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Pratanporn Arirachakaran

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Review Article
บทความปริทัศน์

Highly active antiretroviral therapy and its oral manifestations in HIV patients

Pratanporn Arirachakaran D.D.S., Grad. Dip. in Clin. Sc. (Oral Medicine), Ph.D.

Infectious Disease Clinic, Dental Hospital

Department of Microbiology, Faculty of Dentistry, Chulalongkorn University

Abstract

Oral manifestations such as candidiasis and hairy leukoplakia are common lesions found in patients infected with human immunodeficiency virus. Those who are on antiretroviral drugs may demonstrate various orofacial effects. Immune reconstitution reflects a patient's improved immune response, but this may be accompanied by excessive response to previously exposed antigens, resulting in opportunistic infection. Common adverse effects of antiviral therapy include xerostomia and erythema multiforme, which are mostly related to use of protease inhibitors and nucleoside reverse transcriptase inhibitors. Perioral paresthesia, mucosal hyperpigmentation and lichenoid reaction may also be seen, along with an increased probability of oral warts and salivary gland disorders. Oral adverse effects from drugs, as well as oral manifestations in patients with immune reconstitution syndrome, need to be generously investigated in order to fully comprehend the effect of drugs for proper and safe usage in the future. This article summarizes reported orofacial effects found in HIV-infected patients who used antiretroviral drugs.

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Key words: *antiretroviral; HIV; oral*

Introduction

Acquired immunodeficiency syndrome (AIDS) is a life threatening disorder defined by serious opportunistic infections and neoplasm. However, the evolution of antiretroviral therapy has altered the management of patients with human immunodeficiency virus (HIV) infection to the extent that HIV infection is now treated as a chronic disease.

Since the first reported case of HIV infection in the United States in 1981, a large body of research has propelled the accumulation of knowledge on many aspects of this disease. For dentists, the oral manifestations among HIV/AIDS patients in the pre-antiviral era have been well recognized. Oral lesions were commonly observed and could be accurately diagnosed based on even subtle clinical signs and symptoms. Oral lesions have been useful as clinical markers of viremia and host immune status. In developing countries, the presence of oral lesions was a criterion for predicting disease progression and prognosis. At present, this still holds true for individuals whose diagnoses are unknown. However, the presence of oral lesions has declined as a prognostic indicator since antiviral drug therapy has become more widespread.

Studies in patients receiving highly active antiretroviral therapy (HAART) have revealed a decreased prevalence of common oral lesions that previously defined HIV status. However, HIV salivary gland diseases and oral warts have reportedly been on the rise. Immune reconstitution syndrome, a condition whereby the recovering immune system responds to previously acquired pathogens with an overwhelming inflammatory response, is also increasingly reported. The effects of HAART on a patient's immune response require further investigation to determine the extent to which oral manifestations are attributable to adverse drug effects, and if so, to find means to mitigate these effects. The oral mucosa can reflect a patient's health status.

Knowledge of oral manifestations in patients receiving HAART may not only help in evaluating the success of treatment, but also raise awareness in dental practitioners so that they can tailor dental care to patients who may suffer orofacial side effects or who are susceptible to oral diseases from drug therapy. Furthermore, knowledge of adverse effects associated with HAART will benefit physicians as a part of monitoring drug treatment.

Literature review

According to the most recent epidemiological data by the World Health Organization (WHO),¹ twenty five million people have died of HIV-related causes since the beginning of the HIV epidemic. There are 33.2 million HIV-infected patients globally. Longitudinal studies indicate that, the estimated median survival time after infection with HIV in the absence of antiretroviral treatment is 11 years.^{2–4} At present, the epidemic is outpacing the rate at which drug therapy is being delivered. An estimated 2 million individuals have access to antiretroviral therapy (ART). At best, this number is only about 29% of the at least 7 million who are in need of ART.¹ That means the number of patients receiving ART may rise dramatically should drug administration become more accessible. Access to life-prolonging antiretroviral therapy has led to an increase in the estimated number of people living with HIV, to the point that an HIV-positive status can be considered a chronic disease.⁵ This review discusses with changes in oral manifestations after the introduction of HAART and the adverse effects that may accompany drug therapy.

Oral lesions as a diagnostic tool

For people at high risk, routine screening for HIV infection can be easily accessed in industrialized countries, but availability is a problem in developing

ones. Systemic symptoms alone are not reliable for diagnosis as individuals with HIV may be subclinical for many years. Oral lesions have been suggested as a diagnostic tool.⁶⁻¹⁰ In 1993, the EC-clearinghouse on oral problems related to HIV infection and the WHO collaborating center on oral manifestations of the immunodeficiency virus revised classification and diagnostic criteria for oral lesions associated with HIV infection (Table 1) based upon numerous studies of oral manifestations in HIV/AIDS infected patients.^{11,12} A patient, unaware of his/her HIV infection status presenting to a dental office may show signs of oral

lesions, defined as group 1 lesions, that are strongly associated with HIV infection (Table 1). These are oral candidiasis (OC), oral hairy leukoplakia (OHL), Kaposi's sarcoma (KS), and non-Hodgkin's lymphoma (NHL). Certain types of periodontal disease including linear gingival erythema and necrotizing gingivitis are also included. Presentation with such an opportunistic infection may reflect an abnormal immune response that is most likely acquired. An initial finding of a group 1 lesion can be used as a basis for ordering additional testing that could result in a definitive diagnosis.

Table 1 Revised classification of oral lesions associated with HIV infection*

Group 1 Lesions strongly associated with HIV infection

- Candidiasis
 - Erythematous
 - Pseudomembranous
 - Hairy leukoplakia
 - Kaposi's sarcoma
 - Non-Hodgkin's lymphoma
 - Periodontal disease
 - Linear gingival erythema
 - Necrotizing (ulcerative) gingivitis
 - Necrotizing (ulcerative) periodontitis
-

Group 2 Lesions less commonly associated with HIV infection

- Bacterial infection
 - Mycobacterium avium-intercellulare*
 - Mycobacterium tuberculosis*
 - Melanotic hyperpigmentation
 - Necrotizing (ulcerative) stomatitis
 - Salivary gland disease
 - Dry mouth due to decreased salivary flow rate
 - Unilateral or bilateral swelling of major salivary glands
 - Thrombocytopenic purpura
 - Ulceration NOS (not otherwise specified)
 - Viral infection
 - Herpes simplex virus
 - Human papillomavirus (wart-like lesions)
 - Verruca vulgaris
-

Group 3 Lesions seen in HIV infection

Bacterial infections

*Actinomyces israelii**Escherichia coli**Klebsiella pneumoniae*

Cat-scratch disease

Drug reactions (ulcerative, erythema multiforme, lichenoid, toxic epidermolysis)

Epithelioid (bacillary) angiomatosis

Fungal infection other than candidiasis

*Cryptococcus neoformans**Geotricum candidum**Histoplasma capsulatum**Aspergillus flavus*

Neurologic disturbances

Facial palsy

Trigeminal neuralgia

Recurrent aphthous stomatitis

Viral infections

*Cytomegalovirus**Molluscum contagiosum*

*The EC-Clearinghouse oral problems related to HIV infection meeting, London, September, 1993.¹²

Significance of oral lesions as a monitoring tool for disease progression and prognosis in HIV/AIDS infection

Patients presenting with oral lesions usually have underlying immunosuppression leading to the suggestion that oral lesions are indicative of immune status.¹³ Unless suffering from systemic conditions associated with a known immunodeficiency, or with the use of immunosuppressive drugs, the presence of OC, OHL or KS are strongly suggestive of HIV infection.⁶⁻⁹ In many cases, lymphocyte counts in blood panels from HIV-infected patients may be the only available monitoring tool. Oral manifestations, especially OC and OHL, are accepted as signs of AIDS in conjunction with total numbers of lymphocytes. This combination can be very useful in situations where more advanced diagnostic tools, such as flow

cytometry or polymerase chain reaction for identifying CD4+T cell count or plasma HIV RNA, are not accessible.¹⁴⁻¹⁶

OC has been by far the most commonly found opportunistic infection affecting more than 90% of all HIV infected individuals during the transition from the asymptomatic stage to AIDS.¹⁷⁻¹⁹ Therefore, it has been considered as one means of monitoring disease progression and prognosis.^{17,18,20,21}

Lymphocyte counts and the presence of oral lesions, such as OC or OHL, are also considered to be indicators for the start of antiretroviral therapy or participation in a vaccine trial.^{22,23} OHL is commonly found to be associated with high viral load.^{24,25} Other oral lesions caused by infection, such as necrotizing ulcerative periodontitis, histoplasmosis, and penicilliosis, or malignant neoplasms such as NHL and KS, although

not exclusively affecting HIV/AIDS patients, are associated with disease progression to AIDS.^{1,12,26-29} Many of these lesions can be painful, interfering with oral function including speaking, chewing and swallowing. Oral lesions have a close connection to the quality of life of HIV infected patients since good oral health significantly improves a patients' physical and mental status.³⁰

Highly active antiretroviral therapy

As of 2008, there are more than 20 approved antiretroviral drugs against HIV infection across five mechanistic classes. These include the nucleoside/nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, fusion inhibitors and integrase inhibitors.³¹ Only the first three types have well established information on oral adverse effects. In contrast, there have been no reports on the oral effects of the latter two.^{32,33}

The US Department of Health and Human Services Panel recommends initiation of antiretroviral therapy in patients with a history of AIDS-defining illness or with a CD4⁺T cell count of < 350 cells/ml. Subsequent studies have provided strong support for the recommendation that therapy should always be initiated before the CD4⁺T cell counts decline to < 200 cells/ml.³⁴⁻³⁶ Early initiation in those with CD4⁺T > 350 cells/ml may not benefit patients as there is a very low risk for development of AIDS or mortality,³⁷ though there is a positive benefit to public health in reducing HIV transmission.³⁸

When several antiretroviral drugs, typically three, are taken in combination to treat HIV infection, the approach is known as highly active antiretroviral therapy, or HAART. Drug combinations offer additive or synergistic activity against the target virus. In order to understand how the drugs are used, mechanisms of each class have been briefly described below.

Nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) are the first drugs available that work by inhibiting the viral reverse transcriptase (RT) before the virus integrates into the host cell genome. They act as competitive inhibitors of both reverse transcriptase and DNA chain terminators by competitively replacing the active site of the viral enzyme, thus blocking normal DNA replication and resulting in HIV proviral DNA chain termination.³⁹ Widely used nucleoside RTIs are zidovudine (AZT), stavudine (D4T), didanosine (DDI), lamivudine (3TC), zalcitabine (DDC), abacavir (ABC), and emtricitabine (FTC). The nucleotide RTI is tenofovir (TDF).

Non-nucleoside reverse transcriptase inhibitors (NNRTI) are a structurally diverse group of agents that bind to RT, leading to conformational change that halts enzyme activity. They have been shown to be highly specific, thus, exhibiting high antiviral activity and relatively low toxicity *in vitro*.⁴⁰ Emerging of resistant strains from single point mutations in the RT gene resulted in loss of antiviral effect. To improve the chance of successful treatment, delivery is recommended in combination with other antiretroviral drugs, usually NRTI.^{41,42} NNRTIs include nevirapine (NVP), efavirenz (EFZ), delavirdine (DLV) and etravirine. A large randomized, controlled study using efavirenz as a part of its regimen demonstrated a potent viral suppression of HIV-1 RNA to less than 50 copies per milliliter.⁴³

Protease inhibitors (PI) bind competitively to the substrate site of viral protease, which is an enzyme responsible for viral post-translational modification by cleaving the large core protein. PI results in production of immature virus particles.⁴⁴ Indinavir, ritonavir, saquinavir, nelfinavir are in this category. They have proven to be very potent against HIV, and substantially reduce the morbidity and mortality rate.⁴⁵ However, compliance is a problem since PI is associated with adverse effects (Table 2).

Table 2 Adverse effects of antiretroviral therapy

Class	Name of drug	Trade name	Adverse effects ³¹	Oral lesions
NRTI [†]	Abacavir ABC	Ziagen [®]	Lactic acidosis Nausea Diarrhea Rash	Erythema multiforme ⁵⁴
NRTI [†]	Didanosine DDI	Videx [®]	Nausea Diarrhea Lactic acidosis Pancreatitis Abnormal liver function Peripheral neuropathy Retinal damage	Erythema multiforme ⁵⁵ Xerostomia ^{56,57}
NRTI [†]	Lamivudine 3TC	Epivir [®]	Nausea Diarrhea Pancreatitis Abnormal liver function	Xerostomia ⁵⁸
NRTI [†]	Stavudine D4T	Zerit [®]	Neuro-psychiatric reaction Abnormal liver function	Questionable ⁵⁹
NRTI [†]	Zalcitabine DDC	Hivid [®]	Nausea Diarrhea Lactic acidosis Pancreatitis Abnormal liver function	Erythema multiforme ⁶⁰ Oral ulcers ^{61–63}
NRTI [†]	Zidovudine AZT	Retrovir [®]	Nausea Diarrhea Bone marrow suppression Lactic acidosis Myopathy	Erythema multiforme ⁶⁴ Lichenoid reaction ^{65,66} Hyperpigmentation ^{67,68}
NNRTI ^{††}	Efavirenz EFZ	Sustiva [®]	Neuro-psychiatric reaction Interfere with liver enzymes (drug metabolites)	Erythema multiforme ⁶⁹
NNRTI ^{††}	Nevirapine NVP	Viramune [®]	Abnormal liver function Induce liver drug metabolizing enzymes	Erythema multiforme ^{70,71} Oral ulcers ^{70,71} Taste disturbance ⁷² Xerostomia ⁷²
PI ^{†††}	Amprenavir APV	Agenerase [®]	Interfere with liver drug metabolizing enzymes Dyslipidemia	Perioral paresthesia ^{73,74} Parotid lipomatosis ⁷⁵

Class	Name of drug	Trade name	Adverse effects ³¹	Oral lesions
PI ^{†††}	Indinavir IDV	Crixivan [®]	Interfere with liver drug metabolizing enzymes Dyslipidemia Hemolysis Osteophagitis Nephrolithiasis	Cheilitis ^{76,77} Parotid lipomatosis ⁷⁵ Xerostomia ⁷⁸⁻⁸⁰ Taste disturbance ⁸¹
PI ^{†††}	Nelfinavir NFV	Viracept [®]	Nausea Diarrhea Interfere with liver drug metabolizing enzymes Dyslipidemia	Xerostomia ⁷⁸⁻⁸⁰ Parotid lipomatosis ⁷⁵
PI ^{†††}	Ritonavir RTV	Norvir [®]	Nausea Diarrhea Interfere with liver drug metabolizing enzymes Dyslipidemia Flushing	Perioral paresthesia ⁸² Parotid lipomatosis ⁷⁵ Xerostomia ⁷⁸⁻⁸⁰ Taste disturbance ⁸¹
PI ^{†††}	Saquinavir SQV	Fortovase [®] Invirase [®]	Nausea Diarrhea Interfere with liver drug metabolizing enzymes Dyslipidemia	Parotid lipomatosis ⁷⁵ Xerostomia ⁷⁸⁻⁸⁰ Ulcers ^{76,77,83}
Fusion inhibitor	Enfuvirtide	Fuzeon [®]	Erythema Diarrhea Fatigue Nausea	NR
Fusion inhibitor	Maraviroc MVC	Selzentry [®]	Cough, fever, dizziness Headache Nausea Bladder irritation. Hepatotoxicity Orthostatic hypotension Cholesterol level increase	NR
Integrase inhibitor	Raltegravir	Raltegravir [®]	Nausea Headache Diarrhea Pyrexia	NR

† nucleoside/nucleotide reverse transcriptase inhibitors
 †† non-nucleoside reverse transcriptase inhibitors
 ††† protease inhibitors
 NR not yet reported

Fusion inhibitors One drug in this group is enfuvirtide, trade name, Fuzeon® (originally named T-20®). This costly, recently FDA approved drug works by disrupting the HIV-1 molecular machinery at the final stage of fusion with the target cells, preventing uninfected cells from becoming infected. Enfuvirtide was rationally designed to mimic components of the HIV-1 fusion machinery, a portion of transmembrane glycoprotein 41 (Gp41). It competitively binds to a specific region of the Gp41, inhibits the conformational change of the Gp41, resulting in displacement. The drug prevents the creation of an entry pore for the capsid of the virus, keeping it out of the cell.⁴⁶

The CCR5 antagonist (maraviroc: Selzentry®), maraviroc is so far the most recently FDA approved (2007) medication. It is used for the treatment of CCR5-tropic HIV-1 in treatment-experienced adult patients, combined with other antiretroviral treatment. It works by blocking CCR5, a proteinaceous chemokine receptor that HIV uses as a co-receptor to bind and enters helper T cells.⁴⁷ Maraviroc belongs to a new class of antiretrovirals that could provide alternative therapy for HIV-positive people who have developed resistance to multiple drugs.⁴⁸ Adverse effects associated with this drug are listed in Table 2.

Integrase inhibitor, trade name Raltegravir®, is the first-in-class small molecule compound that blocks an early stage in the HIV life cycle, specifically the integration of the virus into host cell DNA. It is well tolerated with few side effects. A similar safety and side effects profiles were observed in placebo patients (Table 2).⁴⁹ This drug was very recently approved by the FDA.

Combination therapy with three or more antiretroviral drugs has been successful in elevating the number of CD4⁺T cells and reducing the plasma viral load to undetectable levels.⁴² Administration of drug combinations requires taking several pills at various times during the day. If a patient misses a dose, drug

resistance is more likely to develop. Fixed dose combination (FDC) was developed to overcome such problems, improve tolerability, convenience and compliance.⁵⁰ Ideally, the first-line of drug combinations are to be used in treating naive patients, whereas the costly newly developed drugs are reserved for those who acquire drug resistance. First line FDCs are now widely used in developing countries, where approximately 30% of infected HIV/AIDS patients have access to drug treatment. They are most often combinations of 2 nucleoside RT inhibitors and a non-nucleoside RTI or PI. In Thailand, approximately 140,000 out of 338,890 HIV-infected patients are receiving the widely used generic FDC, GPO-vir.¹ It is composed of either the stavudine (D4T) + lamivudine (3TC) + nevirapine (NVP) or zidovudine (AZT) + 3TC + NVP combinations.⁵¹ Although these drugs decrease HIV RNA viral load, increase CD4⁺T cell counts, and decrease the frequency and severity of opportunistic diseases, incidences of drug resistance and various adverse effects are increasing. Lipodystrophy, dyslipidemia, insulin resistance, diabetes, and bone metabolic abnormalities such as osteoporosis and osteopenia have been reported.^{31,52,53} Furthermore, osteoporosis seemed to be associated with PI⁵² and NNRTI.⁵³

The cost of treatment is another factor for consideration. The average cost of first line drugs is only US\$87 per year, whereas other regimens are far more costly because of patents. The cost of treatment creates a dilemma for some countries forcing them to decide between treating a greater number of patients on more affordable HAART, or fewer patients with drugs that cause less adverse effects but are more costly.

Oral lesions in patients taking HAART

Principally, HAART increases CD4⁺T cell counts, decreases HIV RNA viral load, improves immune

status and decreases incidences of opportunistic infections.⁸⁴ Significant drops in incidences of oral lesions are noted after the introduction of antiretroviral therapy.^{79,85-87} Many studies in developed countries have reported decreases in oral lesions of 10-50%.⁸⁸ One study claimed a decrease from 47.6% during the pre-antiretroviral era to 37.5% after the inception of HAART.⁷⁸ In another study, a 50% reduction in OC was reported for patients taking HAART.⁸⁷ An explanation for this latter result is that the action of protease inhibitors also affects candida aspartic proteinase.⁸⁹ Incidences of OHL, KS and necrotizing ulcerative periodontitis are also reported to be decreasing,^{78,87} whereas no significant decreases are found in other types of lesions.⁸⁶ Improvement in immune status naturally prevents patients from developing opportunistic infections.

On the negative side, orofacial adverse effects of HAART are more common, especially with the use of NRTI, particularly, AZT.^{64,65,90} Oral ulcers secondary to neutropenia in a patient with bone marrow suppression,^{61,62} xerostomia,⁵⁶ mucositis,^{32,91} hyperpigmentation,^{67,68} erythema multiforme (EM)⁶⁴ and lichenoid reactions have been reported,^{65,66} whereas NNRTI is less commonly associated with oral lesions. EM was found in a patient using nivarapine.^{70,71} Indinavir, a protease inhibitor, may cause cheilitis.^{76,77} Despite being a potent antiretroviral drug, some protease inhibitors such as amprenavir and ritonavir can cause perioral paresthesia.^{74,75,82} Change of taste has also been reported in patients taking this group of drugs.^{75,81} An increased incidence of salivary gland diseases has been reported including parotid lipomatosis, an abnormal accumulation of fat in salivary gland tissue.^{75,78-80} The abnormal fat deposition is hypothesized to come about by PI inducing peripheral lipodystrophy, which is caused by the inhibition of two proteins that regulate lipid metabolism. This results in reduced differentiation and an increase in apoptosis of peripheral adipocytes with impaired fat

storage and lipid release.⁹² Greenspan, et al. described the parotid lipomatosis with diffuse infiltration of CD8⁺T cells in salivary glands.⁷⁹ Effects of HAART on salivary glands include a decrease in salivary flow rate and dry mouth (Table 2). There is no explanation why salivary gland disease affects women predominantly. Xerostomia is a predisposing factor for the development of dental caries, especially cervical lesions.⁹³ Reduced salivary flow rate in patients taking HAART may result in an increase of dental caries risk.⁹⁴⁻⁹⁶

A higher incidence of herpes virus infections was also reported in patients who take maraviroc.⁹⁷ The most common drug-related adverse symptoms in a combined double-blinded randomized study of 703 patients taking raltegravir were diarrhea, nausea, and headache. This group also experienced drug-related lab chemistry changes that included increased levels of serum cholesterol, triglycerides, and aminotransferase.⁴⁹ Overall, however, raltegravir is known to be safe and effective in treating multiple drug resistant HIV with no reports to date on oral effects. A study in Argentina by Casariego, et al. observed exfoliative cheilitis in HIV-1 patients receiving HAART. No particular drug was pinpointed as the cause since patients were on a variety of combinations of NRTIs and PIs.⁵⁹

Human papillomavirus (HPV) infection, once less commonly seen in HIV-infected patients, has become increasingly found in patients taking HAART.^{79,83,85,98,99} HPV-associated oral lesions include papilloma, condyloma, focal epithelial hyperplasia (oral warts), and HPV-16-associated oral cancers.⁹⁹⁻¹⁰² Prior infection with herpes simplex 2 virus (HSV2) or hepatitis B virus (HBV) infections are risk factors.^{99,103} It is not yet clear why HPV infection occurs more often in HAART patients. Cell-mediated immunity is thought to be a critical element in controlling HPV infection.¹⁰⁴ The increased risk of oral warts may also be associated with immune reconstitution syndrome (IRS) in response to improved cell-mediated immune function, as well

as a sign of drug resistance or unsuccessful treatment.³¹ Oral HPV infections are more common among HIV-infected women who also had cervical HPV infections than those without a cervical HPV infection.¹⁰⁵ Patients who were infected by HPV at both oral cavities and cervixes held different types of the virus at each site.^{105,106} Interestingly, a recent report of HIV-infected patients who first developed HPV-related anal squamous cell carcinoma were later diagnosed with oral squamous cell carcinoma.¹⁰⁶

Apart from drug-related adverse effects, IRS and its oral effects are increasingly common. IRS reflects a patient's rejuvenated immune system that may response excessively as the host recognizes a state of ongoing infection. HIV infected patients with low CD4⁺T cell counts are more at risk for IRS if they are starting HAART for the first time, or if they have recently been treated for an opportunistic infection. This syndrome highlights the potential damage that can occur independent of the infectious agent when the host immune response is too aggressive.¹⁰⁷ Ortega, et al. reported that HAART patients taking HAART who developed IRS, displayed significant enlargement of parotid salivary glands three months after the initiation of drug therapy, whereas HAART patients without IRS were more likely to develop candidiasis.¹⁰⁸ However, a separate study in IRS patients who received long term HAART found that erythematous candidiasis was the most prevalent oral lesion in this group as well.¹⁰⁹ The time-frames of the studies may explain the contradictory results since the latter investigation found that the development of candidiasis tended to occur 24 months after initiation of treatment.

Patients receiving HAART were found to experience a decreased prevalence of common oral lesions that earlier were defined to be associated with HIV status, including OC, OHL, KS and necrotizing periodontal diseases.^{13,80,85–87,100,110–114} On the other hand, HIV salivary gland diseases, HPV-associated oral lesions,

xerostomia, and recurrent oral ulceration have been on the rise in the HAART era.^{79,85,87,99–101} Whether the increased incidences of these conditions are related to adverse effects from HAART therapy will require future research. This is an important matter that will serve as a guide for proper and safe treatments that can anticipate and mitigate adverse drug reactions. Interestingly, studies in HIV infected children receiving HAART indicated no change in the prevalence of oral lesions when compared to children who were not on HAART,^{115,116} indicating that HAART does not significantly increase oral soft tissue disease in HIV-infected children. Furthermore, lesions that were present, were associated with decreased immunity and may have signaled advancing disease.^{115,116} Table 3 summarizes the orofacial effects related to antiretroviral drugs.

As AIDS-defining malignancies (ADMs) have declined significantly,^{85,87} the incidence of non-AIDS-defining malignancies (non-ADMs) not known to be associated with immunosuppression has increased 2 to 3 times when compared to a general population.¹¹⁷ They are Hodgkin's disease, hepatocellular carcinoma, lung cancer, anal cancer and oral cancer.^{106,117–121} Reported oral cancers are squamous cell carcinoma, Hodgkin's disease, and NHL related to oncogenic HPV, and Epstein-Barr virus.^{106,117,121}

Discussion

There does not yet exist a vaccine or drug combination that can eradicate, or prevent HIV infection. But there is no debate regarding the benefits of HAART in controlling disease progression in HIV infected patients. Common adverse effects notwithstanding, the drugs prolong life expectancy, and improve the quality of life. As a consequence of the improvement in life expectancy, patients are living in a chronically infected state for longer periods of time, and may experience new forms of drug or disease related adverse effects. Oral manifestations not only

Table 3 demonstrates the orofacial effects from each group of the drugs

Orofacial effect	Drug related	Class of drug
Erythema multiforme	ABC, DDI, DDC, AZT	NRTI [†]
Xerostomia	DDI, 3TC	
Oral ulcers	DDC	
Lichenoid reaction	AZT	
Hyperpigmentation	AZT	
Dental caries	DDI, 3TC	
Erythema multiforme	EFZ, NVP	NNRTI ^{††}
Oral ulcers	NVP	
Taste disturbance	NVP	
Xerostomia	NVP	
Cheilitis	IDV	PI ^{†††}
Erythema multiforme	SQV	
Parotid lipomatosis	APV, IDV, NFV	
Perioral paresthesia	APV, RTV	
Taste disturbance	IDV, RTV	
Ulcers	SQV	
Xerostomia	IDV, NFV, RTV, SQV	
NR	Fusion inhibitor	Fusion inhibitor
NR	Integrase inhibitor	Integrase inhibitor
[†] nucleoside/nucleotide reverse transcriptase inhibitors ^{††} non-nucleoside reverse transcriptase inhibitors ^{†††} protease inhibitors NR not yet reported		

have a role as a diagnostic tool in newly infected cases, but may also play a part in monitoring disease progression. Dental practitioners must be cognizant of oral conditions that may be encountered in HAART patients, especially serious orofacial effects as described in Table 3. Oral discomfort, painful ulcers or paresthesia can lead to avoidance of oral care in those who suffer. Overgrowth of oral microflora is an inevitably consequence, and the main source of infectious diseases of the teeth, gingiva and oral soft tissues. Dentists may

provide palliative treatment to a patient with painful oral lesions. Treatment modalities for some conditions such as dry mouth are still limited in Thailand due to the limited availability of drugs or oral lubricants. New classes of drugs such as fusion inhibitors and integrase inhibitors are very costly and so can be used in few patients. Although no reports on orofacial effects of these latter two classes of drugs have been published, close monitoring should be done.

Conclusion

The condition of the oral mucosa can be an indicator of health status. Therefore, study of oral manifestations in patients receiving HAART may not only help in evaluating the success of treatment, it may also raise awareness in dental practitioners of the proper standard of dental care when oral adverse effects occur. Patients may suffer emerging oral diseases associated with drug therapy as well as orofacial side effects. Oral manifestations in patients taking antiretroviral therapy may also suggest disease progression or drug resistance. Seeking treatment that aims towards reconstitution of the immune response has been the priority. More information from longitudinal studies is needed. There is still a necessity to study effects of long term HAART on oral manifestations.

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การรักษาด้วยยาต้านไวรัสที่มีฤทธิ์สูงและ อาการแสดงในช่องปากของผู้ติดเชื้อเอชไอวี

ประธานพร อาริราชการณย์ ท.บ., ป. บัณฑิตวิทยาศาสตร์การแพทย์คลินิก (เวชศาสตร์ช่องปาก), วท.ด.

หน่วยผู้ป่วยติดเชื้อ โรงพยาบาลคณะทันตแพทยศาสตร์
ภาควิชาจุลชีววิทยา คณะทันตแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

บทคัดย่อ

รอยโรคจากการติดเชื้อราและเฮอร์ปีส์ไวรัสพบได้มากในช่องปากของผู้ติดเชื้อเอชไอวี ผู้ติดเชื้อที่ได้รับยาต้านไวรัสอาจมีอาการแสดงอื่น ๆ ที่พบได้บริเวณช่องปากและใบหน้า เมื่อภูมิคุ้มกันของร่างกายดีขึ้นจากการได้รับยาผู้ป่วยอาจเกิดปฏิกิริยาการตอบสนองของภูมิคุ้มกันต่อเชื้อฉวยโอกาสที่แฝงอยู่และแสดงอาการติดเชื้อให้เห็นภาวะปากแห้งและอิริทเมา มัลติฟอร์ม เป็นอาการแสดงในช่องปากที่พบได้บ่อยจากผลข้างเคียงของการใช้ยาต้านไวรัสโดยเฉพาะยากดภูมิคุ้มกันที่ยับยั้งการทำงานของเอนไซม์โปรตีเอสและเอนไซม์ที่ยับยั้งการทำงานของนิวคลีโอไซด์รีเวิร์สทรานสคริปเทส อาการชารอบริมฝีปาก การมีเม็ดสีมากกว่าปกติ หรือรอยโรคไคนอยด์ที่เยื่อช่องปากก็พบได้เช่นกัน นอกจากนี้ยังพบหูดและโรคของต่อมน้ำลายได้มากขึ้น ผลข้างเคียงที่เกิดในช่องปากจากการใช้ยาต้านไวรัสรวมถึงรอยโรคช่องปากที่เกิดจากภาวะภูมิคุ้มกันที่ต่ำจำเป็นต้องได้รับการศึกษาอย่างถี่ถ้วนต่อไปเพื่อนำไปสู่การใช้ยาที่เหมาะสมและปลอดภัยแก่ผู้ป่วยบทความปริทัศน์นี้จึงได้รวบรวมสรุปอาการในช่องปากและใบหน้าในผู้ที่ใช้ยาต้านไวรัส

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คำสำคัญ: ช่องปาก; ยาต้านไวรัส; เอชไอวี