

## OROFACIAL ADVERSE EFFECTS OF ANTIRETROVIRAL THERAPY

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**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).<sup>1</sup> 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.*<sup>3</sup> *Patients may discontinue HAART secondary to QoL declines<sup>4</sup> – 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.<sup>5</sup> 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.<sup>6</sup>

**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 management<sup>1-11</sup>**

Orofacial adverse effect	Drug class	Drug (Brand name)	Management
<b>Xerostomia (may increase risk for dental caries)</b>	<b>NRTI</b>  <b>NNRTI</b>  <b>PI</b>	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"> <li>• Replacement/stimulation of saliva: suggest saliva substitutes, sucking on sugar-free hard candies/ ice chips, chewing sugar-free gum.</li> <li>• Recommend increased water intake</li> <li>• Systemic treatment with pilocarpine HCl 5 mg</li> <li>• Consider Fluoride varnish/chlorhexidine rinse/Fluoride toothpaste/rinse</li> <li>• Reinforce oral hygiene</li> <li>• Recommend diet modification</li> </ul>
<b>Parotid lipomatosis (may increase risk for dental caries)</b>	<b>PI</b>	Amprenavir (Agenerase); Indinavir (Crixivan); Nelfinavir (Viracept); Ritonavir (Norvir); Saquinavir (Invirase)	<ul style="list-style-type: none"> <li>• Refer for evaluation of surgical management in patients concerned about facial esthetics</li> <li>• Recommend increased water intake</li> <li>• Reinforce oral hygiene</li> <li>• Recommend diet modification</li> <li>• Consider Fluoride varnish/chlorhexidine/Fluoride toothpaste/rinse</li> </ul>
<b>Bleeding Disorder</b>	<b>NNRTI</b>  <b>PI</b>	Delavirdine (DLV);  Tipranavir (Aptivus)	<ul style="list-style-type: none"> <li>• Consultation with physician regarding need for therapy prior to dental procedures</li> <li>• Ensure vigilance during dental procedures</li> <li>• Placement of absorbable gelatin, collagen/micro-fibrillar collagen/oxidized regenerated cellulose.</li> <li>• Advise soft diet/avoiding behaviors that may provoke bleeding</li> </ul>
<b>Taste disturbances</b>	<b>NRTI</b>  <b>NNRTI</b>  <b>PI</b>	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"> <li>• Zinc sulfate may be useful, but may negatively impact the immune system if used in excess.</li> <li>• Recommend consuming foods that are cold/at room temperature</li> <li>• Recommend avoiding use of silver metallic silverware</li> </ul>

<b>Oral Ulceration with or without stomatitis</b>	<b>NRTI</b>  <b>NNRTI</b>  <b>PI</b>	Emtricitabine (Emtriva); Zidovudine (Retrovir)  Delavirdine (Rescriptor)  Nelfinavir (Viracept); Ritonavir (Norvir); Saquinavir (Invirase); Tipranavir (Aptivus)	<ul style="list-style-type: none"> <li>• Recommend topical corticosteroids (dexamethasone elixir) swished for one minute, then expectorated. Systemic corticosteroids such as prednisone may be used for more severe/recurrent occurrences</li> <li>• Manage pain using topical or systemic analgesics. <ul style="list-style-type: none"> <li>• Topical analgesic use may blunt taste buds and impact nutrition.</li> </ul> </li> <li>• 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</li> </ul>
<b>Oral warts</b>		Specific drugs not documented	<ul style="list-style-type: none"> <li>• Refer to oral and maxillofacial surgeon for surgical excision/directed liquid nitrogen sprays/Intralesional treatment with bleomycin/interferon-alfa</li> </ul>
<b>Increased salivation</b>	<b>NNRTI</b>	Delavirdine (Rescriptor)	No guidelines exist for pharmacologic management.
<b>Erythema multiforme</b>	<b>NRTI</b>  <b>NNRTI</b>  <b>PI</b>	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"> <li>• 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).</li> <li>• Severe lesions: start patient on both topical and systemic steroids (Prednisone)</li> </ul>
<b>Hyperpigmentation of oral mucosa or lip</b>	<b>NRTI</b>	Zidovudine (Retrovir); Emtricitabine (Emtriva)	<ul style="list-style-type: none"> <li>• Rule out Hairy Leukoplakia</li> <li>• Recommend use of lip moisturizers containing sunscreen and avoid sun exposure.</li> </ul>
<b>Cheilitis</b>	<b>PI</b>	Indinavir (Crixivan)	<ul style="list-style-type: none"> <li>• Application of Nystatin and Triamcinolone cream 2 to 4 times/day.</li> </ul>

\*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.

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