

## Overview and research agenda arising from the 7th World Workshop on Oral Health and Disease in AIDS

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### Abstract

The Research Agenda generated by the 7th World Workshop on Oral Health and Disease in AIDS (WW7) is delivered in this paper. Panels of international experts presided over nine workshops that constituted the conference held in November 2014 in Hyderabad, India. The main goal of the Workshop was to bring together clinician and scientists interested in the subject to debate with world-wide perspectives current issues related to the oral manifestations in HIV/AIDS. The workshops were structured around three themes; basic science, clinical/translational science and social science and were attended by 135 participants from 31 countries. The research questions debated at the workshops are presented in nine consensus papers published in this issue and are summarised in this paper along with an outline of the identified research needs in the field.

### Introduction

Like the six previous workshops, the main goals of the 7th World Workshop on Oral Health and Disease in AIDS (WW7) were to bring together clinician, laboratory social scientists and health science officials to identify research needs pertaining to HIV/AIDS-related oral manifestations, taking into account the evolution of this global pandemic along with worldwide perspectives and opportunities. WW7, which was held in Hyderabad, India, in November 2014, provided an opportunity for a unified global approach to the challenges of oral aspects of the HIV pandemic and attempted to identify the key research questions of international significance.

WW7 brought together 135 participants from 31 countries, and was structured around three themes: basic science, clinical/translational science and social science. There were nine workshops (three within each of the themes), addressing current research questions previously developed by the International Scientific Committee. These questions addressed a variety of topics within pathogenesis, immunopathogenesis, epidemiology, clinical research and social/behavioural research. A panel of experts led each of the workshops by preparing and reviewing the relevant topics comprehensively. The panels were diverse and constituted experts from different continents, with different economies and healthcare systems. The workshops were concluded by identifying the research needs in the field. This paper is a summation of the nine consensus papers reporting the findings of each of the panels of experts, and the summary of the discussions of each of the workshops published in this issue.

## **Clinical transitional research workshops**

### **Co-morbidities associated with HIV and antiretroviral therapy**

The discussions in the workshop centred around the effect of current antiretroviral therapy (ART) regimes on oral health in the context of the immune reconstitution syndrome (IRIS), and the management and risk assessment of IRIS-related oral conditions (Vernon *et al*, [2016](#)). The influence of ART on the progression of periodontal diseases, risk of osteonecrosis and dental caries was discussed. Current knowledge of anatomical reservoirs of HIV in different anatomical compartments and the implications and the risk of virus shedding into oral fluids and the development of oral and/or oropharyngeal cancer were debated. The workshop discussion also took into consideration the uneven availability of ART, which leads to inequalities in oral health of people living with HIV/AIDS (PLWHA), around the world (Challacombe, [2016](#)).

At the conclusion to this workshop, the experts identified future research needs in the field as follows:

- What are the biological mechanisms and immunological determinants of dental caries, xerostomia, periodontal disease and oral mucosal conditions in the context of HIV?
- Can large-scale longitudinal (pre- to post-ART) study designs or translational studies tease out the differential contributions of HIV and ART on oral conditions in PLWHA?
- How can oral health providers better address global inequalities? How can dentists be ‘first responders’, that is help detect HIV infection earlier and advocate for optimal treatment with respect to overall health for all HIV-positive individuals?
- Among populations receiving successful ART:
  - Where are the major latent reservoirs of HIV located in the head and neck region?
  - Is the genetic code of HIV detected in saliva/oral mouth rinse fluid and is it potentially infectious?
  - Why are herpes viruses (HHVs) suppressed, but not human papilloma viruses (HPV)?
  - Is there viral divergence in the molecular and pathological nature of HIV in saliva/oral fluids compared with HIV elsewhere in the body?
  - What can be done to reduce the risk of HPV-related head and neck cancers?
- Do pathologies associated with HIV therapy (kidney/renal dysfunction, metabolic syndrome, immune activation, residual inflammation) affect oral health? Does nadir CD4 count influence long-term tooth loss?

### **The global burden of oral diseases in paediatric HIV-infected populations**

The experts running this workshop set out to discuss the literature and summarize the current understanding of the global burden of oral disease in HIV-infected children with the aim to identify research needs in the field (Arrive *et al*, [2016](#)). The topics that were addressed were as follows: the oral manifestations of HIV in children and their impact on quality of life, the effect of ART exposure *in utero* on craniofacial and dental development, the complications of ART in children, and the value atraumatic paediatric dental treatment.

It was concluded that the impact of ART in HIV-infected children has raised novel challenging questions in the field of oral health warranting future research to address the following questions:

- What is the prevalence of oral diseases (mucosal, dental, and periodontal) in HIV-infected compared with uninfected children in resource-limited countries?
- Is quality of life affected by oral disease burden in HIV-infected children in resource-limited countries?
- What is the effect of antiretroviral therapy exposure *in utero* on craniofacial and dental development in children?
- Which are the most important co- infections and complications due to antiretroviral therapy in HIV-positive children?
- Is the atraumatic restorative technique a feasible solution for caries control and prevention in HIV-infected children in resource-limited countries?

### **Oral mycoses and other opportunistic infections in HIV: therapy and emerging problems**

The participants in this workshop debated the role of oral mycoses and other opportunistic infections in HIV disease (Vidya *et al*, [2016](#)). A review of the literature was presented of the prevalence of deep fungal infections of the head and neck among HIV-infected populations and whether the carriage of specific organisms indicates risk of disease. The virulence of candida specifically in immunosuppressed individuals, emerging resistance to fluconazole and the role of alternative medicine as antifungal therapy were also discussed.

The nature of the issues discussed in this workshop was such that the literature discussed overlapped between basic science and clinical translational research. The participants in the workshop concluded that the list of research questions to be addressed in future in this field are as follows:

- What are the factors explaining the increasing prevalence of non-albicans candida species?
- What is the association between concurrent tuberculosis and candidiasis in India, South East Asia and China?
- What role do specific ART regimens play in the incidence of candidiasis?
- What are the factors necessary for detachment of *C. tropicalis* cells from biofilms?
- What are the stress adaptation and the specific signaling pathways?
- How can reduction in candidaemia and other blood stream fungal septicaemia-related mortality be achieved in an efficient and cost-effective manner in immune-compromised individuals?
- How can we develop new generation antifungals to counteract the emerging resistance to fluconazole?

## Basic science research workshops

### The gut and oral microbiome in HIV disease

Experts participating in the workshop recognized the substantial progress in the understanding of the interactions within the gut and oral microbiome (Moyes *et al*, [2016](#)). There have been significant improvements in sequencing techniques, which lead to revealing the genetic richness in the human microbiome.

There is evidence in the literature that HIV infection perturbs the host–microbiota, but it is not clear how the microbial communities change in the context of HIV infection. The application of probiotics and prebiotics to manage a variety of symptoms in HIV-infected individuals was debated. However, this is a novel research area and future research directions were suggested to address the following questions:

- Which comes first? The changes in the oral mucosa observed during HIV infection, or the changes in the oral microbiome?
  - Are the changes in the oral microbiome due to changes in the immune system, or are they independent of the immune state of the host?
  - Does perturbation of the oral microbiome affect the metabolic and specialized synthetic activities of the oral mucosa in the context of HIV infection?
  - What is the effect of the changes in the oral microbiome on the oral, gut and vaginal mucosa in the context of HIV infection?
  - What are the changes in the oral mycobiome and virome, and how do they relate to the progression of HIV disease?
- Do probiotics change the oral microbiome in HIV-infected individuals with and without ART and standard therapies?
  - How do probiotics change/alter the immunology in HIV-infected individuals with and without ART and standard therapies?
  - Do probiotics have a clinically beneficial effect in HIV-infected individuals with or without ART and standard therapies?
  - What are the drawbacks of giving probiotics to HIV-infected individuals with or without ART and standard therapies?

### Innate immunity in HIV-1 infection: epithelial and non-specific host factors of mucosal immunity

The literature addressing the interaction between HIV-1 and epithelial cells and the natural resistance of the oral mucosa to HIV-1 transmission was discussed in this workshop (Nittayananta *et al*, [2016](#)). The debate at the workshop explored the current knowledge of the fate of HIV-1 after interactions with oral epithelial cells, the contribution that keratinocyte and other anti-HIV effector oral factors contribute to mucosal protection, HIV-1 interactions with oral epithelium effect on activation and populations of local immune cells and whether HIV-1 interactions alter functions of oral epithelial cells. In conclusion, it was acknowledged that the degree to which local innate

immune factors contribute to HIV-1 resistance of the oral mucosa is not yet known in detail and the following questions were suggested for future research in the field:

- To what degree do local innate immune factors contribute to HIV-1 resistance of the oral mucosa?
- How can research into the oral innate immunity against HIV be translated into transmission prevention strategies?
- How is HIV transmitted through oral sex and breast feeding?
- What are the factors that are making the oral cavity less susceptible to retroviral infection when compared with the rectal and vaginal sites?
- What new strategies can be employed for reducing transmission at the genital and anorectal sites, where most HIV infections occur *in vivo*?

### **Viral infections associated with oral cancers and diseases in the context of HIV**

The discussions in this workshop focused on the increased risk of disease caused by HHVs and HPV infections and cancers caused by the oncoviruses EBV, HHV-8 and HPV, in HIV-infected patients (Speicher *et al*, 2016). This workshop examined the viruses associated with oral cancers disease in the HIV-infected and uninfected populations, the immune response, and biomarkers useful for accurate diagnostics of these infections and their sequelae. The discussions focused on the viral associations with cancer and the coinfections of EBV, HPV and HHV-8 in the head and neck area and whether the immune response to these coinfections is altered in HIV-infected people. At the end of the workshop, the participants identified a number of key areas where further research in this field is required and the following research questions were prioritized:

- How can the sensitivity and specificity of biomarkers in identifying oral cancers be improved?
- How can the risk stratification of cancer in HIV-positive patients be improved?
- How can the standardization of collection, storage and testing of saliva be optimized for use in biomarker studies of oral cancer?
- Can the development and validation of new biomarkers help to indicate the risk of precancer and HPV- associated cancer in HIV patients?

### **Social and ethical research workshops**

#### **Ethics, research and HIV: lessons learned**

The participants of this workshop debated whether in the context of present experience and available evidence, the educational needs of the dental team treating PLWHA has been met (Reznik *et al*, 2016). The benefit of screening for HIV by the dental team in the dental setting was considered. The delegates discussed whether the international experience of managing PLWHA can be applied to provide information regarding future new infection control risks in the dental setting. The conclusion of this workshop took into consideration the diversity of reports presented by all the

international participants and recommended future research questions in this field to include the following:

- What are the cofactors that contribute to the variability in the quality of the response to the dental needs of PLWHA that exists between developed and developing countries?
- In addition to resource availability, what is the role of other factors which may be delaying or preventing access to health care for PLWHA?
- How can the quality of life for everyone living with HIV/AIDS worldwide be optimized?
- How can the dental healthcare worker in screening patients for HIV in the dental setting be supported?
- How can the integrated approach by the dental and medical professionals be advocated?

### **Oral health needs assessment world-wide in relation to HIV: oral health needs and inequalities, oral health promotion, co-ordinating research and enhancing dissemination in relation to HIV**

In this workshop, the participants discussed the meaning of 'health need' and considered the oral health inequalities and oral health promotion among PLWHA (Koyio *et al*, 2016). The approaches of co-ordinating and standardizing research methodology and disseminating results were debated. The discussion concluded that professional organizations and governments have a role in leading and advocating better oral health of PLWHA. Several research questions to address challenges in this field were suggested to include:

- Against a background of finite healthcare resources, how can we stratify and quantify the increasing general and oral health needs of HIV patients, irrespective of the country of residence.
- What is the relationship between social gradients and the distribution of HIV infection in countries around the world?
- What are the interventions that can reduce social inequalities in HIV health care?
- How can we coordinate research efforts and harmonize research protocols in resource-poor countries?
- How can we promote advocacy for oral health care for people with HIV to become universally and equitably accessible; free from prejudice or discrimination and evidence-based?

### **Access and management of HIV-related diseases in resource constrained settings**

This workshop was concerned with the current management and access to therapy for PLWHA in resource constraint settings (Dimba *et al*, 2016). The provision of basic oral health in developing countries and the role primary, early diagnosis of HIV-related comorbidities and improvement of treatment outcomes were discussed. Future research needs in this field were identified around prevention using the common risk factor approach, in an ageing PLWHA population, to include the following research questions:

- How can the common risk factor approach be employed to address risk factors that the ageing PLWHA are faced with?
- How can we evaluate the current health models in provision of essential health and social services and in meeting patients' treatment needs?
- How can we improve the engagement of healthcare providers in decision-making to improve the healthcare system?

## Conclusion

The diverse scientific presentations attempted to answer current important questions in relation to oral aspects of HIV infection in social, laboratory and clinical science. In addressing and answering these questions (see references and this issue), the workshops also identified those questions still needing to be answered and research questions for the future derived from the discussions. They also highlighted a number of factors that may be contributing to the disparity between developed and resource-restrained countries. Best practice in research, cost-effective clinical intervention and accessible social care should be identified and applied globally to improve HIV/AIDS care. Much was achieved at this workshop but the overall consensus of the international speakers contributing to the 7th World Workshop on Oral Health and Disease in AIDS was that there continues to be a need for multidisciplinary research spanning basic, translational, clinical and social sciences in the field of oral HIV/AIDS.

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