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(A2) Oral Health and General Health

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The interactions between oral and systemic health are bi-directional and complex, involving many pathways. Regarding health as not merely the absence of disease, but as a state of total well-being, these interactions profoundly influence the progress of many diseases, and the quality of life and economic performance of HIV-infected individuals and populations. The evidence base for specific interactions is currently weak, partly because few good-quality studies have been published, partly because of the naïveté of the instruments currently available for recording these interactions and their inherent complexity. Recording quality of life should be a fundamental aspect of all future studies. The most significant conclusion of this Workshop is the need for all involved in oral health research and oral health care to be seen as, and to act as, essential partners in comprehensive care for whole patients and communities.

Introduction

First principles

All patients and healthcare providers recognize that there exists a relationship between oral diseases and systemic health, especially if 'health' is regarded as overall 'well-being', within the definitions of the World Health Organization—*i.e.*, "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (<http://www.who.int/about/definition/en/>). Some of these interactions directly cause, or exacerbate, real diseases; some affect disabilities; others might be regarded as contributing to handicaps, within the conceptual model enunciated by Locker (1988). *Inter alia*:

- These affects and inter-relations occur through a variety of direct and indirect effects: structural, functional, cognitive, emotional, and social. Many pathophysiological and psychosomatic pathways are involved. Though not related specifically to HIV disease, Hollister and Weintraub (1993) explain clearly how adverse oral health conditions affect aspects of daily living through influences on systemic health, quality of life, and economic productivity: they give cogent examples.
- Xerostomia is an apposite example. It is common in the HIV-affected individual, through diseases such as Diffuse Infiltrative Lymphocytic Syndrome and as a drug side-effect, among other causes. It affects speech, mastication, taste, swallowing, halitosis, inosulation (especially kissing), aesthetics, and more. By analogy with patients whose salivary function is affected by radiation therapy for malignant diseases, for example, it is reported as the most distressing of all complications (Chambers *et al.*, 2004). Nittayananta *et al.* (2006) confirms, in a group of Thai patients, that reduced salivary flow rates and feelings of oral dryness are common and mostly associated with the use of xerogenic drugs.
- The mouth is a reservoir of potential pathogens—fungal,

bacterial, and viral—which can multiply and cause disease in the immunosuppressed patient. Many of the organisms associated with oral opportunistic infections are either part of the normal flora, or are common in the environment and would be expected to pass fleetingly through the mouth, and are quickly eliminated in the immunocompetent.

- There is potential for the spread of oral pathogens and their toxins to other organs and tissues: directly, as in the case of necrotizing gingivitis and periodontitis spreading to cause some degree of localized necrosis of soft tissues (necrotizing stomatitis) (Ibeziako *et al.*, 2003), and oral candidiasis to pharyngeal and esophageal candidiasis; and indirectly *via* lymphatics and the blood stream—possibly even to the central nervous system.
- Localized oro-pharyngeal infections, in the broadest sense, create and exacerbate systemic inflammation and malaise *via* the production of cytokinemias, leukocytosis, leucopenias, and other leukodyscrasias. Kerdpon *et al.* (2006) documented the peripheral blood abnormalities in a group of Thai patients and suggested that lymphopenia might be a practical indicator of HIV-associated oral lesions, especially in resource-poor settings, where more sophisticated diagnostic testing is not readily available.

The Focal Infection Hypothesis

Scores of distant or generalized diseases have been attributed to local—including oral—infections, ranging from osteomyelitis, nephritis, heart disease, through diabetes, to psychoses. Hippocrates reported curing arthritis by tooth removal. W.D. Miller (1890) and William Hunter (1901) believed that oral infections caused many systemic diseases and questioned contemporary practices in what they termed 'conservative dentistry'. Controversy came and went throughout the 20th century and has seen a resurgence in the last decade, especially in attempts to explain associations between periodontal diseases and ischemic heart disease and stroke (Armitage, 2000; Gordon *et al.*, 2005), and pre-term low birthweight (Buduneli *et al.*, 2005). Biological plausibility is certainly established. 'Traditional' oral pathogens—such as *Candida* spp., Gram-negative periodontal species, and several Human Herpes Viruses—have been suggested as playing a part in the pathogenesis of distant or systemic diseases in immunocompetent individuals, and could be significant in immunosuppressed subjects. The mechanisms involving perturbations of the humoral and cellular components of the inflammatory process are, in the case of HIV infection, exacerbated by the immune dysfunction itself, and by side-effects of drug therapy.

The literature contains much speculation and limited evidence. Intervention studies will be key to quantifying the inter-relationships of oral and systemic diseases. Though only a small study so far, the demonstration by Montebugnoli *et al.* (2005), that periodontal care in coronary heart disease patients improves systemic inflammatory and hemostatic markers, is an important demonstration of the principle. Specific questions asked of this Workshop are addressed below.

Key Words

Health, oral, general, care.

Presented at the Fifth World Workshop on Oral Health and Disease in AIDS, Phuket, Thailand, July 6-9, 2004, sponsored by Prince of Songkla University, Thailand, the International Association for Dental Research, the World Health Organization, the NIDCR/National Institutes of Health, USA, and the University of California-San Francisco Oral AIDS Center.

List of Questions

- Question 1. Does oral disease affect the general health of patients with HIV?
- Question 2. Does the state of health in the oral cavity influence other anatomical regions of the body?
- Question 3. What is the relationship among the nervous system, the brain, and oral tissues?
- Question 4. Are neurological pathologies influenced by oral-systemic health?
- Question 5. Do oral-systemic interactions influence social behavior?
- Question 6. Do HIV-infected individuals have systemic diseases or conditions that have a unique direct or indirect effect on oral health?
- Question 7. Does concurrent tuberculosis infection modify the oral manifestations of HIV infection?
- Question 8. What is the role of hepatitis B and C in HIV infection?

Question 1. Does oral disease affect the general health of patients with HIV?

The most important way in which this question can be answered in the affirmative is in respect of patients' quality of life (QoL). Robinson (2006) addresses these aspects in more detail in his paper. In general, this aspect has been given inadequate attention. In 1996, Coates *et al.* showed that HIV-positive subjects attending a special clinic in Adelaide, Australia, had significantly greater levels of social impact than a control Adelaide sample, with 16.7% avoiding going out because of dental problems. More than a quarter of Cape Town's HIV-positive patients had oral soft tissue discomfort necessitating treatment (Arendorf *et al.*, 1998).

In the wider literature, relationships between clinical variables and quality of life often appear weak, because the links between them are complex and mediated by numerous factors, with many confounders unavoidably operating in most studies (Wilson and Cleary, 1995). Earlier papers do not support a strong relationship. Discrepancies arise because of the appropriateness or inappropriateness of the instruments used for assessing QoL. Inconsistent reporting of subjective patient assessments *vs.* clinician assessments of normative measures of oral diseases may also be a contributory factor. Unfortunately, well-validated instruments, such as the Medical Outcomes Study (Wachtel *et al.*, 1992), do not consider oral symptoms (Cleary *et al.*, 1993). At this meeting, Sujak *et al.* (2006) compared 509 HIV-positive with 408 HIV-negative drug abusers and found that oral mucosal lesions had only a minor effect on QoL.

The most recent studies to examine oral QoL issues well are those of Coulter *et al.* (2002) and Yengopal and Naidoo (2006). Coulter *et al.* (2002) conducted a longitudinal study using interview data collected in a probability sample of 2864 adults with HIV and receiving health care in the USA. Physical and mental health were assessed based on 28 items, and oral health was assessed relative to 7 items on oral-related pain and discomfort, worry, appearance, and function; oral health was significantly associated with both physical and mental health. In a South African cohort, Yengopal and Naidoo (2006) administered the standardized 49-item Oral Health Impact Profile questionnaire (Slade and Spencer, 1994) to a convenience sample of 150 HIV-positive adult patients, 71 cases with, and 79 controls without, oral lesions. The majority were black and female. Oral candidiasis, angular cheilitis, and oral hairy leukoplakia were the most common conditions, and cases had significantly higher DMFT scores, dry mouth and taste problems, and significantly lower oral-health-related QoL. Thus, as Yengopal and Naidoo (2006) wrote, "The implications of these findings for the management of the HIV-positive patient are obvious: Oral lesions associated with HIV infection should be considered as debilitating to the patient,

and an overall treatment strategy, whether based on treatment of symptoms or on the provision of anti-retrovirals, should include the management of oral conditions associated with HIV infection."

A stronger way of confirming the relationship between oral lesions and general health is to measure the impact of good-quality dental care on QoL in HIV-infected persons. Brown *et al.* (2002) showed, in a well-designed two-arm longitudinal study, that active decay, gingivitis, oral pain, impact of oral health on functioning, and global functional status improved in both groups, with additional benefit from 'enhanced care' comprised of bi-monthly protective treatment and twice-daily chlorhexidine mouthrinses to treat gingivitis. However, no effects on acquired immunodeficiency syndrome (AIDS)-related complications, symptoms, or mortality were observed.

It is also clear that the neuropsychological deficits associated with HIV/AIDS result in impairments of 'everyday functioning' (Heaton *et al.*, 2004). Though under-studied, these are bound to affect oral health behaviors and exacerbate oral disease and discomfort, forming a vicious cycle.

Questions 2, 3, and 4

Although the workshop had agreed beforehand that these were important questions to be asked, in the event, members felt that, in the absence of specific studies, there was an insufficient academic base for addressing them usefully. It is recommended that they form part of the research agenda.

Question 5. Do oral-systemic interactions influence social behavior?

The limited research referred to above implies a positive answer to this question. Since oral diseases may spread and exacerbate systemic diseases, and *vice versa*, discomfort and stigma increase, with potentially profound effects on social behavior. We suggest that the strongest factor will be pain—*e.g.*, pain from oral ulcers, or from necrotizing gingivitis and periodontitis, can clearly inhibit social functioning in sufferers, as demonstrated in a recent study of South African HIV-positive persons (Ayo-Yusuf, personal communication, unpublished). Loss of taste, distortion of taste, burning mouth, dry mouth, dysphagia, and loss of appetite all have a negative impact on the patient as a whole. To this must be added the socio-economic impact of medical services and drug costs to both the patient and his or her family, friends, peers, and employers. Especially in developing countries, but also in lower socio-economic groups worldwide, household belongings are often sold to meet long-term medical and medicine costs, to pay transport to and from relatives often living far away, and to feed people caring for the patient at home. Family and relatives use a large part of remaining resources to cover burial costs, mourning costs, and clearing the debts of the dead. Surviving family members, including children, are forced into very low-paying work, often sex work. Children depend on grandparents or become 'street children'. There is loss of schooling and increased crime (Haacker, 2004; World Bank, 2004).

The well-known fact that HIV/AIDS strikes predominantly the 15- to 45-year-old age group results in pressure from employers and resignations, reduced motivation and capacity to work, discrimination in the work place, abandonment by peers resulting in loss of self-esteem, and reduced personal employment and income.

Especially in developing countries, there is still little documented information on oral-systemic HIV/AIDS impacts at personal and community levels. Two reasons suggested by the Workshop are: lack of knowledge and relevant skills among oral health professionals to address these needs, and a concomitant lack of appreciation among the wider medical and care-giving communities of the prevalence, extent, and severity of oral signs and symptoms in HIV-positive individuals.

Question 6. Do HIV-infected individuals have systemic diseases or conditions that have a unique direct or indirect effect on oral health?

There is little or nothing in the literature to suggest that these interactions are unique, with the possible exceptions of xerostomia and dental caries, if they are regarded as uniquely oral disease processes, and the pain and discomfort and functional impairment they cause. All systemic diseases result in behavior modification, as has been discussed, and this will exacerbate oral disease.

The fact that the mouth may be the first site of wider disease, as amplified by Hodgson *et al.* in their Workshop report (2006) (*e.g.*, candidiasis, CMV infection, and Kaposi's sarcoma), might be regarded as evidence of a direct effect.

Question 7. Does concurrent tuberculosis (TB) infection modify oral manifestations of HIV infection?

Oral TB is seen because pulmonary- and non-pulmonary-disseminated TB is so common in HIV-infected subjects, especially in sub-Saharan Africa (Kennedy *et al.*, 2004), but there is no direct evidence that this significantly influences any other oral condition beyond immunosuppression. Disseminated TB can lead to multiple organ failure, with widespread systemic consequences. A specific example affecting the mouth is renal TB, producing adrenal damage with Addisonian signs, including oral hyperpigmentation (Kumar *et al.*, 2003). Disseminated TB contributes to depression, malnutrition, cognitive loss, and other non-specific complications of HIV/AIDS. Patients may die from generalized TB before they develop serious oral lesions, making it difficult for investigators to address this question.

The frequent co-existence of TB and HIV is a special challenge to oral health-care practitioners, in terms of minimizing cross-infection and patient management, as admirably discussed by Naidoo and Mahommed (2002).

Question 8. What is the role of hepatitis B and C in HIV infection?

There are numerous studies on co-infectivity with hepatitis B, C, and HIV infection, but none addressing oral changes. Other detailed aspects of the question are covered in the report from Workshop C1. (Unfortunately, the manuscript for Workshop C1 is not included in these Proceedings.)

Suggestions for Future Research

To improve knowledge and understanding of the issues allocated to this Workshop, and to improve patient care, the Workshop participants regarded the following as research priorities:

- (1) Longitudinal cohort studies of HIV-positive and -negative populations, better to address the interrelation of oral and systemic diseases. These need better collaboration with, and education of, all care providers involved in HIV prevention and treatment. It is especially important to design intervention arms in longitudinal studies to establish causality.
- (2) Studies of the outcomes of oral/dental interventions on general health and quality of life.
- (3) Improved animal models to explore: the interrelation between oral and wider mucosal immune systems and systemic immune responses, the ability of these systems to limit new infections with HIV and other opportunistic pathogens, their ability to limit spread of pathogens from and to the mouth and other tissues and organs, and mechanisms to enhance mucosal and systemic immunity.
- (4) Inclusion of QoL measures in all clinical studies, with improved, well-validated, and internationally agreed instruments.
- (5) Studies documenting the impact of oral symptoms and

diseases on psycho-social functioning: *e.g.*, stigma from showing an AIDS-associated oro-facial lesion; their impact on aesthetics, sexual attractiveness, social exclusion, and related outcomes.

- (6) Increased involvement of oral health professionals in policy development.
- (7) Improved education and integration of oral health workers and other health professionals, especially physicians, plus research to identify barriers to improved integration.

In the continuing global tragedy of the HIV pandemic, there are signs of hope. The WHO "3 by 5" program for bringing anti-retroviral treatment (ART) to more of the world (http://www.who.int/3by5/en/HIV_AIDSplan.pdf) is making progress, but still covers only around 12% of the 5.8 million currently needing ART in developing and transitional countries (WHO/UNAIDS Joint Fact Sheet 283, January, 2005), and the numbers in need continue to grow. There is, therefore, a growing need for efforts in primary prevention and integrated care. The most significant conclusion of this workshop is the need for all involved in oral health research and oral health care to be seen as, and to act as, essential partners in comprehensive care for patients and whole communities.

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