A GUIDE FOR EPIDEMIOLOGICAL STUDIES OF ORAL MANIFESTATIONS OF HIV INFECTION

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A GUIDE FOR EPIDEMIOLOGICAL STUDIES OF ORAL MANIFESTATIONS OF HIV INFECTION

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The World Health Organization is a specialized agency of the United Nations with primary responsibility for international health matters and public health. Through this organization, which was created in 1948, the health professions of some 185 countries exchange their knowledge and experience with the aim of making possible the attainment by all citizens of the world by the year 2000 of a level of health that will permit them to lead a socially and economically productive life.

By means of direct technical cooperation with its Member States, and by stimulating such cooperation among them, WHO promotes the development of comprehensive health services, the prevention and control of diseases, the improvement of environmental conditions, the development of human resources for health, the coordination and development of biomedical and health services research, and the planning and implementation of health programmes.

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PREFACE

The International Collaborating Group on Oral Manifestations of HIV Infection was established in March 1988 as a forum for the development of collaborative activities in this area. It is composed of representatives of the Oral Health programme of the World Health Organization, Geneva, Switzerland; the Pan American Health Organization, Washington, DC, USA; the National Institute of Dental Research, National Institutes of Health, Bethesda, MD, USA; the Dental Disease Prevention Activity, Centers for Disease Control, Atlanta, GA, USA; the WHO Collaborating Centre on Oral Manifestations of HIV Infection, Copenhagen, Denmark; and the International Dental Federation (Fédération dentaire internationale, FDI), London, England.

In 1989, an FDI/WHO Joint Working Group on AIDS was formed to help implement some of the recommendations generated by the International Collaborating Group. It focused on four areas: health education and health promotion, aimed at both the public and the oral health profession; infection control; patient care; and epidemiology and surveillance.

As part of the activities relating to epidemiology and surveillance, the International Collaborating Group recommended the development of this guide, which is intended to provide a systematic approach to the design of epidemiological studies of oral conditions associated with human immunodeficiency virus (HIV) infection; to provide guidelines for the collection, management, analysis, reporting, and dissemination of data from these studies; and to facilitate the comparison of findings from different studies and different populations. It aims also to encourage oral health personnel, researchers, and public health practitioners to make oral health status an integral part of optimum case management and of surveillance activities of the diseases associated with HIV infection.

To achieve these aims, the publication provides:

- guidelines for implementing epidemiological studies of HIV-associated oral diseases;
- concise clinical diagnostic criteria for the major HIV-associated oral conditions;
- a standardized procedure for examining the head, neck, and oral cavity;
- an outline of suggested data collection variables;
- a guide for analysis and comparison of results for different populations;
- recommendations for reporting results.

Ideally, the guide should be included in epidemiological training activities, such as those of the Fogarty International Center's International Research and Awards Branch and of the National Institute of Dental Research. It builds upon the series of guides developed by the WHO Oral Health programme, especially the *Guide to epidemiology and diagnosis of oral mucosal diseases and conditions.*[1]

[1] World Health Organization. Guide to epidemiology and diagnosis of oral mucosal diseases and conditions. *Community dentistry and oral epidemiology*, 1980, **8**: 1–26.

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CONTENTS

BACKGROUND

History

Within the past decade, HIV infection has assumed pandemic proportions. By 1992, 11 years after the acquired immunodeficiency syndrome (AIDS) was first reported, it was estimated that 11 million people of all ages worldwide had become HIV-infected. Many of these people have no signs or symptoms and are unaware that they are infected.

The infection is life-long and, once acquired, can be transmitted to others. Three modes of HIV transmission have been classified by WHO: sexual, parenteral (through direct inoculation of blood or blood products), and perinatal (from an infected woman to her fetus or infant, before, during, or after birth). As a result, the infants and sex partners of infected individuals, and people who share needles are at risk. People with haemophilia and other transfusion recipients are also at high risk in places where blood and blood products are not adequately screened for HIV.

Clinical symptoms appear as the virus destroys blood cells important for maintaining immunity. The most serious consequence of HIV infection is a decline in the number and function of the helper-inducer (T4, $CD4^+$) subset of lymphocytes. Progressive destruction of immune function allows the development of opportunistic infections and neoplasms, and leads finally to the full acquired immunodeficiency syndrome.

Despite progress in almost all aspects of HIV and AIDS research, understanding of the disease is still inadequate. Important questions remain about the determinants of individual susceptibility to the virus; factors that retard or accelerate disease progression; modes of entry into, and spread of the virus within, the body; interaction of the virus with various cell types; and reasons for the wide variety of immunological problems experienced by HIV-infected people. Knowledge of the modes of transmission and their relationship to the clinical course of the disease in different geographical locations is important in identifying behavioural and/or infectious co-factors that may be associated with the spread of HIV and the clinical course of the infection.

Oral lesions in HIV-infected individuals are frequent and varied (Table 1) and are among the first symptoms of infection. Moreover, the presence of pseudomembranous oral candidiasis and oral hairy

leukoplakia indicates a strong likelihood that the HIV infection is progressing towards AIDS. It is not surprising that early indicators of immunodeficiency occur in the oral cavity: concurrent immune suppression allows normally non-pathogenic microbes to proliferate, resulting in characteristic oral lesions.

Rationale

The objective of this guide is to lay the foundation for a standard system of designing epidemiological studies of HIV-associated oral diseases; of examining, identifying, and recording oral conditions that are — or may be — associated with HIV infection; and of analysing and interpreting study results. Conducting worldwide studies according to common principles will permit valid comparison of large quantities of data, and may well allow the identification of oral conditions with previously unsuspected links with HIV.

Comprehensive descriptions of the global spectrum of oral manifestations of HIV infection will come only from research in the

Table 1. Classification of oral lesions associated with HIV infection[1]

Group 1. Lesions strongly associated with HIV infection

candidiasis:
  erythematous
  hyperplastic
  pseudomembranous
Note: angular cheilitis is often associated with *Candida albicans*.
hairy leukoplakia
HIV-gingivitis
HIV-necrotizing gingivitis
HIV-periodontitis
Kaposi sarcoma
non-Hodgkin lymphoma

Group 2. Lesions less commonly associated with HIV infection

atypical ulceration
salivary gland diseases:
  dry mouth due to decreased salivary flow rate
  unilateral or bilateral swelling of major salivary glands
thrombocytopenic purpura
viral infections (other than Epstein-Barr virus[2]):
  cytomegalovirus[3]
  herpes simplex virus[4]
  human papilloma virus (warty-like lesions)
  - condyloma acuminatum
  - focal epithelial hyperplasia
  - verruca vulgaris
  varicella zoster virus[5]
  - zoster
  - varicella

Table 1 *(continued)*

Group 3. Lesions possibly associated with HIV infection
bacterial infections (excluding gingivitis/periodontitis):
Actinomyces israelii
Enterobacter cloacae
Escherichia coli
Klebsiella pneumoniae
Mycobacterium avium intracellulare
Mycobacterium tuberculosis
cat-scratch disease
drug reactions (ulcerative, erythema multiforme, lichenoid)
exacerbation of atypical periodontitis
fungal infections other than candidiasis:
Aspergillus flavas
Cryptococcus neoformans
Geotrichum candidum
Histoplasma capsulatum
Mucoraceae
melanotic hyperpigmentation
neurological disturbances:
facial palsy
trigeminal neuralgia
osteomyelitis
sinusitis
submandibular cellulitis
squamous cell carcinoma
toxic epidermolysis

[1] As agreed at a meeting of the EEC-clearinghouse on Oral Problems Related to HIV Infection, Amsterdam, 30–31 August 1990.
[2] human (gamma) herpesvirus 4
[3] human (beta) herpesvirus 5
[4] human (alpha) herpesvirus
[5] human (alpha) herpesvirus 3

greatest possible number of countries and cultures. Studies of this nature, and optimum comparability of their findings, are thus critically important.

This guide is intended for use by oral health practitioners who are not specialists in epidemiology and by epidemiologists who are interested in HIV-associated oral lesions but who may not be familiar with the full range of these disorders and the subtle distinctions between them. It emphasizes the need to adopt standardized procedures for investigation that reduce the chances of error in diagnoses based on clinical examinations alone.

Usage of terminology

Note: Terms printed in bold type in this and other sections of the guide are fully defined in the annex.

Epidemiological studies are concerned with the occurrence of disease or health conditions in human populations and usually fall into one of

two principal categories. In a **cross-sectional** or **prevalence study** every individual in the study group is examined once, at essentially the same time, in order to ascertain the **prevalence** of a particular disease or other condition. A **longitudinal** or **incidence study**, on the other hand, examines the population at specific intervals, over a period of time, in order to determine the **incidence** of a disease or condition, i.e. the number of new cases that occur in a defined population during the study period. Both types of study are **observational**, rather than experimental: nature is allowed to take its course and there is no intervention by the investigator.

Observational studies may be descriptive or analytical. A **descriptive study** is limited to describing the occurrence of a disease or condition in the study population, whereas an **analytical study** seeks to analyse the relationships between health status and other variables. This guide focuses on the development and implementation of descriptive studies.

The simplest epidemiological measurement is a count of the number of individuals presenting a given disease or condition at a given time. However, a more valuable indicator of health status may be obtained by dividing this count, or **numerator**, by the number of people at risk (which may be the entire study population) as the **denominator**; this yields a proportion known as the **prevalence rate**. Careful choice of an appropriate denominator allows valid comparisons to be made among and between different study populations. Prevalence rates are derived using cross-sectional study designs. **Incidence rates**, on the other hand, derive from longitudinal studies; the numerator is the number of new cases of a disease or condition arising during a specified period, and the denominator is the population at risk during this period.

Role of prevalence and incidence in epidemiological studies

In the particular case of an oral lesion associated with HIV infection, studies of prevalence are unlikely to reveal which condition preceded the other. Longitudinal studies of incidence rates, however, provide a better indication of the sequence of events and generally more information about the causes of disease. They also allow assessment of the risk — or likelihood — of an individual developing a specific disease or condition.

Unfortunately, there are many situations in which longitudinal studies are not feasible, because of the expense and/or difficulty of maintaining contact with the particular population under study. In these circumstances, investigations of HIV-associated oral conditions must rely on whatever information can be gleaned from prevalence studies of the conditions and of identified risk factors.

DESIGNING THE STUDY

Determining the objectives

The objectives of a study will determine the study design, the kinds of data to be collected and the form in which they will be recorded, and the sources of information. For instance, a study intended to estimate the proportion of a population suffering from a particular oral lesion should be designed as a cross-sectional — or prevalence — study. However, where the intention is to determine the number of individuals developing new oral lesions during a specified period, a longitudinal — or incidence — study would be necessary.

Although descriptive studies cannot be used to test hypotheses directly, their use may well shed light on assumed or expected associations. Complementary use of both types of study might be valuable, for instance, in testing whether the prevalence of oral lesions is different at different stages of HIV infection, and whether the incidence of specific oral lesions in HIV-infected individuals differs from that in uninfected people.

Appropriate areas of study, and even detailed objectives, may also be suggested by a review of the relevant literature. Whatever their rationale, it is essential that the objectives — and any underlying hypotheses — are fully established before detailed study design begins.

Selecting the study population

Types of population

The study objectives will determine the number and type of populations necessary. Appropriate populations for studies of the type addressed in this guide are those in which oral lesions are likely to exist or to develop; obvious examples are HIV-infected individuals and groups of patients attending oral care clinics. Studies of groups drawn from among the general public would be inefficient: both HIV infection and the oral lesions of interest are relatively uncommon, so that very large numbers of people would have to be examined in order to find any with both conditions. It is essential that the study population is clearly defined. Rules for inclusion should be clearly formulated and rigidly applied to all potential subjects.

It may not always be feasible to conduct large-scale epidemiological studies devoted solely to oral lesions, and it is therefore suggested that, wherever possible, oral conditions be studied in conjunction with other

clinical aspects of HIV infection. This has the advantage of making studies relatively inexpensive. However, cost is not the only factor in making this a rational approach: patients' medical histories and other clinical manifestations of HIV infection are critical in analysing oral findings.

Study and comparison groups

Use of a comparison group uninfected by HIV may not always be possible in an epidemiological study, but it is highly recommended. A comparison group is particularly important for studies of conditions such as periodontal diseases, which are common in the absence of HIV infection. Findings in the study population can then be compared with those in the comparison group, so that any increased risk of oral disease resulting from HIV infection can be estimated.

The selection of appropriate individuals for comparison is a critical component of study design and one that is influenced by the study objectives. Comparison groups should be as similar as possible to the infected population with respect to characteristics that may affect the prevalence or incidence of oral lesions, such as age, sex, race, ethnic group, health-related behaviour (including sexual practices and use of tobacco, alcohol, and drugs), and occupational factors. For example, if the study is designed to estimate the increased risk of oral candidiasis in HIV-infected individuals with haemophilia, the comparison group should consist of haemophiliacs who are not HIV-infected but who resemble the study group in all the other characteristics noted above.

As a general rule, the comparison group should contain at least as many individuals as the study group. The same diagnostic procedures and criteria should be applied to the examination of both groups. Ideally, the examiner should be unaware of the health status of any individual — in this particular case, unaware of whether an individual is HIV-infected or not — although this may not always be possible.

Selecting the sample size

The number of subjects who should be included in a study is an important consideration, and it is recommended that a biostatistician be consulted before the study is initiated. For cross-sectional studies, for example, it is essential to have an estimate of the proportion of the population likely to have the condition of interest, and of the magnitude of allowable error of the population mean. In some cases, an estimate may be available in the relevant literature, and may even be specific to the population to be studied.