. Prescribers should refer to the latest edition of the Physicians Desk reference for full prescribing information.

lence of pseudomembranous candidiasis in the HAART era, this is still one of the most common oral manifestations seen in HIV disease. Treatment should be based on the extent of the infection with topical therapies (nystatin, clotrimazole) utilized for mild to moderate cases and systemic therapies (fluconazole) used for moderate to severe presentations. Antifungal therapy should last for two weeks to reduce the colony forming units to the lowest level possible to prevent recurrence.

As HIV disease progresses and immunosuppression becomes more severe, the incidence and severity of oropharyngeal candidiasis increase. The introduction of oral azoles, most notably fluconazole, has led to the increased incidence of azole resistant Candida albicans as well as the emergence of non-albicans species such as Candida glabrata, which are inherently resistant to this class of drug.[15] Factors that increase the probability of azole resistant strains of Candida presenting in the oral cavity include previous exposure to azoles, low CD4 count and the presence of non-albicans species.[16,17] To minimize the risk of resistance, topical therapies should be considered for first-line treatment of initial or recurrent cases of mild to moderate oropharyngeal candidiasis.[15] Systemic therapies should be utilized for moderate to severe cases.

The clinical presentation of **Angular cheilitis** is erythema and/or fissuring of the corners of the mouth. Angular Cheilitis can occur with or without the presence of erythematous candidiasis or pseudomembranous candidiasis. Angular cheilitis can exist for an extensive period of time if left untreated. Treatment involves the use of a topical antifungal cream directly applied to the affected areas four times a day for the two-week treatment period.

A periodontal disease, **linear gingival erythema** presents as a red band along the gingival margin, which may or may not be accompanied by occasional bleeding and discomfort. Linear gingival erythema is seen most frequently in association with anterior teeth, but commonly extends to the posterior teeth. Linear gingival erythema can also present on attached and non-attached gingiva as petechia-like patches.



Linear gingival erythema: fiery, red band on free gingival margin of maxillary lateral and central incisors.

Research has indicated there may be a relationship between sub-gingival colonization of Candida species and HIV-related periodontal conditions including linear gingival erythema.[18] The most recent classification of periodontal diseases by the American Academy of Periodontology grouped LGE under "gingival disease of fungal origin".[19] Treatment for this condition would include debridement by a dental professional followed by twice daily rinses with a 0.12 percent chlorhexidine gluconate suspension for two weeks and improved oral hygiene home care.

Chronic adult periodontal disease occurs frequently in persons living with HIV disease. Three unique presentations of periodontal disease seen in association with HIV-infection are: 1) the previously discussed linear gingival erythema, 2) necrotizing ulcerative gingivitis and 3) necrotizing ulcerative periodontitis.

The demarcation between necrotizing gingivitis and necrotizing periodontitis was created to define the difference between the rapid destruction of soft (necrotizing ulcerative gingivitis) and hard (necrotizing ulcerative periodontitis) tissues. It has not been determined whether or not these two presentations are the same or unique entities and both have been classified as "Necrotizing Periodontal Diseases" by the American Academy of Periodontology. Due to the lack of significant differences in the microbial profile of these two conditions and similarity in treatment, this discussion will be limited to necrotizing ulcerative periodontitis, which is a marker of severe

immune suppression.[20]

Necrotizing ulcerative periodontitis is characterized by severe pain, loosening of teeth, bleeding, fetid odor, ulcerated gingival papillae and rapid loss of bone and soft tissue. Patients often refer to their pain as "deep jaw pain." Prompt referral to a dental professional for removal of dental plaque, calculus and necrotic soft tissues utilizing a 0.12 percent chlorhexidine gluconate or 10 percent povidone iodine lavage will alleviate symptoms. Patients should be placed on antibiotic therapy effective against gram-negative flora such as metronidazole or Augmentin®.

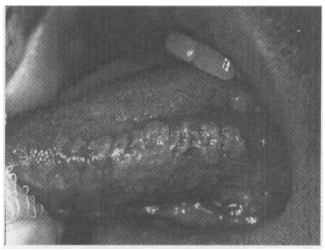
The healthcare team should address pain management, nutritional supplementation and stress the importance of oral hygiene. Timely referral to the primary care team is indicated to rule out other systemic opportunistic infections.

VIRAL DISEASES

HSV-1 infection is widespread and oral manifestations of the herpes type are common. Seventeen percent of the U.S. population over age 12 experienced an oral herpetic lesion over a 1-year period.[21] Recurrent intraoral herpes simplex may start as a small crop of vesicles that rupture to produce small, painful ulcerations which may coalesce. Although these herpetic ulcerations are often self-limiting, the use of an antiviral medication such as acyclovir is sometimes necessary to control the outbreak. Medications such as acyclovir stop viral replication and allow the affected area to heal.

Herpes Zoster, a reactivation of the varicella zoster virus, can occur along any branch of the trigeminal nerve; therefore an intraoral or extraoral presentation along branches of this nerve is possible. The external lesions will start as vesicles, break open and then crust over. The intraoral lesions will start as vesicles, burst and then present as oral ulcerations. Since both of these presentations are along the trigeminal nerve, the patient's chief complaint may be toothache of unknown origin. Treatment options include higher doses of acyclovir (800 mg, five times a day for 7 to 10 days) or famciclovir 500 mg three times a day for 7 days.).

Oral hairy leukoplakia is caused by the Epstein-Barr virus and presents as a white corrugated, nonremovable lesion on the lateral borders of the tongue. Studies have shown a significant decrease in the incidence of oral hairy leukoplakia in the HAART era.[7,8] This condition is normally asymptomatic and does not require therapy unless there are cosmetic concerns. Patients who present with this condition while on HAART may be experiencing a failure in their present antiretroviral regimen.



Oral hairy leukoplakia on lateral border of tongue.

Oral warts due to Human papillomavirus (HPV) have dramatically increased in the HAART era.[6,7] Previously classified as an oral manifestation less strongly associated with HIV disease, the clinical observation of oral papillomas has increased, particularly noted since antiretroviral combination therapy has become the guidelines in the medical management of the HIV infected patient. It has been well documented that immunosuppression, HIV-related or not, predisposes the immunosuppressed patient to numerous opportunistic infections. In turn, it has been suggested that immunosuppression may likely cause the enhanced replication of HPV resulting in the increase susceptibility to infection with HPV in the HIV+ patient since oral papillomas containing HPV DNA has been observed in immunosuppressed transplant patients also.[22,23,24]

On the other hand, improvement in the immune status of the HIV+ patients as a result of HAART has not been sufficient to stop the epithelial cell proliferation stimulated by HPV infection. The immunologic goal of HAART is quantitative and qualitative reconstitution of the

immune system.[25] While an increase in CD4 cell count may occur with HAART, this may result in the production of less immunocompetent cells.[26] One study noted the risk of oral warts was associated with a > one-$\log_{10}$ decrease in HIV RNA in the 6 months prior to oral HPV diagnosis, which suggests that this may in part be related to immune reconstitution.[6]

In a retrospective study where charts were randomly selected from an overall clinic population of 1280 patients seen between 1990 and 1999, an increase in the number of oral warts was particularly noted between 1996 and 1999, i.e., after the introduction of protease inhibitors as a part of antiretroviral therapy. An increase in the occurrence of oral warts was observed in a greater percentage of charts reviewed where patients were on HAART which included a protease inhibitor as opposed to patients who were on a HAART regime that did not include a protease inhibitor.[7] While this study may suggest that the increased incidence of oral warts is possibly a complication of the protease inhibitors, more research is warranted.

More than 100 subtypes of HPV have been described, all of which can infect epithelial cells. At least 17 HPV DNA types have been detected in oral mucosal lesions, the more common of which include HPV DNA subtypes 2, 6, 11,13, 32 and 57.[22,27]

However, the presence HPV 16 and 18, more commonly observed in warts of the anogenital area, has also been reported in the oral cavity.[28,29] When analyzed with type-specific HPV probes, HPV 16 and 18 is observed in oral papillomas biopsied from HIV+ patients.[30] HPV 16 and 18 has been described as the etiologic factor in cervical carcinoma in women as well as the premalignant, cervical intraepithelial neoplasia. In addition, the risk of premalignant anal squamous intraepithelial lesions among HIV+ homosexual men was associated with high levels of HPV 16 or HPV 18 and depressed CD4 counts.[31] Additional research may be indicated to demonstrate if, long-term, a malignant potential exists when HPV DNA subtypes 16 and 18 are found in oral epithelial tissues.

Further noted, a correlation exists between the incidence of HPV lesions and the seroprevalence of HPV antibodies in patients infected with HIV through sexual contact and a higher number of sexual partners.[32,33] In a study by Lopes & Meeks[34] analyzing 16 oral papillomas in five HIV seropositive male patients who acquired HIV through sexual contact, nine lesions that tested positive for HPV 16 and 18 were found in the heterosexual subjects. In a continuation of this study where seven additional oral papillomas in three HIV seropositive male patients (one heterosexual; two homosexual) were analyzed, unpublished results by the researchers showed all seven lesions tested positive for HPV 16 and 18. The presence of HPV 16 and 18 in oral papillomas may be related to oral sexual behavior. However, when found in an HIV+ heterosexual male, identification and examination (medical and/or gynecological) of the female sexual partner may be warranted due to the association of HPV 16 and 18 and cervical carcinoma in women, and, the fact that cervical carcinoma is an AIDS-indicator condition in HIV seropositive females.[34,35,36]

Oral warts may appear cauliflower-like, spike or raised with a flat surface. Treatment, which may involve surgery, laser surgery or cryotherapy, is problematic, as these lesions tend to recur.

NEOPLASTIC DISEASES

Kaposi's sarcoma (KS) is still the most frequent oral malignancy seen in association with HIV infection, although the incidence has dramatically decreased in the HAART era.[8] For homosexual men with AIDS, incidence of all presentations of KS is highest in the 30-39 age group with 5 cases/100 person-years.[37] Kaposi's sarcoma-associated herpesvirus (KSHV) has been implicated as a co-factor in the presentation of KS in persons living with HIV disease. The overall prevalence of KSHV in Texas blood donors

proved to be 15 percent, which is higher than studies performed in other states.[38]

The clinical appearance of KS can be macular, nodular, or raised and ulcerated; the color can range from red to purple. Early lesions tend to be flat, red and asymptomatic, with the color becoming darker as the lesion ages. As lesions progress they can interfere with the normal functions of the oral cavity and become symptomatic secondary to trauma or infection. A biopsy is necessary for a definitive diagnosis. Treatment of oral lesions ranges from localized injections of chemotherapeutic agents, such as vinblastine sulfate, to surgical removal. For persons who present with extraoral and intraoral KS, systemic chemotherapy may be the treatment of choice. It is important that the entire primary health care team, including the primary care provider, dentist and oncologist work closely together in order to facilitate the best possible outcome. Oral hygiene should be stressed for people with oral KS.

Non-Hodgkin's lymphoma is an AIDS defining condition that, on occasion, presents in the oral cavity. This lesion tends to present as a large, painful, ulcerated mass on the palate or gingival tissues. A biopsy is necessary for a definitive diagnosis. The oral health care team should refer patients with a diagnosis of non-Hodgkin's lymphoma to an oncologist for treatment.

MISCELLANEOUS

Salivary Gland Disease and xerostomia

Salivary gland disease is clinically apparent by an increase in the size of the major salivary glands, most notably the parotids. Biopsy of suspect enlarged parotid salivary glands has revealed an increase in lymphocytic infiltrates, more specifically, CD8 cells.

This condition usually presents as a bilateral enlargement of the parotid salivary glands and is often times accompanied by symptoms of dry mouth. There has been a reported increase in the presentation of salivary gland disease in the HAART era, which may be related to a reconstitution syndrome.[11]

Xerostomia or dry mouth is common complaint among people living with HIV disease. Approximately 29 percent of those participating in the HIV Cost and Utilization Study cohort reported symptoms of xerostomia. Factors which proved to be significant in the presentation of xerostomia included the previously observed salivary gland disease, use of medications to manage HIV and other conditions, smoking, and a viral load of > 100,000/mm.[39]

Symptoms of dry mouth can be temporarily alleviated by sucking on sugar-free hard candies, chewing sugar-free gum and by using oral moisturizers. The change in the quantity and quality of saliva may lead to increased dental decay and therefore meticulous oral hygiene should be stressed and use of prescription topical fluoride preparations encouraged.

Recurrent aphthous ulcerations

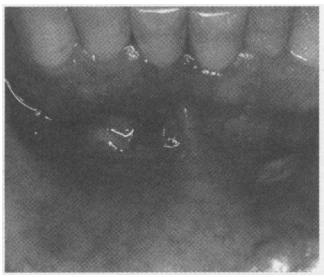
Recurrent aphthous ulcerations (RAU) are a common occurrence with approximately 17 percent of the U.S. population reporting an episode within a twelve-month period[17].

RAU present on non-keratinized or non-fixed tissues such as labial and buccal mucosa, the floor of the mouth, ventral surface of the tongue, posterior oropharynx and the maxillary and mandibular vestibules. RAU are characterized by a halo of inflammation and a yellow-gray pseudomembranous covering.

RAU, which last between 7 and 14 days in the general population, may last longer and be more painful in immunocompromised individuals. Increased pain is usually noted upon eating salty, spicy or acidic foods and beverages as well as due to trauma when consuming hard or rough foods. Treatment involves the use of topical corticosteroids such as dexamethasone elixir (0.5mg/5ml) 5 ml swished for one minute then expectorated, or for more severe occurrences, systemic corticosteroids such as prednisone. While the use of

immunoactive agents contribute to a reduction in inflammation and therefore speed healing, these agents do not immediately address pain.

Pain as a result of recurrent aphthous ulcerations is typically managed by using topical anesthetics or systemic analgesics. Topical anesthetics do offer some relief from the pain associated with these lesions, although such relief is usually of short duration. Another consequence of use of anesthetic mouthrinses is the numbing effect on the taste buds, which results in decreased desire to eat. Diminished nutritional intake further negatively impacts patients' overall well-being. Systemic analgesics are somewhat effective, but do not specifically address localized pain associated with oral ulcerative disease. A new over-the-counter oral formulation of 2-octyl cyanoacrylate has shown promise as a barrier product for managing localized oral pain due to ulcerative disease. [40]



HIV disease oral ulcerative disease. Recurrent aphthous ulcer on left. Ulceration probably due to leukopenia on right.

CONCLUSION

It is important that physicians and dentists recognize the earliest signs and symptoms of HIV infection in order that a timely diagnosis and patient referral can be made for early counseling testing, and treatment [41]. Candidiasis, ulcerative diseases, and periodontal disorders are the most common. Other lesions may be observed in varying stages of the disease. [42] A definitive diagnosis is very important to differentiate many HIV/AIDS -related oral diseases because there are many oral lesions that have similar presentations.[43] Greenspan noted that not only are oral lesions a significant part of HIV-related illness, but certain oral lesions play a specific part in the diagnosis and staging of HIV infection [42].

There is a broad consensus that persons with HIV should see a dentist regularly.[44] Available evidence suggests that socially marginalized populations are more likely to report unmet needs for these services. Racial and ethnic groups, women, and injection drug users with HIV have relatively greater unmet needs for medical and dental care than do less disadvantaged groups. Several studies have shown that individuals reported unmet needs for dental care at a greater level .[45, 46]

Dentists have not been universally receptive to caring for persons with HIV/AIDS. In many communities it was reported that it was extremely difficult to find a dentist willing to treat HIV patients. Dentists have seen themselves at considerable risk from HIV infection. Some dentists believe that they may also be more at risk from stigma than other providers if they treat HIV patients [47, 48].

In the future there needs to be a greater emphasis placed on the dental health and unmet needs of the HIV-infected patients [45,46]. Several reports from Ryan White Programs have indicated the number one unmet need in clinical services is oral health care [49]. In the Georgia HIV Consumer Survey Report 1999-2000, dental care was the most frequently reported service needed, but yet, not received [50].

It is important for primary health care teams to note that severely compromised oral health in persons infected with HIV/AIDS can result in difficulty in chewing, swallowing, maintenance of salivary flow, and tasting foods. These functions are necessary to maintain an optimal quality of life and minimize the affects of other systemic diseases.

Medical and dental providers of HIV infected persons can play a significant role in the prevention and long-term successful treatment and management of HIV/AIDS infected individual. It is important to completely understand the state-of-the-art treatment methods and for health care providers to receive current updates. Education and training will better ensure the delivery of quality care for the patient.

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