November 16, 2018

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National Institutes of Health
Building 31, Room 2C39
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Re: Oral and Dental Health in People Living with HIV and Co-Occurring Non-Communicable Diseases

Dear Dr. Somerman:

On behalf of the 3,400 individual and 103 institutional members of the American Association for Dental Research (AADR), thank you for the opportunity to provide input on the NIDCR 2030 proposed research initiative, “Oral and Dental Health in People Living with HIV and Co-Occurring Non-Communicable Diseases.”

Over a span of 24 years, AADR and its members have facilitated a total of 7 World Workshops on Oral Health and Disease in AIDS with the goals of assessing the current state of dental, oral and craniofacial HIV/AIDS research, identifying critical research needs and educating researchers and health professionals to advance the state of the science on an international scale. The proceedings from the latest World Workshop (WW7) were published in Oral Diseases, Volume 22, Issue S1. We recommend reviewing the proceedings from this workshop for a complete understanding of the dental, oral and craniofacial research community’s recommendations on the future direction of this research. Many of the recommendations in this response were derived from the article, “Comorbidities Associated with HIV and Antiretroviral Therapy (Clinical Sciences): A Workshop Report” (Vernon et al. Oral Diseases 22(S1): 135-148). This response provides recommendations of overarching characteristics for future studies with specific examples of conditions to which these studies can be applied.

Studies which focus on the immunology of oral conditions in HIV/AIDS are recommended, ensuring that researchers measure, analyze and report their cohort’s immunological framework in HIV/AIDS research. The inclusion of this framework can open a new era of oral health research in people living with HIV/AIDS (PLWHA); however, without this immunological framework, epidemiological clinical studies lack an essential context by which to compare findings across studies. Exposure to HIV-associated immunosuppression prior to antiretroviral therapy (ART) can affect both oral and systemic outcomes long after ART improves host immune function. Essential components of the immunological framework include: cohort-level median nadir CD4 count; HIV RNA “viral load” (if possible, as a variable that expresses life-time exposure, similar to pack-per day years of smoking exposure); the percent of the cohort effective ART and type of ART; the percent of the cohort with “undetectable” HIV RNA virus (<50 copies/mL); time since seropositive and time on highly active ART (HAART)—in addition to baseline CD4 count and level of HIV RNA. For longitudinal studies, changes over time in these variables, especially changes in CD4 and level of HIV RNA, must be either controlled for (entire cohort with “undetectable” HIV RNA) or addressed as primary covariates and/or potential confounding variables. Alternatively, cohorts can be stratified by nadir CD4 or level of HIV RNA.
Consider confounders and sociological factors in addition to the immunological framework. Studies should thoroughly explore relevant potential confounding variables such as access to and type of dental care provided, the quality of oral hygiene/home care and exposure to HIV/AIDS-related stress and stigma. How such factors may influence type of ART (confounding by indication) should also be explored.\(^1\) In resource-poor countries, cardiotoxic (older generation) and/or suboptimal ART should be well documented, with links to oral HIV conditions explored.

There is also a need for multisite studies with centers based in populations with varying racial and socioeconomic demographics. A study at one site will only be relevant to that population’s demographic with access to the models of care available (e.g., varying levels of integration of dental and medical care), uniquely to that individual study site.

The highest priority studies should be led by a multidisciplinary team of investigators. Clinical studies should include clinicians and well-trained epidemiologists in order to create, direct and analyze proposed clinical studies. In addition, the integration of basic scientists into these multidisciplinary teams can help to address translational questions that no one researcher can effectively investigate alone, particularly regarding molecular and biological mechanisms underpinning clinical outcomes. Such studies may have the highest potential to prevent and treat oral conditions associated with HIV/AIDS.

Future research studies should expand beyond and/or probe deeper into oral manifestations of HIV. Generally, if the patient is on effective ART, the prevalence of such well-described traditional oral manifestations is low. Investigations that explore deeper into immunology, virology, biological mechanisms and sociological influences will help to increase knowledge of how best to promote oral health in PLWHA. Some research questions include:

- Does immunosuppression-associated gingival recession complicate oral hygiene (increase difficulty of plaque control) and thus worsen long-term oral health prognosis and increase risk for periodontal disease, tooth loss and root caries?
- What is the long-term risk of osteonecrosis of the jaw in PLWHA?
- What is the long-term risk for developing head and neck squamous cell carcinoma in PLWHA?
- What are the clinical characteristics of oral lesions in the context of immune reconstitution inflammatory syndrome?
- How does HIV affect risk for periodontal disease, xerostomia (HIV-related and/or treatment-induced) or caries?
- Can immunological factors (e.g., copy number viral years, CD4 nadir or CD8/CD4 ratio) be used to assess risk for periodontal disease, xerostomia or tooth loss?
- What are the failure and success rates of implants in PLWHA? How do immune characteristics influence bone healing, osseointegration and implant survival? How do patients’ HIV and immunological profiles influence guidelines on when to place implants and predict implant survival? A review of studies on the success of implants in PLWHA yielded an insufficient level of evidence to determine the long-term success of implants in PLWHA. Of the studies included in the review, over 50% were case reports and the studies with sufficient sample sizes had short follow-up times. None of the studies seemed to have a control group.\(^2\)
- Research on the dental status of PLWH should, if relevant, include children as a portion of the cohort. A recent study showed that caries progression was associated with the type of ART used to treat perinatally HIV-infected youth.\(^3\)
Finally, AADR encourages NIDCR to explore opportunities for synergy with other institutes and centers conducting HIV research. In June 2018, AADR submitted comments in response to the request for information, “Development of the FY 2021-2023 Trans-NIH Strategic Plan for HIV and HIV-Related Research.” PLWHA offer a window of opportunity into how immunology and inflammation impact oral health, and the oral health community should not miss out on this opportunity. AADR stands ready to work with NIDCR to advance research in this important area.

Once again, AADR appreciates the opportunity to provide input on this important proposed research initiative. If you have any further questions, please contact Dr. Seun Ajiboye, Director of Science Policy and Government Affairs, at sajiboye@iadr.org.

Sincerely,

Christopher H. Fox, DMD, DMSc
Chief Executive Officer

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President

References


