American Association for Dental Research comments in response to Request for Information (RFI) on the Development of the FY 2021-2023 Trans-NIH Strategic Plan for HIV and HIV-Related Research.

What are the emerging areas of science in HIV/AIDS prevention, treatment, disease progression and cure that may impact the NIH research priorities?

Prevention
HIV vaccines: The potential exists to incorporate novel oral adjuvants with systemic vaccines to enhance both potency and immunogenicity. Tonsillar tissue and the floor of the mouth/base of the tongue provide the opportunity for direct immunization of oral lymphoid tissue to induce local and systemic immunity. Researchers are experimenting with the use of various vaccine delivery vectors such as S. mitis (NIDCR R01DE027249).

Microbicides & PrEP: The mouth provides a convenient delivery system for local and topical targeted oral formulations targeting HIV and oral pathogens, for administration of long acting antiretroviral therapy (ART), and oral microbicides.

Treatment
Effect of ART on different populations: One study has shown that mandibular bone mineral density in older women with HIV+ is lower than in uninfected older women (Caputo et al. 2013. Braz Oral Res 27: 231–237) but more studies are needed on the consequence of ART on the orofacial bones (Vernon et al. 2016. Oral Diseases. 22(S1): 135-148). The studies on caries risk in HIV-infected children vary, and more and better studies are needed (Arrive et al. 2016. Oral Diseases. 22(S1): 149-157). There also needs to be more research on the consequence of using ART during pregnancy on the development of the fetus. Animal studies have shown reduced calcium ion concentration in both and teeth and delayed organic dental matrix development, but no human studies have been done to verify these results (Arrive et al. 2016).

The OAR is interested in receiving input to guide NIH research investments to end the pandemic and improve the health outcomes for people living with or at risk for HIV infection. Please provide feedback on the questions below for consideration by the NIH:

• What are the research gaps and promising opportunities?

Oral microbiome:
b. Early probiotics and prebiotics research is promising for relieving symptoms associated with HIV, but studies so far have been small and are often conducted by food and nutrition companies. Larger, independently verified studies are needed to understand the microbiome in disease and treatment and what, if any, effect probiotics and prebiotics have in HIV (Moyes et al. Oral Diseases. 52(S1): (166-170)).

**Oral lesions:** The results of studies on the relationship between ART and oral lesions vary with time and location. Long-term prospective studies are needed with a standardized methodology, including research on oral disease related to immune reconstruction inflammatory syndrome (IRIS; Vernon et al. 2016).

**Oral diagnostics:** Development of oral diagnostic platforms should focus on standardizing collection, storage and testing of saliva samples; validating biomarkers for HIV-associated head and neck cancers; and decreasing the cost of the technology.

**Oral lymphoid HIV reservoirs:** There are oral HIV reservoirs, likely in oral lymphoid tissue. Future research should focus on locally targeting these reservoirs in order to cure patients.

**Fungal infections:** Candida infections are still more common in people living with HIV than without HIV, even after treatment with ART. Long-term usage of antifungal treatments is leading to the emergence of resistance. Novel alternatives are needed (Vidya et al. 2016. Oral Diseases. 52(S1): 158-165).

**Reducing or eliminating oral comorbidities associated with HIV/AIDS to improve health outcomes:** Areas needing more research include distinguishing between oral conditions caused by HIV vs. those caused by ART, particularly around the long-term risk of gingival recession and root caries leading to tooth loss. It is also unknown how secondary systemic diseases contribute to oral disease in the context of HIV infection. Additional concerns include any role ART may play in the development in osteonecrosis of the jaw, especially when bisphosphonates are used to counteract bone loss due to ART, and the prevalence of dental caries in HIV+ v. uninfected populations (Vernon et al. 2016).

- **What are the relevant scientific developments?**

**Oral diagnostics:** Rapid testing systems are currently being developed that can return results in an hour or less (NIDCR R44DE021672; NIDCR R44DE024456). The goal of these projects is to develop point-of-care diagnostic systems that not only deliver rapid results but are also portable to enable use in both the field and clinic. These developments will assist in the test-and-treat model of care that aims to transition people who test positive for HIV into early treatment.
Oral lymphoid HIV reservoirs: A team of U.S. based and international researchers found that the mTOR protein complex regulates HIV latency and that inhibition of mTOR prevented viral reactivation (Besnard et al. 2016. Cell Host Microbe. 20(6): 785–797.). These studies were conducted in in vitro systems and should be further investigated.

3. In support of key NIH-funded domestic and global programs, what are the critical training and capacity-building needs that are vital to support HIV/AIDS-related research activities? (limit 500 words)

Globally, significant investments are needed in training a workforce of both clinician and non-clinician scientists in resource-poor countries to address geographically- and socially-specific research needs as well as investments in infrastructure to increase ability to run large clinical trials in Asia and Africa to replicate efforts like the AIDS Malignancy Consortium around research on head and neck cancer in patients treated with ART (Vernon et al. 2016. Oral Diseases. 22(S1): 135-148). Furthermore, global inequalities in oral health still exist and are affected by social determinants of health and variability in the availability of ART (Vernon et al. 2016) that could be addressed with the aforementioned investments.