OMPJ

10.5005/jp-journals-10037-1004

REVIEW ARTICLE

Antiretroviral Therapy: What to Look Out For!

[1]Divya Uppala, [2]Sumit Majumdar, [3]Lokesh Reddy, [4]Aparnna Suresh

ABSTRACT

Antiretroviral therapy, though has its distinct advantages, it comes along with its due flip sides. Numerous studies have time and again proved the effects of this therapy on the general body. But a minuscule of it is targeted on its effect on the oral tissues. Effects such as gingival epithelial changes to pigmentation of the palate, tongue and buccal mucosa have been documented and new studies are needed to highlight this aspect. These changes can be taken into highlight and be used as an important diagnostic aid and also indicating toward treatment failure. This review article encompasses the side effects and adverse effects of this type of therapy on the general body as well as the oral aspect.

Keywords: Antiretroviral therapy, Side effects, Adverse effects, Oral cavity, HAART.

How to cite this article: Uppala D, Majumdar S, Reddy L, Suresh A. Antiretroviral Therapy: What to Look Out For!. Oral Maxillofac Pathol J 2014;5(1):429-433.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Globally, 34.0 million (31.4-35.9 million) people were living with HIV at the end of 2011. Worldwide, the number of people newly infected continues to fall: the number of people (adults and children) acquiring HIV infection in 2011 was 20% lower than in 2001. The number of people dying from AIDS-related causes began to decline in the mid-2000s because of the steady decline in HIV incidence and scaled-up antiretroviral therapy since the peak in 1997. Antiretroviral therapy reached 8 million people by the end of 2011—a 20-fold increase since 2003. Since 1995, antiretroviral therapy has added 14 million life-years in low- and middle-income countries.[1] Twenty-five years after the discovery of the antiviral effect of AZT (Broder, 2010; Mitsuya et al, 1985), there are 25 approved single antiretroviral drugs in 6 mechanistic classes.[2,3] These six classes include the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) (Cihlar and Ray, 2010) (Martin et al 2010), non-nucleoside reverse transcriptase inhibitors (NNRTIs) (de Bethune, 2010), protease inhibitors (PIs) (Wensing et al 2010), entry/fusion inhibitors (FIs) and CCR5 antagonists (Tilton and Doms, 2010), and integrase inhibitors (McColl and Chen, 2010).[2-9] In India, the National AIDS Control Organization (NACO) introduced inexpensive and generic ART drugs.[10] So, with the availability of generic HAART at low cost, an increasing number of HIV-infected individuals in India are now receiving therapy.[11] Adverse events are common and may lead to discontinuation of therapy, dose interruption, and significant reductions in quality of life. Adherence may be compromised because of adverse events, and adherence is increasingly recognized as an important determinant of successful antiretroviral therapy.[12]

HIV care facilities in developing countries have witnessed dramatic decreases in mortality that are similar to those previously recorded in developed countries. One by-product of increased access to HAART, however, is that management of antiretroviral drug-related toxicities is becoming an important component of HIV care in developing countries.[13]

Each antiretroviral medication is associated with its own specific adverse effects or may cause problems only in particular circumstances. Similarly, class specific adverse effects may occur. (Adverse effects of antiretroviral therapy for HIV infection). This review focuses on the well-known adverse and side effects of ART on the general body as well as the oral cavity.

A significant proportion of patients had adverse effects of a lower grade severity after HAART. A significant proportion of those started on ART substitute therapy due to adverse effects and those on NVP-based regimens are more likely to do so when compared with those on non-NVP- based regimens.[14] All antiretroviral drugs can have both short-term and long-term adverse events. The risk of specific side effects varies from drug to drug, from drug class to drug class, and from patient to patient.[15]

Working Mechanism

Current treatments against human immunodeficiency virus type 1 (HIV-1) infections include six different classes of

[1,3]Senior Lecturer, [2]Head
[4]Assistant Professor

[1,2]Department of Oral Pathology, GITAM Dental College Vizag, Andhra Pradesh, India

[3]Department of Oral Pathology, Vydehi Institute of Dental Sciences, Bengaluru, Karnataka, India

[4]Department of Periodontics, Vydehi Institute of Dental Sciences, Bengaluru, Karnataka, India

Corresponding Author: Divya Uppala, Senior Lecturer Department of Oral Pathology, GITAM Dental College, Rushikonda Vizag, Andhra Pradesh, India, Phone: 9966413710 e-mail: uppala.divya@gmail.com

drugs, targeting the three viral enzymes (more than 20 different compounds in clinical use target the protease, reverse transcriptase and integrase), the virus fusion process (enfuvirtide/T-20 targets the viral gp41) or viral entry (maraviroc targets the human CCR5 cellular coreceptors) [Novel targets for HIV therapy. Antiviral Res. 2008] Combinations of these drugs are used in a treatment strategy known as HAART.

NRTIs were the first class of drugs to be approved by the FDA (Young 1988). Reverse transcriptase (RT) inhibitors are divided into two classes: nucleoside and nucleotide RT inhibitors (NRTIs), and non-nucleoside RT inhibitors (NNRTIs). NRTIs compete with the natural nucleoside triphosphate (dNTP) for binding the RT polymerase active site, and after their incorporation into the primer strand, act as terminator of DNA synthesis due to the lack of a 3'-hydroxyl group. NNRTIs do not interfere with dNTP binding, but rather lead to unproductive complexes by altering the conformation or mobility of RT, thereby exerting a noncompetitive inhibition. NNRTIs are highly specific for HIV-1 RT and result in less adverse effects than NRTIs.[16] The stable integration of the reverse transcribed viral genome into host chromatin forms an important point-of-no-return during HIV infection. Strand transfer integrase inhibitors bind in the catalytic core domain of the enzyme and compete for binding with host DNA.[17]

The HIV protease is the enzyme responsible for the cleavage of the viral gag and gag-pol polyprotein precursors during virion maturation. HIV-protease inhibitors prevent cleavage of gag and gag-pol protein precursors in acutely and chronically infected cells, arresting maturation and thereby blocking the infectivity of nascent virions. The main antiviral action of HIV-protease inhibitors is thus to prevent subsequent waves of infection; they have no effect on cells already harboring integrated proviral DNA.[18] The fusion inhibitor enfuvirtide and the small-molecule CCR5 antagonist maraviroc are the first two licensed entry inhibitors. They bind to different regions of CCR5 and thereby disruption of sequential steps on viral entry.[19] Maturation inhibitors are a novel mechanistic class of antiretroviral drug that target protease cleavage sites in Gag. Bevirimat is the first-in-class maturation inhibitor, which specifically inhibits cleavage of SP1 from the C-terminus of Capsid.[20]

Side Effects and Adverse Reaction

Adverse drug reaction is a response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function (WHO, 1972). Side effect is any unintended effect of a drug occurring at normal dosage which is related to the pharmacological properties of the drug.[21]

Factors Associated with Side Effects

Women have higher chances of acquiring Steven Johnsons syndrome, hepatotoxicity with nevirapine and higher toxicity rates of lactic acidosis from NRTIs.[22]

Other factors that can have an add on effect on ARTs are the simultaneous usage of medications that have an additive toxic effect, conditions that can exacerbate the side effects, e.g. viral hepatitis, alcoholism that have an added burden on the liver, drug interactions, drug related toxicities (use of ribavirin with didanosine) and genetic factors (patients sensitive to abacavir), history of psychiatric illness. The most common cause of nonadherence, mortality and discontinuing therapy are the adverse effects caused due to ART (Bersoff-Matcha et al 2001).[22-24]

Some Common Adverse Effects

Effect on Fat, Lean and Bone Mass

Lipodystrophy (Fig. 1), also called fat redistribution, is a disturbance in the way your body produces, uses, and stores fat. It is associated with side effects, such as peripheral fat wasting, central adiposity, dyslipidemia and insulin resistance. Monocyte CD36 levels are affected with the patient exposure to antiretroviral therapy, mainly protease inhibitors. The protease inhibitors act on the peroxisome proliferator activated receptor (PPAR) by impairing the production of 9 cis retinoic acid. PPAR is further, associated with the activation of CD36 which is a scavenger receptor present on macrophages. CD36 present on macrophages takes in lipoproteins and also acts as a high affinity transporter to adipose tissues. Fall in the PPAR dramatically increases the serum fatty acids, triglycerides and cholesterol levels (Abumrad NA et al 1993).[25-28]

Protease inhibitors adversely affect the differentiation of fat on transcription factors, such as sterol regulatory element binding protein-1 (SREBP- 1). In a study done by Yelmokas et al in 2001 in a cohort of 203 HIV-positive men and

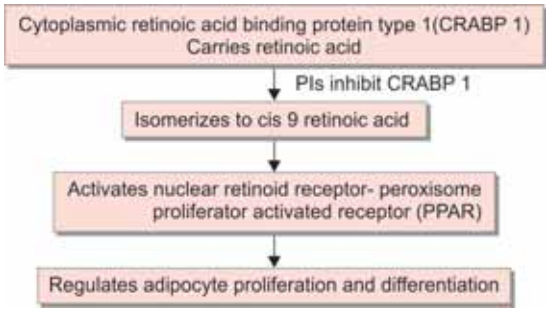

Fig. 1: Pathway of lipodystrophy

63 HIV-positive women, they observed that patients who had protease based HAART treatment had redistribution of fat mass from the legs to the trunk. They further also noted that HAART was associated with a significant reduction in bone mineral content suggesting osteoporosis.[29]

The pathogenesis of HIV associated lipodystrophy most likely involves mechanisms, such as inhibition of mitochondrial enzymes by NRTI`s which leads to mitochondrial dysfunction and abnormal fat accumulation. Carr et al (1998) expressed that the genetic sequence of the catalytic region of HIV-1 protease has 60% similarity to proteins that are involved in the lipid metabolism. They were cytoplasmic retinoic acid binding protein type 1 (CRABP-1) and low-density lipoprotein receptor-related protein (LRP).[30-34]

Studies on the effect of antiretroviral therapy on body composition by Mallon et al (2003), the limb fat, central abdominal fat and lean mass was calculated in HIV seropositive patients who were on antiretroviral therapy with stavudine as a compulsory regimen. Stavudine was the single independent factor associated with increased limb fat loss and increased central abdominal fat. The other factors associated were increase in HIV RNA. This prospective study observed that there was a progressive, selective loss of limb fat during the period.[56]

Nucleoside reverse transcriptase inhibitors particularly didansine and stavudine was commonly associated with Pancreatitis. But studies have found that Tipranavir, a protease inhibitor can also induce pancreatitis via the induction of hypertriglyceridemia.[35,36]

Hepatotoxicity: Hepatotoxicity is defined as an increase of at least three-fold in serum alanine aminotransferase or aspartate aminotransferase levels compared with baseline values. Hepatoxicity is most commonly associated with the administration of nevirapine. Though nevirapine was the first NNRTI introduced it was very soon associated with hepatotoxicity with more than 6 months of treatment with the drug. The risk of hepatotoxicity increased with associated risk factors, such as HCV infection and hepatoxic agents such as alcohol, antitubercular drugs and abnormal baseline alanine aminotransferase were identified as patient risk factors.[37,38]

Blood Pressure and Antiretroviral Therapy

Crane et al (2006) suggested that antiretroviral therapy can cause raise systolic blood pressure (SBP), hence the baseline value of SBP should be noted before ART is initiated. Those patients who were initiated on protease inhibitors more specifically on lopinavir/ritonavir were found to be associated with the increase in SBP. Rosario et al (2007) further suggest that the increase in blood pressure could be a result in the overall improvement of the general health of the patient and the people with a lower SBP in the start of the treatment had a steady improvement in the blood pressure as the treatment continued.[39,40]

Atherosclerosis

Protease inhibitors have also been implicated in the pathogenesis of increased fibrinogen levels in patients with HIV infection. Madden et al (2008) in their study of 1131 HIV infected patients and 281 controls found and assessed the cardiovascular risk in these patients. The patients were on individual PIs like ritonavir and indinavir. They found that protease inhibitors had the single univariate association with the higher levels of fibrinogen in HIV infected patients compared to normal subjects.

Candidiasis also was one of the most prevalent groups in a study done in a Mexican HIV seropositive patients undergoing highly active antiretroviral therapy and the prevalence was found to be highest in the HAART/PI group. Among the other oral lesions were, Herpes labialis, HIV associated periodontitis, xerostomia, hairy leukoplakia and nonspecific oral ulcers. Among the fungal organisms, *Candida albicans* has been shown to be present at a higher frequency among patients with HIV undergoing antiretroviral therapy (indinavir/ritonavir/saquinavir + zidovudine [AZT] + lamivudine [3TC].[40,41]

Antiretroviral Therapy and the Oral Cavity

Studies have shown that short term usage of HAART has a very good effect on the oral cavity by preventing oral lesion, however the long term usage of the same can result in side effects.[42] HAART has a very good effect on the oral cavity as it reduces the number of HIV associated oral lesions like oral candidiasis and oral hairy leukoplakia. Studies have shown that long term usage can result in the development of other side effects such as pigmentation, salivary gland disorders being salivary gland enlargement sometimes being tender and painful (Ranganathan 2007).[42-44] Protease inhibitor based antiretroviral therapy has resulted in the decrease in the incidence of oral candidiasis and studies have proven the same. However, some studies proved otherwise, PI usage and oral lesions had no significant relation (Cauda R et al, 1999).[45]

Gingival Epithelium

On a study, on the gingival epithelium it was found that protease inhibitors (Amprenavir) severely affected the proliferation and differentiation of gingival keratinocytes by affecting cytokeratins PCNA and cyclin A. IRIS and the oral cavity: there has been an increase in the incidence of salivary

gland diseases in the era of HAART which has been linked to immune reconstitution syndrome. In a study done by Ortega et al, it was found that among the oral manifestations parotid enlargement was the most common (57.14%) with candidiasis among the most frequently seen lesion among the nonimmune reconstitution group.[46-48] On the salivary gland: studies have shown that antiretroviral therapy has an effect on salivary gland. However, the pathogenesis is not clearly understood. In a study done on a cohort of 668 HIV seropositive women in Africa, Navazesh et al had concluded that protease inhibitors was a significant risk factor in the development of salivary gland disorders.[49] Salivary gland manifestations were put in the category of unstimulated and stimulated flow rate changes, complaints of dry mouth, painful, tender or any enlargement of the salivary gland. The authors also pointed that salivary structure and composition could have been altered or the lipodystrophic changes induced by PI itself could lead to deposition of adipose layer on the gland therby reducing salivary flow rate (Aguirre-Urizar et al 2004; Olive et al 1998; Ceballos-Salobrena et al 2000). These findings were in significant contrast to the study done by Ramirez-Amador et al 2003 were no changes were found to be present.[47,50-52] Further still Nicolatou-Gatis et al (2004) also reported there was no change in the incidence of salivary gland diseases in their cohort of 95 HIV seropositive patients.[53,54]

Hyperpigmentation: A known complication of antiretroviral therapy is melanotic hyperpigmentation ($p < 0.05$) this type of pigmentation was most commonly associated with ART especially in those whom zidovudine was administered.[55]

CONCLUSION

This article thus briefly summarizes the most commonly seen effects associated with antiretroviral therapy. Further, studies are needed to actually correlate ART and its intra-oral effects and its true pathogenesis.

REFERENCES

1. Global report: UNAIDS report on the global AIDS epidemic 2012.
2. Broder S. The development of antiretroviral therapy and its impact on the HIV-1/AIDS pandemic. Antiviral Res 2010 Jan; 85(1):1-18.
3. Mitsuya H, Weinhold KJ, Furman PA, St Clair MH, Lehrman SN, Gallo RC, Bolognesi D, Barry DW, Broder S. 3'-Azido-3'-deoxythymidine (BW A509U): an antiviral agent that inhibits the infectivity and cytopathic effect of human T-lymphotropic virus type III/lymphadenopathy-associated virus in vitro. Proc Natl Acad Sci USA 1985 Oct;82(20):7096-7100.
4. Cihlar T, Ray AS. Nucleoside and nucleotide HIV reverse transcriptase inhibitors: 25 years after zidovudine. Antiviral Res 2010 Jan;85(1):39-58.
5. Martin JC, Hitchcock MJM, De Clercq E, Prusoff WH. Early nucleoside reverse transcriptase inhibitors for the treatment of HIV: a brief history of stavudine (D4T) and its comparison with other dideoxynucleosides. Antiviral Res 2010.
6. De Bethune MP. Non-nucleoside reverse transcriptase inhibitors (NNRTIs), their discovery, development, and use in the treatment of HIV-1 infection: a review of the last 20 years (1989-2009). Antiviral Res 2010.
7. Wensing AMJ, Van Maarseveen NM, Nijhuis M. HIV protease inhibitors. Antiviral Res 2010.
8. Tilton JC, Doms RW. Entry inhibitors in the treatment of HIV-1 infection. Antiviral Res 2010.
9. Esté JA, Cihlar T. Current status and challenges of antiretroviral research and therapy. Antiviral Res 2010 Jan;85(1):25-33.
10. Pattanapanyasat K, Thakar MR. CD4+T cell count as a tool to monitor HIV progression and anti-retroviral therapy. Indian J Med Res 2005 Apr;121(4):539-549.
11. Kumarasamy N, Vallabhaneni S, Cecelia AJ, Yepthomi T, Balakrishnan P, Saghayam S, Flanigan TP, Carpenter CC, Solomon S, Mayer KH. Reasons for modification of generic highly active antiretroviral therapeutic regimens among patients in Southern India. J Acquir Immune Defic Syndr 2006 Jan 1; 41(1):53-58.
12. Max, Blake Sherer, Renslow. Management of the adverse effects of antiretroviral therapy and medication adherence. Clinical Infectious Diseases 2000;(Suppl 2)(30): p96.
13. Subbaraman R, Chaguturu SK, Mayer KH, Flanigan TP, Kumarasamy N. Adverse effects of highly active antiretroviral therapy in developing countries. Clin Infect Dis 2007 Oct 15; 45(8):1093-1101.
14. Sreenivasan S, Dasegowda V. Adverse effects after HAART Initiation in resource-limited settings: a prospective study from Mysore, India. J Infect Dev Ctries 2010 Nov 24;4(11):750-753.
15. Montessori V, Press N, Harris M, Akagi L, Julio SG. Montaner adverse effects of antiretroviral therapy for HIV infection. CMAJ 2004 Jan 20;170(2).
16. Maga G, Radi M, Gerard MA, Botta M, Ennifar E. HIV-1 RT inhibitors with a novel mechanism of action: NNRTIs that compete with the nucleotide substrate. Viruses 2010 April; 2(4):880-899.
17. Messiaen P, Wensing AM, Fun A, Nijhuis M, Brusselaers N, Vandekerckhove L. Clinical use of HIV integrase inhibitors: a systematic review and meta-analysis. PLoS One 2013;8(1):e52562.
18. Flexner C. HIV-protease inhibitors. N Engl J Med 1998;338: 128-129.
19. Latinovic O, Kuruppu J, Davis C, Le N, Heredia A. Pharmacotherapy of HIV-1 infection: focus on CCR5 antagonist. Clin Med Ther 2009;1:1497-1510.
20. Protease-mediated maturation of HIV: inhibitors of protease and the maturation process. Molecular Biology International 2012 (2012), Article ID 604261, 13 pages.
21. Glossary of terms used in Pharmacovigilance.
22. Bersoff-Matcha SJ, Miller WC, Aberg JA, et al. Sex differences in nevirapine rash. Clin Infect Dis 2001;32(1):124-129.
23. Keiser O, Fellay J, Opravil M, et al. Adverse events to antiretrovirals in the swiss HIV cohort study: effect on mortality and treatment modification. Antivir Ther 2007;12(8):1157-1164.
24. Fagot JP, Mockenhaupt M, Bouwes-Bavinck J-N, for the EuroSCAR study group. Nevirapine and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. AIDS 2001; 15(14):1843-1848.

25. Moyle GJ, Datta D, Mandalia S, et al. Hyperlactataemia and lactic acidosis during antiretroviral therapy: relevance, reproducibility and possible risk factors. AIDS 2002;16(10):1341-1349.
26. Geddes R, Knight S, Moosa MY, et al. A high incidence of nucleoside reverse transcriptase inhibitor (NRTI)-induced lactic acidosis in HIV-infected patients in a South African context. S Afr Med J 2006;96(8):722-724.
27. Bolhaar MG, Karstaedt AS. A high incidence of lactic acidosis and symptomatic hyperlactatemia in women receiving highly active antiretroviral therapy in Soweto, South Africa. Clin Infect Dis 2007;45(2):254-260.
28. Abumrad NA, el-Maghrabi MR, Amri EZ, Lopez E, Grimaldi P. Cloning of a rat adipocyte membrane protein implicated in binding or transport of long chain fatty acids that is induced during preadipocyte differentiation: homology with human CD36. J Biol Chem 1993;268:17665-17668.
29. McDermott AY, Shevitz A, Knox T, Roubenoff R, Kehayias J, Forbach S. Effect of highly active antiretroviral therapy on fat, lean, and bone mass in HIV-seropositive men and women. Am J Clin Nutr 2001 Nov;74(5):679-686,
30. Carr A, Samaras K, Chisholm DJ, Cooper DA. Pathogenesis of HIV-1-protease inhibitor-associated peripheral lipodystrophy, hyperlipidaemia, and insulin resistance. Lancet 1998 Jun 20; 351(9119):1881-1883.
31. Dauden, Estaben. Alaverez eruptive angiolipomas associated with antiretroviral therapy. AIDS 16(5)805.
32. Li E, Norris AW. Structure/function of cytoplasmic vitamin A-binding proteins. Annu Rev Nutr 1996;16:205-234.
33. Chambon P. A decade of molecular biology of retinoic acid receptors. Faseb J 1996;10:940-954.
34. Tontonoz P, Hu E, Spiegelman BM. Regulation of adipocyte gene expression and differentiation by peroxisome proliferator activated receptor gamma. Curr Opin Genet Dev 1995;5:571-576.
35. Reisler RB, Murphy RL, Redfield RR, Parker RA. Incidence of pancreatitis in HIV 1 infected individuals enrolled in 20 adult AIDS clinical trials group studies: lessons learned. J Acquir Immune Defic Syndr 2005;39:159-166.
36. Chapman SJR, Woolley IJ, Visvanathan K, Korman TM. Acute pancreatitis caused by tipranavir/ritonavir-induced hypertriglyceridaemia. Correspondence, AIDS 2007;21(4): 532-533.
37. Marinez E, Blanco JL, Arnaiz JA, Perez-Cuevas JB, Mocroft A, Cruceta A, Marcos MA. Hepatotoxcity in HIV 1 infected patients receiving nevirapine-containing antiretroviral therapy. AIDS 2001;15:1261-1268.
38. Baylor MS, Johann-Liang R. Hepatotoxicity associated with nevirapine use. J Acquir Immune Defic Syndr 2004;35(5): 538-539.
39. Crane HM, Van Rompaey SE, Kitahata MM. Antiretroviral medication associated with elevated blood pressure among patients receiving highly active antiretroviral therapy. AIDS 2006;20:1019-1026.
40. Palacios R, Santos J. Blood pressure and antiretroviral therapy. Correspondence AIDS 2007;21:529-538.
41. Madden E, Lee G, Kotler DP, Wanke C, Lewis CE, Tracy R. Association of antiretroviral therapy with fibrinogen levels in HIV-infection. AIDS 2008;22(6):707-715.
42. Umadevi KMR, Ranganathan K, Pavithra S, Hemalatha R, Saraswathi TR, Kumarasamy N, et al. Oral lesions as diagnostic markers of immune failure in HIV patients on highly active anti-retroviral therapy-Southern India, JOPM 2007 Mar;36(3): 136-141.
43. Nittayananta W, Chungpanich S. Oral lesions in a group of Thai people with AIDS. Oral Dis 1997;3(Suppl 1):1-5.
44. Nitayananta J, Sineepat T, Jaruratanasirikul S, Chayakul P. Effects of long term use of HAART on oral health staus of HIV infected subjects. Oral Pathol Med 2010 May;39(5):397-406.
45. Cauda R, Tacconelli E, Tumbarello M, Morace G, De Bernardis F, Torosantucci A, Cassone A. Role of protease inhibitors in preventing recurrent oral candidosis in patients with HIV infection: a prospective case-control study. J Acquir Immune Defic Syndr 1999 May 1;21(1):20-25.
46. Cassone A, Tacconelli E, De Bernardis F, Tumbarello M, Torosantucci A, Chiani P, Cauda R.Antiretroviral therapy with protease inhibitors has an early, immune reconstitution-independent beneficial effect on Candida virulence and oral candidiasis in human immunodeficiency virus-infected subjects. J Infect Dis 2002 Jan 15;185(2):188-195.
47. Aguirre-Urizar JM, Echebarria-Goicouria MA, Eguia-del-Valle A. Acquired immunodeficiency syndrome: manifestations in the oral cavity. Med Oral Patol Oral Cir Bucal 2004;9 Suppl:153-157.
48. Wipawee N, Sineepat T, Jaruratanasirikul S, Kachornsakdi S, Panthip C, Ampaipith N, Pruphetkaew N. Effects of long-term use of HAART on oral health status of HIV infected subjects. J Oral Pathol Med 2010 May;39(5):397-406.
49. Navazesh M, Mulligan R, Karim R, Mack WJ, Ram S, Seirawan, Greenspan HJ, Greenspan D, Phelan J, Alves M. Effect of HAART on salivary gland function in the women›s interagency HIV study (WIHS). Oral Dis 2009 Jan;15(1):52-60.
50. Olive A, Salavert A, Manriquez M, Clotet B, Moragas A. Parotid lipomatosis in HIV-positive patients: a new clinical disorder associated with protease inhibitors. Ann Rheum Dis 1998;57:749.
51. Ceballos-Salobrena A, Gaitan-Cepeda L, Ceballos-Garcia L, Lezama-Del Valle D. Oral lesions in HIV/AIDS patients undergoing highly active antiretroviral treatment including protease inhibitors: a new face of oral AIDS? AIDS Patient Care and STDs 2000;14(12):627-635.
52. Greenberg RG, Berger TG. Nail and mucocutaneous hyperpigmentation with azidothymidine therapy. J Am Acad Dermatol 1990;22:327-330.
53. Nicolatou-Galitis O, Velegraki A, Paikos S, Economopoulou P, Stefaniotis T, Papanikolaou I, et al. Effect of PI-HAART on the prevalence of oral lesions in HIV-I infected patients. A Greek study. Oral Diseases 2004;10:145-150.
54 Sharma G, Pai KM, Suhas S, Ramapuram JT, Doshi D, Anup N. Oral manifestations in HIV/AIDS infected patients from India. Oral Dis 2006;12:537-542.
55. Poizot-Martin I, Lafeuillade A, Dhiver C, et al. Cutaneo-mucosal hyperpigmentation in AIDS. 4 cases (in French). Presse Med 1991;20:632-636.
56. Mallon PWG, Sedwell R, Rogers G, et al. Effect of rosiglitazone on peroxisome proliferator-activated receptor gene expression in human adipose tissue is limited by antiretroviral drug–induced mitochondrial dysfunction. J Infect Dis 2008;198:1794-1803.