

Orofacial Manifestations of Highly Active Antiretroviral Therapy (HAART) and Pre-Exposure Prophylaxis (PrEP)

Implications for Dental Care and Guidelines for Management

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Abstract

HAART and PrEP have demonstrated reduction of HIV-related mortality and HIV infection, respectively. A range of orofacial side effects has been associated with both HAART and PrEP. As PrEP usage has increased, there has also been an increase in sexually transmitted infections that have orofacial symptoms. As oral health care providers, it is important that we recognize these orofacial side effects and symptoms. Further, we offer clinical recommendations for dental professionals treating patients who are on either HAART or PrEP and their associated risk factors.

Human immunodeficiency virus (HIV) is a viral pathogen that attacks the body's immune system, weakening it over time and making it increasingly susceptible to a range of infections and diseases. If left untreated, HIV can progress to acquired immunodeficiency syndrome (AIDS), a severe and often life-threatening condition. Although there is no definitive cure for HIV, the disease can be managed effectively with highly active antiretroviral therapy (HAART). Comprising a combination of at least three antiretroviral drugs, HAART aims to suppress the viral load, thereby improving the quality of life and minimizing the risk of HIV transmission.¹ Table 1 summarizes different classes of HAART medications and their mechanisms of action.

Beyond the management of people living with HIV, the

Table 1 — Classes of HAART Medications and Mechanism of Action

HAART Classes	Mechanism Of Action	Examples
Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)	Competitively bind to reverse transcriptase and cause premature DNA chain termination	Abacavir, Didanosine, Lamivudine, Stavudine, Tenofovir, Zidovudine
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Inhibit nucleoside binding and inhibition of DNA polymerase	Delavirdine, Efavirenz, Nevirapine, Risperivine
Protease Inhibitors (PIs)	Lead to immature, noninfectious virions	Delavirdine, Efavirenz, Nevirapine, Risperivine
Integrase Strand Transfer Inhibitors (INSTIs)	Prevent incorporation of viral DNA into the host cell chromosome	Dolutegravir, Cabotegravir, Elvitegravir, Raltegravir
Fusion inhibitors (Fis)	Prevent viral fusion to the CD4 T-cells	Enfuvirtide
Chemokine Receptor Antagonists (CCR5 Antagonists)	Block viral entry into the CD4 T-cells selectively and reversibly	Maraviroc

prevention of HIV transmission plays a crucial role in the comprehensive approach to tackling this health challenge. Pre-exposure prophylaxis (PrEP) has revolutionized HIV prevention since its FDA approval. These drug regimens are now commonly prescribed to high-risk patients, making it a standard aspect of preventive health care. Its widespread use and accessibility through health-care providers means it's not just a specialized treatment but a broadly applicable preventive measure. Major PrEP medications include Truvada,[®] Descovy,[®] and Apretude.[®] Table 2 summarizes available PrEP medications, their components, and their respective routes of administration.

Like HAART, these medications function by inhibiting essential enzymes involved in the life cycle of HIV. Both HAART and PrEP have demonstrated reduction of HIV-related mortality and HIV infection, respectively. However, like many medical interventions, these therapies are not without their drawbacks.^{2,3} Specifically, a range of orofacial side effects has been associated with both HAART and PrEP medications.^{4,5} Certain medications, such as Truvada[®] and Descovy,[®] are used in both HAART and PrEP regimens. Specifically, the components emtricitabine, tenofovir, and tenofovir alafenamide found in these medications could induce similar orofacial side effects in both HAART and PrEP.

This brief aims to discuss the oral manifestations associated with the use of HAART and PrEP medications. Further, we offer recommendations for dental professionals treating patients who are on either HAART or PrEP and their associated orofacial risk factors.

Orofacial side effects of HAART and PrEP

The adverse systemic and orofacial effects associated with antiretroviral drugs impact the quality of life of

patients and significantly contribute to noncompliance. Because these medications are administered long-term, typically dosed daily, and require a high level of adherence to be effective, understanding and managing their side effects are essential to successful treatment.

In addition to the established systemic effects of anti-retroviral drugs, such as gastrointestinal disturbances, reduced bone mineral density, and altered kidney and liver function, a subset of associated orofacial manifestations has been documented. HAART regimens are associated with a variety of adverse orofacial effects, including xerostomia, taste disturbances, ulcers, erythema multiforme, toxic epidermal necrolysis, facial lipoatrophy, perioral paresthesia, exfoliative cheilitis, oral mucosal hyperpigmentation, and oral warts.⁴

NRTIs, NNRTIs, and PIs commonly used in HAART also cause changes in the growth and differentiation of gingival epithelium, including loss of tissue integrity, increased tissue proliferation, impaired healing ability, and cell cycle dysregulation. These cytologic alterations may present clinically as fragile gingival tissue, ulcers, and blisters. This may also increase patients' susceptibility to viral tumors and opportunistic infections.⁶

HAART-associated oral conditions include xerostomia, which results in

increased caries risk and vulnerability of mucosa to mechanical injury. While most HAART-related adverse oral effects are not exclusive to a specific class of antiretroviral agent, it has been suggested that erythema multiforme is common in NNRTIs.⁴ Ulcers, xerostomia, and lipodystrophy are common in NRTIs.⁴ Taste disturbances, paresthesia, and xerostomia are common in PIs.⁴ Several dentofacial complications specific to HIV-infected children on HAART have also been reported. They include molar-incisor hypomineralization, delayed dental eruption, and lipodystrophy.⁷ Table 3 (See Page 48) summarizes common HAART-related oral complications and their respective clinical presentations.

Though the literature surrounding the adverse effects of PrEP, specifically Truvada[®] and Descovy,[®] is limited, several studies have started to identify oral complications in HIV-uninfected populations taking these preventive medications. The prolonged use of PrEP is associated with xerostomia, increased thirst, and taste disturbances.⁵ Given that PrEP and HAART regimens share common antiretroviral agents, specifically the NRTI tenofovir, preliminary data has suggested that PrEP may also exert a pro-inflammatory effect on the oral mucosa similar to the adverse cyto-

(Continued on Page 48)

Table 2 — Key PrEP Medication, Components and Routes of Administration

PrEP Drugs	Composition	Mechanisms of Action	Routes of Administration
Truvada [®]	Emtricitabine, Tenofovir	Nucleoside Reverse Transcriptase Inhibitors	Oral
Descovy [®]	Emtricitabine, Tenofovir alafenamide	Nucleoside reverse transcriptase Inhibitor	Oral
Apretude [®]	Cabotegravir	Integrase Strand Transfer Inhibitors	Long-acting injection

Table 3 — Common HAART and PrEP Oral Manifestations

Orofacial Complication	Clinical Presentation
Xerostomia	<ul style="list-style-type: none"> • Dry tongue • Cracked lips • Increased caries incidence • Burning sensation • Ulcers • Fragile mucosa • Difficulty chewing, speaking, and swallowing
Taste disturbances	<ul style="list-style-type: none"> • Partial or total loss of taste sensation • Unpleasant change in taste sensation (dysgeusia, bitterness)
Erythema multiforme	<ul style="list-style-type: none"> • Prodrome (fever, malaise, sore throat) one week before the acute onset of ulcerations involving the skin and oral mucosa • Painful, diffusely distributed ulcers and blisters • Hemorrhagic crusting of the lip vermillion • Targetoid skin lesions
Toxic epidermal necrolysis	<ul style="list-style-type: none"> • Severe diffuse skin sloughing • Life-threatening reaction • Ocular damage
Lipodystrophy	<ul style="list-style-type: none"> • Abnormal fat distribution • Apparent fat loss/accumulation in face, limbs, buttocks
Circumoral paresthesia	<ul style="list-style-type: none"> • Tingling, burning, “pins and needles” sensation around mouth
Exfoliative cheilitis	<ul style="list-style-type: none"> • Persistent lip peeling
Mucocutaneous hyperpigmentation	<ul style="list-style-type: none"> • Solitary or multiple black/brown macules on oral mucosa, skin, or nails • Most common in African-American patients
Molar-incisor hypomineralization	<ul style="list-style-type: none"> • White/yellow discoloration • Altered tooth translucency • Tooth hypersensitivity • Post-eruptive enamel breakdown • Rapid caries progression
Delayed tooth eruption	<ul style="list-style-type: none"> • Delayed pattern of permanent tooth emergence
Oral warts	<ul style="list-style-type: none"> • Warts or raised growths in oral cavity

Orofacial Manifestations
(Continued from Page 47)

logic alterations to gingival epithelium reported in HAART patients.⁸

No studies to date have specifically explored the orofacial effects of Aprelude,[®] the newest PrEP formulation. However, allergic reactions to Aprelude[®] can result in swelling of the mouth, face, lips, or tongue. This medication’s route of administration as a long-acting bimonthly injection poses a promising solution to the compliance issues surrounding oral PrEP formulations.

One recent study investigating antibiotic resistance in men who have sex with men (MSM) taking PrEP determined that the oropharynx of MSM on PrEP was significantly enriched with higher levels of bacteria that contain genes that confer resistance to fluoroquinolones, macrolides, tetracyclines, and multidrug efflux pumps when compared to the general population.⁹ This finding emphasizes the importance of minimizing unnecessary prescription of antimicrobial agents to dental patients in this population.⁹

Increased STIs in HAART and PrEP users

The implementation of pre-exposure prophylaxis (PrEP) as a preventive measure against HIV transmission among men who have sex with men has garnered attention for its effectiveness. However, a growing body of research highlights a concerning trend of increased STIs following PrEP initiation. Numerous studies indicate a significant rise in STI rates among individuals starting PrEP.¹⁰ Some studies suggest an escalation in STIs, such as syphilis, especially among MSM, whether people living with HIV or on PrEP.¹¹

There have also been reports of increases in chlamydia, as well as HPV in PrEP users.^{12,13} These findings

underscore the need for comprehensive STI prevention and care strategies in conjunction with PrEP implementation. PrEP users reported an increase in high-risk behaviors, including a decrease in consistent condom use. In those recent reports, approximately 50% of participants were diagnosed with an STI within 12 months of follow-up, highlighting potential challenges in maintaining vigilance against STIs.¹⁴

This data is important because many of the STIs mentioned have oral manifestations necessitating the importance of recognizing these lesions as an effort for early detection and treatment. They include the following:

Syphilis is a bacterial infection caused by the spirochete bacterium *Treponema pallidum*. In the mouth, syphilis can present as mucous

patches or white lesions on the tongue, lips, or inside the cheeks.

Herpes simplex virus (HSV-2) is a common viral infection that can affect the mouth and oral mucosa, causing cold sores or oral herpes. These cold sores typically appear as small, fluid-filled blisters on or around the lips or inside the mouth. While oral herpes is generally not as severe as genital herpes, it can still cause discomfort and pain during outbreaks.

Human papilloma virus (HPV) is a group of viruses known to cause various types of warts, including genital warts. In the context of STIs, high-risk HPV strains are associated with the development of certain cancers, including cervical, anal, and oral cancers. HPV-related oral lesions can appear as warts or raised growths in the mouth, including the oral cavity and back of the throat.

Gonorrhea is a bacterial infection that primarily affects the genital and urinary tracts. Although gonorrhea can cause symptoms, such as painful urination and discharge, it is not a common cause of oral manifestations. However, in rare cases, gonorrhea can be transmitted through oral sex, leading to throat infections (pharyngeal gonorrhea), characterized by sore throat, swollen lymph nodes, and discomfort while swallowing.

Chlamydia is a bacterial infection commonly transmitted through sexual contact. While it primarily affects the genital and urinary tracts, most chlamydia infections in the throat have no symptoms. When symptoms are present, they can include a sore throat.

It's important to note that STIs can vary widely in their presentation and
(Continued on Page 50)

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Orofacial Manifestations (Continued from Page 49)

impact on different individuals. Regular STI testing, practicing safe sex, and maintaining good oral hygiene are crucial steps in preventing and addressing these infections, both in the genital and oral areas (Centers for Disease Control).

Consequently, the integration of STI prevention and care with PrEP programs is gaining significance as a strategic approach to addressing this emerging concern. A recent regimen, doxycycline prophylaxis/post-exposure prophylaxis (DoxyPrEP/PEP), developed to mitigate the rise in bacterial STIs, has been gaining traction in the medical community and may be observed being used in patients,

especially those taking PrEP. Research in this area is promising, although further robust data are required to better understand its efficacy, target population suitability, community acceptability, and potential impact on behavioral risk compensation.

While PrEP remains an essential tool in HIV prevention, it's crucial to consider the broader implications on STI transmission and adopt measures that ensure the holistic well-being of those utilizing PrEP services.

Clinical recommendations for providers

It is important to equip dental health-care providers with essential knowledge to better treat patients taking HAART or PrEP. The following are recommendations for best treating this population.

1. Patient assessment: Perform a

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thorough dental and medical history review, including the patient's HIV status and current medications (including HAART or PrEP).

2. Infection-control measures: Adhere strictly to infection-control protocols to minimize the risk of cross-contamination and transmission of infections.

3. Oral hygiene instruction: Provide oral health education to patients on HAART or PrEP, emphasizing the importance of maintaining good oral hygiene practices.

4. Regular oral examinations: Schedule regular oral examinations, at least every six months, for patients on HAART or PrEP to monitor for any oral manifestations or side effects.

5. Preventive care: Emphasize the importance of preventive dental care, such as regular cleanings and prophylactic treatments, to minimize the risk of oral complications.

6. Counsel on medication-related oral side effects: Educate patients about potential oral side effects of HAART or PrEP. Encourage patients to report any unusual oral symptoms promptly.

7. Collaborative care:
a. Maintain open communication with the patient's HIV care team to ensure coordinated care and management of oral manifestations.

b. If you have any doubts, consider referring the patient to specialty clinics, like oral pathology or orofacial pain, for final diagnosis and management.

8. Management of xerostomia (dry mouth): Recommend sugar-free gum or lozenges to stimulate saliva production. Prescribe artificial saliva substitutes if needed.

During routine dental check-ups, dentists can engage in open, confidential, and nonjudgmental conversations with their patients emphasizing the interconnectedness of oral and general health. Dentists can facilitate referrals to appropriate physicians. This proactive approach not only

enhances patients' awareness but also emphasizes the commitment of dentists to their patients' overall health and well-being. Ultimately, the dental chair can serve as a platform for comprehensive health discussions, contributing to an interdisciplinary approach to health care. ●

Queries about this article can be sent to Dr. Newgard at an2621@cumc.columbia.edu. Reprinted with permission of The New York State Dental Journal (June-July 2025 issue, Vol. 91, No. 4

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