

OROFACIAL ADVERSE EFFECTS OF ANTIRETROVIRAL THERAPY

Abisola Jegede, BDS, MPH; Zohaib Ahmed, BDS, MPH; Kavita P. Ahluwalia, DDS, MPH

Introduction: Highly active antiretroviral therapy (HAART), which reduces viral load to facilitate recovery of immune function, has played a central role in reducing morbidity and mortality associated with HIV/AIDS. HAART consists of a combination of three or more medications from two different classes of antiretroviral drugs (two Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and Integrase Strand Transfer Inhibitor (INSTI), Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) or Protease Inhibitor (PI) with Pharmacokinetic (PK) enhancer).¹ Although *reductions in HIV-associated oral lesions have been documented in patients on HAART, a number of side effects that can increase risk for oral diseases, and impact oral health related quality of life (OHQoL) have been reported.*³ *Patients may discontinue HAART secondary to QoL declines⁴ – dentists can play a central role in managing oral symptoms and discomfort; it is important that dentists work with the medical team to educate patients about the need to adhere to HAART treatment regimens.*

Oral effects of HAART medications: Notable orofacial adverse effects such as xerostomia, oral ulceration, dysgeusia, parotid lipomatosis, and cheilitis have been documented in 7-57% of patients on HAART medications.⁵ Xerostomia and parotid lipomatosis may increase the risk for dental caries and oral candidiasis, and result in difficulty speaking, chewing and swallowing. In addition to drug related adverse effects, immune reconstitution syndrome may result in oral mucosal consequences most notably an increased risk of developing oral warts in patients with HPV infection.⁶

Oral management of the patient on HAART: Patients presenting with orofacial manifestations that are not life threatening (e.g. dyslipidemia) may be managed by pharmacologic interventions, lifestyle modifications or modification of the HAART regimen. Oral side effects associated with specific drugs, and management strategies are indicated in Table 1.

Table 1. Orofacial adverse effects and management¹⁻¹¹

Orofacial adverse effect	Drug class	Drug (Brand name)	Management
Xerostomia (may increase risk for dental caries)	NRTI NNRTI PI	Didanosine (Videx); Emtricitabine (Epivir); Lamivudine (Epivir); Zidovudine (Retrovir) Efavirenz (Sustiva); Etravirine (Intelence); Nevirapine (Viramune) Darunavir (Prezista); Indinavir (Crixivan); Nelfinavir (Viracept); Ritonavir (Norvir), Saquinavir (Invirase)	<ul style="list-style-type: none"> • Replacement/stimulation of saliva: suggest saliva substitutes, sucking on sugar-free hard candies/ ice chips, chewing sugar-free gum. • Recommend increased water intake • Systemic treatment with pilocarpine HCl 5 mg • Consider Fluoride varnish/chlorhexidine rinse/Fluoride toothpaste/rinse • Reinforce oral hygiene • Recommend diet modification
Parotid lipomatosis (may increase risk for dental caries)	PI	Amprenavir (Agenerase); Indinavir (Crixivan); Nelfinavir (Viracept); Ritonavir (Norvir); Saquinavir (Invirase)	<ul style="list-style-type: none"> • Refer for evaluation of surgical management in patients concerned about facial esthetics • Recommend increased water intake • Reinforce oral hygiene • Recommend diet modification • Consider Fluoride varnish/chlorhexidine/Fluoride toothpaste/rinse
Bleeding Disorder	NNRTI PI	Delavirdine (DLV); Tipranavir (Aptivus)	<ul style="list-style-type: none"> • Consultation with physician regarding need for therapy prior to dental procedures • Ensure vigilance during dental procedures • Placement of absorbable gelatin, collagen/micro-fibrillar collagen/oxidized regenerated cellulose. • Advise soft diet/avoiding behaviors that may provoke bleeding
Taste disturbances	NRTI NNRTI PI	Zidovudine (Retrovir) Nevirapine (Viramune) Indinavir (Crixivan); Ritonavir (Norvir); Saquinavir (Invirase)	<p>No guidelines exist for the pharmacologic management of taste disturbances.</p> <ul style="list-style-type: none"> • Zinc sulfate may be useful, but may negatively impact the immune system if used in excess. • Recommend consuming foods that are cold/at room temperature • Recommend avoiding use of silver metallic silverware

Oral Ulceration with or without stomatitis	NRTI NNRTI PI	Emtricitabine (Emtriva); Zidovudine (Retrovir) Delavirdine (Rescriptor) Nelfinavir (Viracept); Ritonavir (Norvir); Saquinavir (Invirase); Tipranavir (Aptivus)	<ul style="list-style-type: none"> • Recommend topical corticosteroids (dexamethasone elixir) swished for one minute, then expectorated. Systemic corticosteroids such as prednisone may be used for more severe/recurrent occurrences • Manage pain using topical or systemic analgesics. <ul style="list-style-type: none"> • Topical analgesic use may blunt taste buds and impact nutrition. • An over-the-counter oral formulation of 2-octyl cyanoacrylate (Orabase Soothe-N-Seal) may be used as a barrier product for managing localized oral pain
Oral warts		Specific drugs not documented	<ul style="list-style-type: none"> • Refer to oral and maxillofacial surgeon for surgical excision/directed liquid nitrogen sprays/Intralesional treatment with bleomycin/interferon-alfa
Increased salivation	NNRTI	Delavirdine (Rescriptor)	No guidelines exist for pharmacologic management.
Erythema multiforme	NRTI NNRTI PI	Abacavir (Ziagen); Didanosine (Videx; Videx EC); Zidovudine (Retrovir) Delavirdine (Rescriptor); Efavirenz (Sustiva); Etravirine (Intelence); Nevirapine (Viramune) Ritonavir (Norvir); Saquinavir (Invirase); Efavirenz (Sustiva)	<ul style="list-style-type: none"> • Mild/localized lesions: topical steroids Fluocinonide/Fluocinonide ointment in Orabase (1:1); Clobetasol ointment in Orabase (1:1); Dexamethasone oral rinse (0.5 mg/5 ml). • Severe lesions: start patient on both topical and systemic steroids (Prednisone)
Hyperpigmentation of oral mucosa or lip	NRTI	Zidovudine (Retrovir); Emtricitabine (Emtriva)	<ul style="list-style-type: none"> • Rule out Hairy Leukoplakia • Recommend use of lip moisturizers containing sunscreen and avoid sun exposure.
Cheilitis	PI	Indinavir (Crixivan)	<ul style="list-style-type: none"> • Application of Nystatin and Triamcinolone cream 2 to 4 times/day.

*Patients may present with other orofacial adverse effects including *Steven-Johnson Syndrome/Toxic Epidermal Necrolysis, Facial Lipodystrophy*, which should be managed in collaboration with the medical team.

REFERENCES:

1. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents [internet]. https://aidsinfo.nih.gov/contentfiles/lvguidelines/AA_Recommendations.pdf. Accessed October 19, 2016.
2. Patton LL, McKaig R, Strauss R, Rogers D, Eron JJ. Changing prevalence of oral manifestations of human immuno-deficiency virus in the era of protease inhibitor therapy. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*. 2000;89(3):299-304.
3. Leao JC, Ribeiro C, Carvalho AA, Frezzini C, Porter S. Oral complications of HIV disease. *Clinics*. 2009;64(5):459-470.
4. Hodgson T, Greenspan D, Greenspan J. Oral lesions of HIV disease and HAART in industrialized countries. *Adv Dent Res*. 2006;19(1):57-62.
5. Scully C, Diz Dios P. Orofacial effects of antiretroviral therapies. *Oral Dis*. 2001;7(4):205-210.
6. Dios PD, Scully C. Adverse effects of antiretroviral therapy: Focus on orofacial effects. *Expert opinion on drug safety*. 2002;1(4):307-317.
7. Shrivastava S, Singh A, Singh S. Adverse side effects of antiretroviral therapy on oral tissues in HIV positive individuals. *Oral & Maxillofacial Pathology Journal*. 2013;4(1).
8. Selected agents used to treat HIV infection or related conditions [internet]. HIV clinical resource. <http://www.hivguidelines.org/wp-content/uploads/2009/06/d-app1.pdf>. Updated 2006. Accessed October 19, 2016.
9. Max B, Sherer R. Management of the adverse effects of antiretroviral therapy and medication adherence. *Clin Infect Dis*. 2000;30 Suppl 2:S96-116.
10. Kalaskar AR. Management of chemotherapy induced dysgeusia: An important step towards nutritional rehabilitation. *International Journal of Physical Medicine & Rehabilitation*. 2014;2014.
11. Reznik DA, O'Daniels C. Oral manifestations of HIV/AIDS in the HAART era. *HIV Dent oral manifestations*. 2011.

Abisola Jegede, BDS, MPH, is a Dental Public Health Postdoctoral Trainee, Columbia University College of Dental Medicine, New York, NY.

Zohaib Ahmed, BDS, MPH, is a Dental Public Health Postdoctoral Trainee, Columbia University College of Dental Medicine, New York, NY.

Kavita P. Ahluwalia, DDS, MPH, is Associate Professor and Director of the Postdoctoral Program in Dental Public Health, Section of Population Oral Health, Columbia University College of Dental Medicine, New York, NY.