

Effect of combination antiretroviral therapy on the frequency of oral candidiasis in HIV/AIDS patient

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ABSTRACT

Oral candidiasis is one of the most common opportunistic infections in HIV/AIDS patients. It serves as important markers of HIV infection, viral load, and CD4 cells count in the blood and predict disease progression to AIDS. The development of oral candidiasis in HIV/AIDS patients associated by imbalances between Candida and impaired host immune defenses that caused by decreased of CD4 cell counts and the increased of plasma HIV-viral load. Since the introduction of antiretroviral therapy combination, commonly known as Highly Active Antiretroviral Therapy (HAART), it has been observed that certain oral lesions, such as oral candidiasis as declined. The aim of this paper is to review the mechanism of combination antiretroviral therapy influenced the frequency of oral candidiasis in HIV/AIDS patient. We conclude that combination antiretroviral therapy generally reduced the frequency and severity of oral candidiasis in HIV/AIDS patient.

Key words: HIV/AIDS, Oral candidiasis, Antiretroviral, HAART

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INTRODUCTION

Acquired immune deficiency syndrome (AIDS) is caused by human immunodeficiency virus (HIV). This virus will be binding with the surface of CD4 cells on the helper T lymphocytes (T4 lymphocyte), subsequently interacts and infects healthy cells. Furthermore, the population of helper T lymphocytes/CD4 cells decreased and viral load increased, causing impaired of immune system.^{1,2}

Once a retrovirus HIV had been identified as an agent caused of AIDS, there has been a concerted effort on the part of physicians, scientists and pharmaceutical industry to discover and develop compound that are effective in inhibiting HIV replication. Initially, were introduced in 1997, treatment for HIV-infected patients relied on nucleoside reverse transcriptase inhibitor (NRTI), namely zidovudine (AZT). Similar to NRTI, were introduced non-nucleoside reverse transcriptase inhibitor (NNRTI). Furthermore, protease inhibitor (PI) were introduced as a new drug in 1996. At present, the recommended treatment for HIV infection is Highly Active Antiretroviral Therapy (HAART) which consists of a combination of NRTI, NNRTI or PI.^{3,4,5}

Since the early reported cases of AIDS in the early 1980s, a number of oral lesions, including oral candidiasis have been associated with HIV infection. Oral candidiasis are reported to have an increased prevalence among patients with HIV-infected or AIDS and has been used as diagnostic and prognostic markers for the disease.^{6,7,8}

The introduction of combination therapies, called HAART as a treatment for HIV-infected patients in the

mid-1990s, however has been accompanied by multiple report of reduction in the incidence and prevalence of oral mucosal diseases including oral candidiasis.⁶ For instance, Patton et al from United States (1995–1999) have reported significant decrease in the prevalence of oral candidiasis from 20.3% to 16.7%.⁹

In this paper, will be review about combination antiretroviral therapy and its effect on oral candidiasis in HIV-infected and AIDS patients.

HIV/AIDS and oral candidiasis

From the earliest periods of AIDS epidemic, oral candidiasis was recognized as an important sign of disease process and its progression. The frequency of Candida isolation and clinical signs of oral candidiasis increases with advancing HIV infection.^{10,11} The prevalence ranges between 30 and 60% among HIV-infected subjects and reaches 90% in patients with AIDS.^{12,13} Oral candidiasis in HIV-infected and AIDS patients may present as pseudomembranous, erythematous, hyperplastic and angular cheilitis variants.^{10,11,12}

The presence of oral candidiasis in HIV-infected and AIDS patients was associated with a number factors including low CD4 counts, increased viral load, xerostomia, age and Secretory aspartyl proteinase (Sap), extracellular hydrolytic enzyme was product by Candida.^{7,10,13,14}

Oral candidiasis occurs more frequently in HIV-infected patients with low CD4 counts. Imam et al found a statistically significant increase in the frequency of HIV-related oral candidiasis in patients with CD4 counts of less than 300 cells/mm³.⁷ This condition made Candida,

normally flora normal of oral cavity was easy develop and inadequate immune system will made resistance to *Candida* decreased and facilitated *Candida* to invasion of tissue.¹⁰

Viral load has important role in the pathogenesis of oral candidiasis in the HIV-infected and AIDS patients. Several investigations had shown that associated of oral lesions with elevated viral load levels because immune system disorders.¹⁵ Migliorati *et al.*¹¹ demonstrated that the risk of developing oral candidiasis in HIV patients is higher when the viral load is above 3,000 copies/mL.

There are reports that salivary anticandidal activities are compromised in AIDS patients and give contribution to increased incidence of *Candida* oral infection. A pilot study of 12 AIDS patients showed that salivary anticandidal activity was decreased as compared with healthy controls. This decrease in salivary anticandidal activity in AIDS patients has been attributed to a decrease in the concentration of salivary histatins and/or to dysfunction of these proteins.¹³ Histatine are a family of histidine-rich polypeptides and are the major antifungal proteins present in human saliva. In addition, many of the specific proteins secreted by the salivary glands have antifungal activities like Ig A, lactoferin and lysozyme were decreased too.¹³

Neutropenia is a frequent hematological complication in HIV infection, detected in 20% to 50% of symptomatic patients, it is usually accompanied by functional alterations of neutrophils. As we know, neutrophils play a pivotal role in the defense mechanism against *Candida*. Dios *et al.*¹⁶ had shown in their study, 6 neutropenic patients with AIDS and neutrophils counts below 1×10^9 per liter have greatest number of episodes of oral candidiasis.

Secretory aspartyl proteinase (Sap) have been the most comprehensively studied has an important key in the presence of oral candidiasis. Sap is an extracellular hydrolytic enzymes produced by *Candida albicans*.¹⁷ One investigation had reported a comparable increase in Sap activity in *Candida albicans* strains isolated from the oral cavities of 44 HIV-positive patients with oral candidiasis compared with that in 30 HIV-negative *Candida albicans* carriers. Apparently, *Candida albicans* isolates from HIV-positive subjects produced significantly more proteinase than did isolates from HIV-negative individuals.¹⁷

Antiretroviral therapy for the HIV/AIDS patients

Until this day, there are three classes of drugs that used treatment HIV-infected patients. They are nucleoside reverse transcriptase inhibitor (NRTI), non-nucleoside reverse transcriptase inhibitor (NNRTI) and protease inhibitor (PI).^{4,18,19}

Nucleoside reverse transcriptase inhibitor (NRTI): NRTI was the first drugs made available for the treatment of HIV-infected patients. The reverse transcriptase inhibitor is phosphorylated in the cell to the triphosphate, which inhibits the HIV reverse transcriptase and leads to premature termination of the HIV DNA chain. Include in this class of drugs are zidovudine (AZT), didanosine (ddI), zalcitabine (ddc), stavudine (d4T) and lamivudine (3TC).^{4,19}

Non nucleoside reverse transcriptase inhibitor (NRTI): non nucleoside reverse transcriptase inhibitor (NRTI) are a group of structurally diverse agents which bind to reverse transcriptase at a site distant to the active site resulting in conformational changes at the active and inhibition of enzyme activity. NRTI consists of nevirapine (NEV) and delavirdine (DLV).^{4,18,19}

Protease inhibitor (PI): protease inhibitor (PI) was introduced in 1996 and has different targeted with the reverse transcriptase inhibitor.^{4,5} The protease inhibitor bind competitively to the substrate site of the viral protease. This enzyme is responsible for the post-translational processing and cleavage of a large structural core protein during budding from the infected cell. Inhibition results in the production of immature virus particles.^{4,18,19}

Protease inhibitor consists of saquinavir (SQV), indinavir (IDV), ritonavir (RTV) and amprenavir.^{19,20}

In the mid-1990s, were introduced combination antiretroviral therapy, so called Highly Active Antiretroviral Therapy (HAART) as a standard treatment for HIV-infected and AIDS patients.³ These therapies consists of a combination of at least 3 antiviral drugs- 2 NRTI with either a protease inhibitor or an NNRTI.^{3,5,18}

The aim of this treatment is to reduce the plasma viral load as much as possible and for as long as possible by attacking the virus at different stages of its replication cycle (Figure 1), inhibiting the multiplication rate of the virus and preventing the development of drug resistance.³

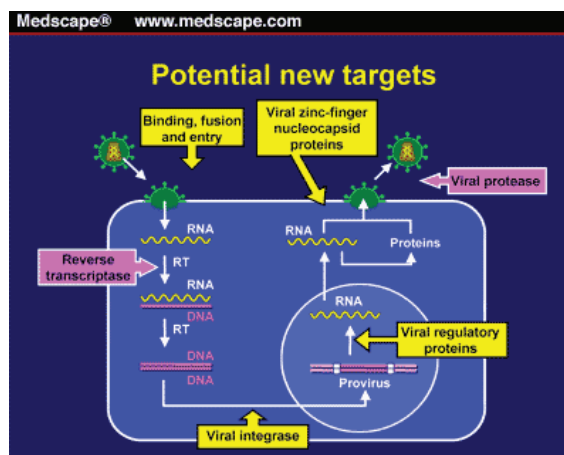


Figure 1. Targets for antiretroviral therapy.⁴

Thus, HAART decreases HIV viral load and leads to the increase of CD4 lymphocytes counts, causing an improvement of immunity and a decrease in the incidence of opportunistic infections.^{11,21}

The presence of oral candidiasis in HIV/AIDS patients after combination antiretroviral therapy

Combination antiretroviral therapy appears have an impact on the oral opportunistic infections. Since the introduction of HAART, there have been striking changes in the frequency and character of the oral complication of HIV disease. Antiretroviral drugs significantly lessen HIV viral

load, increase CD4 cell counts and lessen the frequency and severity of oral opportunistic infections. For instance, Salobrena *et al.*,⁶ from Spain had evaluated the oral lesions from 1995–2000 and described a decrease in the prevalence of oral lesions from 22.4% to 5.2%. Similarly, Patton *et al.*⁹ reported significant decreases in the prevalence of HIV related oral diseases with HAART (from 47.6% to 37.5%) in US patients.

Some studies specifically demonstrated the decrease prevalence of oral candidiasis with the widespread used of HAART. A study in United Kingdom by Tappuni and Fleming comparing subjects on HAART group and non HAART group. From this study showed that subjects on HAART group had significantly less oral candidiasis than did subjects on non HAART group, that is pseudomembranous candidiasis variant from 12% to 8% and erythematous variant from 25% to 8%.³

A study on 807 HIV/AIDS patients in Spain, found a declining rate of oral candidiasis following the introduction of HAART with stabilization or improvement in the immune status of patients.⁶ Cattopadhyay *et al.*²² also reported decreases in oral candidiasis in 283 patients in North Carolina.

The European Community Clearinghouse on Oral Problems Related to HIV Infection and WHO Collaborating Centre showed the greatest reduction in the prevalence of oral candidiasis (from 51.4% to 17.1%), especially of the pseudomembranous variant.²³

DISCUSSION

At present, the recommended treatment for HIV infection is HAART, which consists of a combination of at least 3 antiviral drugs, 2 NRTI with either a PI or an NNRTI. This combination attacking the virus at different stages of its replication cycle.

Combination therapies appears to have a critical role in the prevention of oral manifestations of HIV, probably because of its role in the reconstitution of the immune system.³ As we know, oral lesions strongly associated with HIV, such as oral candidiasis, hairy leukoplakia, Kaposi's sarcoma and necrotizing periodontal diseases, are also strongly associated with reduced of immune system.⁹

In the reduction of frequency of oral candidiasis, combination therapies have several mechanisms. One of them, with these regimens demonstrated increases CD4 cells counts, decreases viral load as much as possible (below 3,000 copies/mL). Such a thing related an improving immunity thereby reduces the potential risk of opportunistic infections such as *Candida* species.^{3,6,9,14}

In addition, combination therapies has been significantly associated with increases in neutrophils count. Neutrophils plays a pivotal role in the defense mechanisms against *Candida*. Neutrophils produce granulocyte-colony stimulating factors (G-CSF) and granulocyte macrophage-colony stimulating factors (GM-CSF) that induce

improvement of their functionality thereby might inhibit oral candidiasis.^{9,16,23}

On the other hand, decreased in prevalence of oral candidiasis in HIV-infected patients might also attributed to the direct effect of antiretroviral protease inhibitor over secretory aspartyl protease, a potent virulence factor of *Candida* species.¹¹ Protease inhibitor therapy has capacity inhibited production and activity of secretory aspartyl protease, which are involved in *Candida* adherence.^{14,22} Some believe that the antifungal effect of antiretroviral protease inhibitor is equivalent to fluconazole.¹¹

However, there were systemic and oral adverse effects can arise with the used of combination therapies. Systemic effects include dry skin, headache, nausea, neuropathy and liver disorder. On the orofacial regions, HAART seems to increase the incidence of HIV-related salivary gland disease, especially enlargement of parotid gland. The other oral side effects are mouth ulcer and oral warts.²⁴

In conclusion, oral candidal infection in HIV-infected patients have shown a decrease in the era of HAART. HAART decreases HIV viral load and lead to increases of CD4 lymphocytes count, causing an improvement of immunity.

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