PREVALENCE OF ORAL MANIFESTATIONS OF HIV INFECTION - A GLOBAL PICTURE

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1 ACKNOWLEDGEMENT

So, finally reached the destination! It (almost) seems like yesterday I started my Masters programme on the European Erasmus Mundus scholarship. Firstly I would like to express my gratitude to the European Union for bestowing on me this wonderful opportunity to study and work with the best strata of people in this field.

Through the work with the present thesis, not only have I been acquainted to this highly interesting subject, I have also learned new aspects of my own abilities. For this I want to express my gratitude to my supervisors, Dr. Paul Erik Peterson, Chief, WHO Oral Health Programme, Geneva, Switzerland and Dr. Pascal Millet, Professor, University Victor Segalen Bordeaux 2. I owe great thanks to both for skilled guidance and for being my mentor throughout the thesis period.

I would also like to use this opportunity to thank my fellow students contributing to a nice and social community.

Special thanks go to my family; my father and mother always taking care of me and being my inspiration to tide over the tough times and my loving sister.

Of course last but not the least I owe my sincere thanks to Catherine Elvin, secretary to Dr. Petersen, for her help in my endeavour.

Finishing my thesis means finishing my days as a master's student, from which I bring along good memories. The knowledge I have earned will hopefully make me able to meet new challenges. I feel privileged!

2 ABBREVIATIONS

- WHO – World Health Organisation
- AFRO – African Regional Office
- AMRO – American Regional Office
- EURO – European Regional Office
- WPRO – Western Pacific Regional Office
- EMRO – Eastern Mediterranean Regional Office
- SEARO – South East Asian Regional Office

3 SHORTCUTS

- HIVSGD – Human Immunodeficiency virus associated salivary gland disease
- OSMF – Oral Submucous fibrosis
- OC – Oral Candidiasis
- OHL – Oral Hairy Leukoplakia
- AC- Angular Cheilitis
- EC – Erythematous Candidiasis
- HC –Hyperplastic Candidiasis
- PC – Pseudomembranous candidiasis
- HSV – Herpes Simplex Viral lesions
- XEROS. – Xerostomia
- NUG – Necrotising Ulcerative Gingivitis
- NUP – Necrotising Ulcerative Periodontitis
- LGE – Linear Gingival Erythema
- NS – Not Specified
- PIG. - Pigmentation

TABLE OF CONTENTS

4 EXECUTIVE SUMMARY

This thesis outlines the current epidemiology of HIV associated oral lesions at global level and stratifies countries according to high, medium and low prevalence of oral manifestations of HIV infection.

INTRODUCTION

Currently there are many knowledge gaps present about the prevalence of oral lesions related to HIV infection from different regions as majority of the countries have no database or referral system for these kind of lesions . This is an obstacle to the implementation of various HIV prevention and health promotion programmes as oral lesions are strong indicators of HIV infection , invariably often are the first lesions to be identified and reportedly , are markers of disease progression and parallel the changes in various laboratory markers like CD4 cell count and HIV viral load. So to have a database of the oral manifestations of HIV can prove to be very pivotal in our fight against AIDS because of its diagnostic and prognostic significance.

METHODOLOGY

The prevalence of different oral lesions associated with HIV infection like oral candidiasis , oral hairy leukoplakia ,herpes virus lesions , HIV salivary gland disease and oral ulcers etc, is retrieved from various databases ,computer assisted search , manual search and tabulated therein.

ANALYSIS

The data was subjected first to simple descriptive statistical analysis. The analysis revealed that oral candidiasis and oral hairy leukoplakia are the two most prevalent oral

lesions associated with HIV infection globally with pseudomembranous candidiasis being the most common form of candidiasis encountered. HIV associated periodontal lesions are NUG , NUP and LGE and these lesions are present in almost all WHO regions with the exception of NUG in SEARO region. Oral ulcers are also ubiquitous with no specific type reported in majority of studies but herpes simplex viral lesions follow closely behind.

Oral submocous fibrosis and oral pigmentation are reported mainly from countries in SEARO region and certain lesions like ranula are showing up in countries like Zimbabwe as a probable HIV associated oral lesion endemically.

Oral Kaposi sarcoma is the most common neoplasm encountered but is not reported from countries in SEARO region.

In the paediatric population, lesser number of studies and reports are retrieved. Oral candidiasis, HIV associated salivary gland disease and oral herpetic lesions dominate the picture in the paediatric population.

The results of the review were consistent and built upon previous reviews performed by Patton et al in 2000 (globally) and Ranganathan & Hemalatha in 2006 (developing countries). However the present study is the first study to show the prevalence globally across countries falling under all six WHO regional offices.

Though the stratification of the countries has been done according to the prevalence but some reports are quite old and as such it becomes difficult to extrapolate the results and stratify them on the map.

FUTURE RESEARCH STRATEGIES

Nevertheless this review definitely poses some questions which should be an eye opener for the countries from where no data is available on the prevalence of HIV associated

oral lesions as the importance of these lesions can not be understated for they are the markers of disease progression and immunosupression and thus need to be incorporated in the overall HIV diagnosis and treatment planning programmes. The thesis concludes with the proposition that it would be most useful to conduct HIV associated oral lesions' prevalence studies globally, specially in the countries which have the major burden of the disease to have a more comprehensive idea of the diagnosis and treatment needs of the HIV infected people.

5 INTRODUCTION

Though we are almost through the third decade of global experience of HIV/AIDS, the HIV epidemic is still the greatest threat to human populations in many parts of the world. There are over 44 million HIV infected people globally in 2005 (UNAIDS, 2005). The developing countries of Africa have the highest burden of disease while the number of HIV infected people in India alone is estimated to be about five million (NACO).

Oral manifestations of HIV infection are the mirror of systemic infection. Oral candidiasis, oral hairy leukoplakia, HIV gingivitis and periodontitis and Kaposi sarcoma are amongst the most frequent oral manifestations of HIV infection .They are often the first lesions to be identified in HIV infected persons and are also markers of disease progression and immunosuppression (Greenspan, 1997 ; Patton et al,1999 ; Margiotta et al,1999). The impact on quality of life is high in people infected by HIV/AIDS as people often suffer from pain, discomfort, dry mouth and poor nutritional status. A wide variety of opportunistic infections and neoplasms are associated with the oral cavity. About 40 different oral lesions can be attributed to HIV infection. (Melnick et al, 1991). HIV infection has a significant negative impact on oral health, 40-50% of HIV positive persons have oral fungal, bacterial or viral infections often occurring early in the course of the disease (Petersen, 2003). Existing literature shows that fewer studies on oral lesions are available from developing countries as compared to developed nations. There is wide variation in the study designs and types of studies performed ranging from case-studies, cross-sectional to some longitudinal studies. Also some studies have included all AIDS patients, some had only HIV infected subjects and the study designs applied range from population based studies to dental clinic population studies.

5.1 SIGNIFICANCE OF ORAL LESIONS

Oral lesions like oral candidiasis and Kaposi sarcoma are amongst the earliest lesions to be identified among the HIV infected homosexuals (Gottlieb et al, 1981; Ziegler et al, 1982). The presence of oral hairy leukoplakia (OHL) and oral candidiasis (OC) paralleling the decline in CD4 cell count and increase in HIV viral load, but also independent of these laboratory indices, indicates progression to AIDS (Greenspan and Greenspan, 2002; Chattopadhyay et al, 2005a, b). Oral lesions are quite easily visible on oral inspection and a wide range of professionally qualified people can easily diagnose them including physicians, oral health care professionals and public health experts and primary health care workers. These lesions can provide a quick and easy insight into the HIV status in high prevalence resource poor settings where other laboratory markers are cost- prohibitory and HIV testing is difficult. One study estimated that more than 90% of patients with AIDS would develop oral candidiasis at some point (McCarthy et al, 1991). Thus oral examination of all individuals at risk of infection, potentially infected and diagnosed HIV infected by health care workers at each clinical interaction is mandatory (Hodgson & Greenspan et al,2006). These lesions also form part of the acute or primary HIV infection syndrome (Vanhems et al, 1997). Therefore they act as early clinical features of HIV disease (Hodgson & Greenspan, 2006) and also serve as clinical markers of symptomatic HIV disease (CDC, 1993).

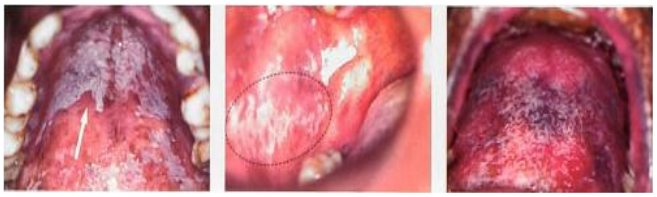
Greenspan et al summarized the role of oral lesions as being indicators of HIV infection, early clinical features of HIV disease, predictors of disease progression, markers for anti-HIV and anti-opportunistic therapy and their very important role in various HIV staging and classification systems (CDC,1986, 1993; Royce et al, 1991; Montaner et al, 1992; Saah et al, 1992; Hilton ,1995).

5.2 CLINICAL PRESENTATION OF HIV ASSOCIATED ORAL LESIONS

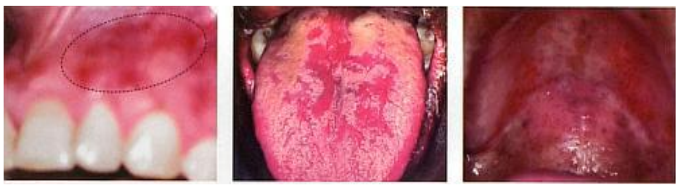
5.2.1 FUNGAL LESIONS

Oropharyngeal candidiasis is the most common fungal infection seen in patients with HIV infection. It can be present in three different forms:

Pseudomembraneous candidiasis is the most common oral lesion seen. It presents as a creamy white or yellow loosely adherent plaque anywhere in the mouth. It can be wiped off to reveal an erythematous surface with or without bleeding.



Erythematous candidiasis presents as multiple flat diffuse or discrete, red non removable plaques. It is usually found on the palate, tongue and occasionally the buccal and labial mucosa. A variant of erythematous candidiasis is median rhomboid glossitis – a red, smooth depapillated area on the middle of the tongue



ANGULAR CHEILITIS and LINEAR GINGIVAL ERYTHEMA are the other two less common oral manifestations in HIV disease

5.2.2 **BACTERIAL LESIONS**

A number of specific periodontal changes have been associated with HIV infection.

5.2.2.1 **NECROTISING ULCERATIVE PERIODONTITIS**

It is characterised by marked necrotic destruction of the periodontium, rapid loss of the periodontal attachment, severe pain, halitosis, loosening of teeth, bleeding and destruction or sequestration of bone. Patient refers it as “Deep jaw pain”. NUP is a marker of severe immunosuppression.

5.2.2.2 **NECROTISING ULCERATIVE GINGIVITIS**

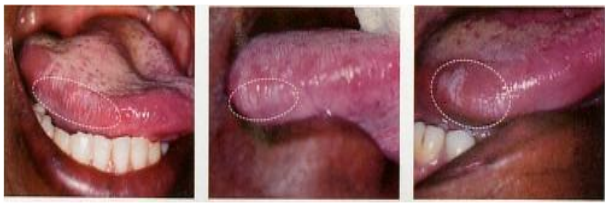
There is destruction of one or more interdental papilla with bleeding, ulceration, necrosis and sloughing. Tissue destruction is limited to the gingival tissues and does not involve alveolar bone. The demarcation between necrotizing gingivitis and necrotizing periodontitis was created to define the difference between the rapid destruction of soft (NUG) and hard (NUP) tissues.

5.2.3 **VIRAL LESIONS**

5.2.3.1 **ORAL HAIRY LEUKOPLAKIA**

Hairy leukoplakia appears as white patches, nearly always on the lateral border (outside edges) of the tongue. These lesions usually have an irregular surface and may have hair-like projections. While this condition may resemble thrush, hairy leukoplakia lesions cannot be wiped off, unlike the lesions of thrush.

Hairy leukoplakia is thought to be caused by the Epstein-Barr virus (also associated with infectious mononucleosis). Since this condition is rarely seen unless the CD4 cell count is low, it is less common in areas where combination anti-HIV therapy is readily available



5.2.3.2 **HERPES SIMPLEX VIRUS-1 INFECTION**

Also termed as Herpes labialis, this is a fairly common problem which appears as blisters on lips. It can also appear inside the mouth as blisters that may rupture and produce painful ulcerations. In HIV infected people, HSV 1 manifests as chronic, recurrent ulcerations that may progress rapidly to cause extensive mucocutaneous involvement. These erosive, painful ulcerations may persist for several weeks or months and eventually may involve oesophagus.

5.2.3.3 **HERPES ZOSTER (SHINGLES)**

It is a reactivation of the varicella zoster virus - the same virus that causes chickenpox, and can occur along any branch of the trigeminal nerve. Intraoral lesions appear as blisters or bubbles, then burst becoming ulcerations. Extraorally also it presents as vesicles which break open and crust over.The occurrence of the secondary form of herpes zoster

infection in HIV positive patients, manifests on the skin as localised, disseminated or typical generalised zoster and may herald seroconversion or immune deterioration. It may take up to four weeks to resolve.

5.2.4 **ORAL ULCERATIONS**

5.2.4.1 **APTHOUS ULCERS**

- Single, multiple, recurrent, well circumscribed ulcers.
- Whitish pseudomembrane surrounded by an erythematous halo.
- Usually limited to mucosa of the soft palate, buccal mucosa, tongue and tonsils.
- They are extremely painful and recur often. Large lesions are progressive, chronic and slow to heal. They often interfere with speech and swallowing and may thus contribute to inadequate oral intake and rapid weight loss. Severe recurrent aphthous ulcers (RAU) may occur in the mouth, oropharynx, and oesophagus of HIV/AIDS patients.

5.2.4.2 **ATYPICAL ULCERS**

- May appear in any location on the oral mucosa.
- Usually deep, crater-like & covered by fibrin.

5.2.5 **ORAL WARTS**

- Oral warts are caused by HPV- Human papilloma virus
- They appear cauliflower like, spiky or raised with a flat surface.

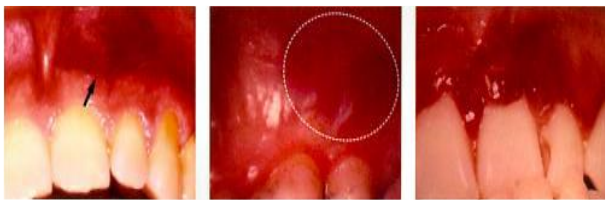
5.2.5.1 **CYTOMEGALOVIRUS INFECTION (CMV)**

It is an HIV related opportunistic infection which may present as a large painful ulcer on any part of the mouth. Its presence in mouth indicates its systemic presence.

5.2.6 **NEOPLASTIC DISEASES**

5.2.6.1 **KAPOSI SARCOMA**

It is still the most frequent oral malignancy seen in association with HIV infection. Oral lesions which can be raised or flat and range in colour from red to purple , may be the first sign of Kaposi sarcoma .Oral Kaposi sarcoma is found on the roof of the mouth but it also can appear on the gums and tongue and at the back of the mouth. As a lesion grows, it can cause problems with chewing, talking or swallowing.



5.2.6.2 **NON-HODGKIN'S LYMHOMA**

An AIDS defining condition, it occasionally appears in oral cavity. It presents as a large, painful, ulcerated mass on the palate or gingival tissues. A biopsy is mandatory for diagnosis and patient usually is treated by an oncologist.

5.2.7 **MISCELLANEOUS**

5.2.7.1 **SALIVARY GLAND DISEASE**

Several salivary gland disorders are found in patients who are HIV positive. Parotid gland enlargement often accompanies a syndrome of persistent generalised lymphadenopathy. It is thought to be caused by lymphoid proliferation in response to HIV infection. It may manifest as unilateral or bilateral non tender gland enlargement with xerostomia. Recurrent parotitis may occur. Xerostomia, with or without parotid swelling, may occur with a severely reduced salivary flow.

Note – The clinical features and the pictures have been adapted from www.hivdent.org.

5.3 **CLASSIFICATION OF ORAL LESIONS**

The EC- Clearinghouse on oral problems related to HIV infection and WHO Collaborating Centre on oral manifestations of Immunodeficiency virus gave their consensus classification of the oral manifestations of HIV infection (EC-Clearinghouse, 1993). This stratification of oral lesions has been done according to the prevalence and frequency of associated oral lesions with HIV infection (Table 1)

Table 1.September 1992 Consensus Classification of Oral Lesions Associated with Adult HIV Infection (EC-Clearinghouse 1993)

Group 1: Lesions strongly associated with HIV infection

- Candidiasis
  - Erythematous
  - Pseudomembraneous
- Hairy leukoplakia
- Kaposi's sarcoma
- Non-Hodgkin's lymphoma
- Periodontal disease
  - Linear gingival erythema
  - Necrotizing (ulcerative) gingivitis
  - Necrotizing (ulcerative) periodontitis

Group 2: Lesions less commonly associated with HIV infection

- Bacterial infections
  - Mycobacterium avium-intracellularae
  - Mycobacterium tuberculosis
- Melanotic hyperpigmentation
- Necrotizing (ulcerative) stomatitis
- Salivary gland disease
  - Dry mouth due to decreased salivary flow rate
  - Unilateral or bilateral swelling of major salivary glands
- Thrombocytopenia purpura
- Ulceration NOS (not otherwise specified)
- Viral infections
  - Herpes simplex virus
  - Human papillomavirus (warty-like) lesions

- Condyloma acuminatum
- Focal epithelial hyperplasia
- Verruca vulgaris

Varicella-zoster virus

- Herpes zoster
- Varicella

Group 3: Lesions seen in HIV infection

Bacterial infections

- Actinomyces israelii
- Escherichia coli
- Klebsiella pneumonia

Cat-scratch disease

Drug reactions (ulcerative, erythema multiforme, lichenoid, toxic, epidermolysis)

Epithelioid (bacillary) angiomatosis

Fungal infection other than candidiasis

- Cryptococcus neoformans
- Geotrichum candidum
- Histoplasma capsalutum
- Mucoraceae (mucormycosis zygomycosis)
- Aspergillus falvus

Neurological disturbances

- Facial palsy
- Trigeminal neuralgia

Recurrent aphthous stomatitis

Viral infections

- Cytomegalovirus
- Molluscum contagiosum

Note: This table is adapted from Patton et al, 2000.

Ramos – Gomez et al in 1999 also came up with the consensus classification for oral lesions associated with pediatric HIV infection (Table 2).

Table 2. Consensus Classification of Orofacial Lesions Associated with Paediatric HIV Infection (Ramos-Gomez et al, 1999)

Group 1: Lesions commonly associated with paediatric HIV infection

- Candidiasis
  - Erythematous
  - Pseudomembraneous
  - Angular cheilitis
- Herpes simplex virus infection
- Linear gingival erythema
- Parotid enlargement
- Recurrent aphthous ulcers
  - Minor
  - Major
  - Herpetiform

Group 2: Lesions less commonly associated with paediatric HIV infection

- Bacterial infections of oral tissues
- Periodontal diseases
  - Necrotizing (ulcerative) gingivitis
  - Necrotizing (ulcerative) periodontitis
  - Necrotizing (ulcerative) stomatitis
- Seborrheic dermatitis

Viral infections

Cytomegalovirus

Human papillomavirus

Molluscum contagiosum

Varicella-zoster virus

Herpes zoster

Varicella

Xerostomia

Group 3: Lesions strongly associated with HIV infection but rare in children

Neoplasms

Kaposi's sarcoma and non-Hodgkin's lymphoma

Oral hairy leukoplakia

Tuberculosis-related ulcers

Note: This table is adapted from Patton et al, 2000.

5.4 **REVIEW OF ANALYTICAL STUDIES ON ORAL LESIONS ASSOCIATED WITH HIV INFECTION**

The literature on the oral manifestations of HIV infection has grown in the last 25 years since HIV infection was initially reported and since then a vast expanding body of work has been published in various bio-medical disciplines. Greenspan and Greenspan in 2002 came up with an analytical study discussing the place occupied by the oral lesions in the natural history and approaches to prevention and control of HIV infection.

They reviewed the significance of HIV associated oral lesions, effect of HAART on oral lesions and their clinical applications in HIV medicine. Recently another review analysed the oral lesions in relation to HAART in industrialized countries (Hodgson & Greenspan, 2006). Recent studies in industrialized countries aim to look into the post –HAART era to answer questions about the changed nature, prevalence and incidence of HIV associated oral lesions, the oral aspects of complications of HIV therapy etc. The impact of HIV associated oral disease on the quality of life and health services research questions like accessibility of health services for HIV infected people and attitudes of oral health care personnel towards HIV positive people. All such questions can be answered and researched and planned for, if the data on the nature and prevalence of oral disease associated with HIV is available and updated.

The intent of this review is to improve our understanding of the prevalence of HIV associated oral lesions across the countries falling under the six WHO regional offices and to categorise the countries accordingly. Data is retrieved mostly from a large number of descriptive, cross-sectional studies based on clinic patient populations though some longitudinal / prospective studies have also been retrieved. This review reinforces, confirms and builds upon certain previous reviews (Ranganathan & Hemalatha, 2006; Patton et al, 2002; Shiboski, 2002). It incorporates the HIV associated periodontal findings too which have been the subject of numerous reviews (Lamster et al, 1995; Robinson, 1994; Ryder, 2000). More detailed accounts of factors which can influence the prevalence patterns (like HAART in developed countries) have been discussed as a separate issue in the discussion part.

6 **AIMS AND OBJECTIVES**

6.1 **AIM**

To have overview of the epidemiology of HIV associated oral disease globally and has a synopsis of geographical prevalence and nature of HIV associated oral lesions.

6.2 **OBJECTIVES**

1. To determine the prevalence of different oral manifestations of HIV infection in the countries falling under six WHO regional offices.

2. To grade the countries according to the prevalence of HIV associated oral lesions and categorise them accordingly into regions of
    a. HIGH (Red colour)
    b. MEDIUM (Yellow colour)
    c. LOW (Green colour)

    Prevalence.

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7 **METHODOLOGY**

A computer assisted search was done of English literature using PUBMED or MEDLINE to identify studies on the prevalence of oral lesions related to HIV infection. Majority of the studies are descriptive, cross-sectional studies populations and less attention is paid to a larger number of analytical epidemiological studies in clinic which are discussed in the introduction and discussion part of this review. The studies range from a period dating

back to 25 years when HIV infection was first documented. The search was conducted using certain key words and the references of certain studies are also referred to in certain instances.

7.1 **KEY WORDS:**

Oral lesions, oral candidiasis, oral hairy leukoplakia, Kaposi sarcoma, HIV infection, prevalence, epidemiology

7.2 **REGIONS SELECTED:**

AFRO
AMRO
EURO
SEARO
EMRO
WPRO

The data retrieval was done according to the nature and prevalence of the oral lesions in different regions and entered into Excel sheets and documented therein. Then analysis was done and graphs were made according to the documented prevalence of each disease. In cases of more than one study from the same region, the data from the more recent study was taken except for in cases where the older study had more number of subjects. In determining the prevalence of any HIV associated oral lesion, sometimes the data pertaining to this very study was missing – so the prevalence of oral candidiasis was included in place of any oral lesion as OC was the most frequent oral lesion documented in almost all the studies from all regions.

8 **RESULTS**

A detailed report of various oral lesions with HIV infection has been given in a tabulated form in Table 1.The majority of studies described are descriptive / cross-sectional studies with a few exceptions such as the Mexican cohort of 1000 patients (Ramirez-Amador et al, 2003) and a prospective study of 61 cases in Kenya (Butt et al, 2001).

The studies are classified by country and according to six WHO Regional Offices .Though many studies have been reported from AMRO,EURO,SEARO & AFRO almost none or a very few has been reported from WPRO & EMRO. Also among the study reports , the majority are quite old while only few are quite recent (Taiwo et al , 2005 ; Chidzonga et al , 2003 ; Ranganathan et al , 2004 , Kerdpon et al , 2004 ; Pinheiro & Marcenes et al , 2004 ; Gileva et al , 2004).

The number of the subjects enrolled in the studies varies from 15 to 200 and in the majority of them, almost more than 50% are males with a few exceptions .(Schimidt – Westhausen et al , 1997 ; Shiboski et al , 1994 ; Schuman et al , 1998 ; Khongkunthian et al , 2001 ; Wanzala & Pindborg , 1995 ; Taiwo et al , 2005)

The major route of transmission in AFRO & SEARO countries is by sexual contact among heterosexuals, except for a study in Thailand where majority were IV drug users. But MSM & IV drug use is more common in EURO & AMRO (74% of Mexican study were MSM - Ramirez-Amador et al, 2003)

The countries are grouped according to the High / Medium / Low according to the prevalence of any oral lesion related to HIV /AIDS. Consequently they are given the colours Red, Yellow & Green.

- High – Red

- Medium – Yellow
- Low – Green

A Global map depicting the stratification is shown in Map1.

8.1 **ADULTS**

8.1.1 **ANY HIV ASSOCIATED ORAL LESION**

The percentage of HIV infected adults with at least one oral lesion ranged from as low as 4% in Italy (Barone et al, 1990) to as high as 99% in Spain (Ceballos - Salobrena et al, 1996). The prevalence was systematically high in almost all studies encountered from SEARO countries ranging from 82% to 90% (Ranganathan et al, 2004; Reichart et al, 2003; Nittayananta & Chungpanich, 1997). The AFRO region shows some fluctuations and the prevalence rate is ranging from 20% in Kenya (Wanzala & Pindborg, 1995) to 92% in Zimbabwe (Jonsson et al, 1998). The pattern is similar for the AMRO region which sees a range of 22% in Minnesota (Little et al, 1994) to 92% in New York (Klein et al, 1991).Only one study is encountered from WPRO region (Singapore) and nothing was retrieved from the EMRO region in the literature.

8.1.2 **ORAL CANDIDIASIS**

Oral candidiasis is the most prevalent HIV-associated oral lesion across all WHO regions. Its overall prevalence varies from 0% in Namibia (Itula et al, 1997) to 95% in Mexico (Ramirez - Amador et al, 2002). In AFRO region, Zaire turned up with the highest percentage of cases of oral candidiasis (Tukutuku et al, 1990); followed by 80% prevalence in Kenya (Butt et al, 2001). The Republic of South Africa surprisingly has the lowest prevalence of 38% (Arendorf et al, 1998).

In the SEARO region, India has the lead with 81% of oral candidiasis cases (Anil & Challacombe, 1997).Thailand is somewhat behind with 55% - 66% 0f oral candidiasis cases (Kerdpon et al, 2004 and Nittayananta & Chungpanich, 1997).

In the EURO region, Spain is at the forefront with 66% cases (Ceballos - Salobrena et al, 1996). A single study from Russia presents the number at 38% (Gileva et al, 2004).

In the AMRO region, the prevalence of oral candidiasis ranges from 95% in Mexico (Ramirez-Amador et al, 2003) to another high level of 92% in New York (Klein et al, 1991) but to as low as 15% in a US Multicentre study (Schuman et al, 1998).

The most common type of oral candidiasis turned out to be the pseudomembranous type which varies from 1% in Kenya (Wanzala & Pindborg, 1995) to 88% in New York (Phelan et al, 1987). In the EURO region Italy has the lowest prevalence of 6% (Margiotta et al, 1999) and the highest at 38% in Spain (Ceballos - Salobrena et al, 1996). In the AMRO region, San-Francisco stands with the lowest reported prevalence of 6% (Feigal et al, 1991) and New York at the highest with 88% (Phelan et al, 1987). In AFRO Kenya stands at the bottom line with 1% prevalence (Wanzala & Pindborg, 1995) and Nigeria at the upper end with 44% prevalence (Anteyi et al, 2003) Pseudomembranous candidiasis is rather prevalent in SEARO region with quite high prevalence rates throughout the region. Thailand stands at 10% (Reichart et al, 2003) & Khongkunthian et al, 2001) with India at 64% being highest up the ladder (Anil & Challacombe, 1997).

The next most common type of candidiasis is the erythematous type which varies in frequency from 0% in Tanzania (Matee et al, 2000) to 35% in Mexico (Gillespie & Marino, 1993). The overall prevalence of erythematous candidiasis remains with the same range and with some fluctuations within the six WHO clusters.

In addition a combination of pseudomembranous and erythematous candidiasis is reported in two studies from Thailand and Cambodia (3% from Northern Thailand - Khongkunthian et al, 2001; 9% in Thailand and Cambodia - Reichart et al, 2003).

Angular cheilitis has also been observed in countries but with levels ranging from 0% in Tanzania (Matee et al, 2000) to 55% in Peru (Gillespie & Marino, 1993). Hyperplastic candidiasis has been reported from Kenya and Zaire in AFRO and from India in SEARO (Wanzala & Pindborg, 1995); Wanzala et al, 1989); Mugaruka et al, 1991) and Tukutuku et al, 1990).No such cases have been reported in countries from AMRO or WPRO. In the EURO region, Spain, Greece, Italy and Netherlands have reported hyperplastic candidiasis (Ceballos - Salobrena et al, 1996; Laskaris et al, 1992; Barone et al, 1990; Moniaci et al, 1990 and Schulten et al, 1989).

8.1.3 **ORAL HAIRY LEUKOPLAKIA**

Oral Hairy Leukoplakia is the second most common oral lesion worldwide. The highest prevalence of 95% has been reported from Mexico (Ramirez-Amador et al, 1998) while this condition was not found in a New York study (Barr & Torosian, 1986) and in Zaire (Mugaruka et al, 1991). But other country reports depict a different picture of higher prevalence (Barr et al, 1992; Klein et al, 1991; Phelan et al, 1987; Tukutuku et al, 1990). In the AFRO region, Lesotho, Nigeria and South Africa have shown higher prevalence of hairy leukoplakia . Reports from India indicate a lower prevalence of 2-7% from different studies (Ranganathan et al, 2004 and Anil & Challacombe, 1997) whereas within SEARO region, Thailand and Cambodia demonstrate higher frequencies of 7-38% (Reichart et al, 2003; Kerdpon et al, 2004 and Nittayananta et al, 2001).

In AMRO region, Mexico takes the lead with 95% prevalence of Oral hairy leukoplakia (Ramirez - Amador et al, 2002) although a year later in a larger study involving 1000 subjects, the prevalence was shown to be much lower at 23%. The Latin American countries – Peru, Chile and Brazil are seen with prevalences in the range of 9-25%, however,

Argentina has a low rate of 3% (Pinheiro & Marcenes et al, 2004 and Gillespie & Marino, 1993). There are reports available from USA with the prevalence range of 0-29% (Barr & Torosian, 1986; Lamster et al, 1994; Barr et al, 1992; Patton et al, 2000).

Reports from EURO region have prevalence in the range of 7-30%, UK and Greece are relatively on the upper front with 30% and 24% prevalence rates, respectively (Palmer et al, 1996 and Laskaris et al, 1992).

Finally, a single report from Singapore in the WPRO region shows the prevalence to be 5% (Lim & Robinson et al, 2001).

8.1.4 **HIV ASSOCIATED GINGIVAL AND PERIODONTAL LESIONS**

HIV associated gingival and periodontal lesions include – Necrotizing Ulcerative Gingivitis (NUG), Necrotizing Ulcerative Periodontitis (NUP) and Linear Gingival Erythema (LGE) have been documented in various countries.

8.1.4.1 **NECROTISING ULCERATIVE GINGIVITIS**

Meanwhile , NUG has not been reported from SEARO region ; the noted prevalence is 2% from Argentina (Gillespie & Marino, 1993) followed by 16% in Zaire (Tukutuku et al, 1990) and 11% in Greece (Laskaris et al, 1992) and in all countries the prevalence falls within the range of 0-24%.

8.1.4.2 **NECROTISING ULCERATIVE PERIODONTITIS**

NUP is reported worldwide with frequencies falling in between 1- 28%. SEARO region has shown frequencies at the level of 23% in India (Anil & Challacombe, 1997) and 14-15% in Thailand and Cambodia (Kerdpon et al, 2004). AFRO region reports indicate

prevalences of 2-5% with an exception of Zaire where NUP is 17% (Tukutuku et al, 1990). In AMRO region, a San-Francisco study reports a prevalence of 19% NUP (Silverman et al, 1986) with the regional range of 2-19%.

8.1.4.3 **LINEAR GINGIVAL ERYTHEMA**

Linear Gingival Erythema (LGE) is also extensively reported for countries of AFRO, SEARO, AMRO and EURO. In SEARO, India & Thailand report a prevalence of 16% and 12%, respectively (Ranganathan et al, 2000; Reichart et al, 2003; Nittayananta et al, 2001). A US multicentre observed the prevalence at 14% (Schuman et al, 1998) and 22% (Lamster et al, 1994) but it could be as low as 0% in some places within the region (Little et al, 1994).

8.1.5 **ORAL KAPOSI SARCOMA**

Oral Kaposi Sarcoma is not reported from the SEARO region but appears quite prevalent in studies carried out in AFRO, AMRO and EURO regions. Zimbabwe presented high prevalence (72%) in a study in 1998 (Jonsson et al, 1998) but the rate was down at 19% in a study conducted a few years later (Chidzonga et al, 2003). In AMRO, Mexico also showed the same trend with 52% prevalence in 1993 (Ramirez-Amador et al, 1993) to 2% in 2003(Ramirez-Amador et al, 2003). Some early studies also point to a high prevalence (Roberts et al, 1988 & Silverman et al, 1986), but generally, the prevalence of kaposi sarcoma has gone down to 2-5%.

8.1.6 **HIV ASSOCIATED ORAL ULCERS**

HIV associated oral ulcers can manifest in a variety of ways – Herpes Simplex Virus associated ulcers (not specified), recurrent and non-recurrent aphthous ulcers, tuberculosis and neoplastic types. (Ranganathan and Hemalatha, 2006).

Herpes Simplex Viral lesions appear to range from 1% to 20%. High figures have been reported from Russia (20%) (Gileva et al, 2004) and in Italy (14%) (Ficarra et al, 1994). Argentina and places in USA also have HSV prevalence in the range of 10-12% (Gillespie & Marino, 1993 & Silverman et al, 1986). The most frequent ulcers are that of non-specified type.

8.1.7 **MISCELLANEOUS**

Amongst others, **HIV Salivary Gland Disease (HIVSGD)** is reported from almost all regions and on an average constitutes 3% of the total oral lesions seen in all Xerostomia is even more common.

Amongst other lesions, HIVSGD is reported mainly from countries of AFRO and in some studies from AMRO and EURO countries and the average rate is approximately 3% of the total oral lesions seen in all. A study from Tanzania reported a quite high prevalence of 47% (Matee et al, 2000).

SEARO region reports present isolated cases of **Oral Submucous Fibrosis (OSMF)** from India and also presence of oral pigmentation which was reported to be as high as 23% and 26%, respectively, in 2 studies (Ranganathan et al, 2000; Ranganathan et al, 2004). Mexico and Peru are countries that also showed cases with oral pigmentation. Other lesions reported by countries from SEARO and AMRO region include leukoplakia, exfoliative cheilitis and non- healing extraction wound in varying frequencies from different studies.

Histoplasmosis and **Penicilliosis** also appear to be prevalent in South - East Asia – they are evident from studies in Thailand (Nittayananta & Chungpanich, 1997; Kerdpon et al, 2004).

Herpes zoster was reported from Nigeria and Zimbabwe with marked prevalences of 23% & 12%, respectively (Agbelusi et al, 2005; Jonsson et al, 1998). Oral Erythema, Human

papilloma virus lesions / warty lesions are also reported with low but varying frequencies from countries in AMRO and EURO regions.

8.2 **PAEDIATRIC POPULATION:**

Oral manifestations are amongst the first signs of illness in children infected with HIV. The overall picture of these oral lesions is quite different from that presented in seropositive adults. Opportunistic infections like that of **oral candidiasis** (predominantly pseudomembranous type) dominate the clinical picture followed by the herpetic lesions. The highest prevalence of 72%of oral candidiasis was reported from San Francisco in USA (Katz et al, 1993). It was closely followed by another study from USA with a prevalence of 67% (Ramos -Gomez et al, 1996). A quite recent report from South Africa places the prevalence there at 63%. Studies from SEARO and EURO also are in concordance with those findings from AMRO region (Ranganathan et al, 2004; Mihalache et al, 2003).

Herpes virus lesions are found mainly in country reports from the AMRO and EURO regions with a prevalence of range 1% - 24%. The highest prevalence of 24% was reported in USA (Katz et al, 1993). A study from Romania informs about a prevalence of 21% (Mihalache et al, 2003).

There are not many studies or data available to substantiate the findings clearly in SEARO and AFRO regions and there is no clear demarcation whatsoever about the ulcers notified there – NS (Not Specified) (Naidoo & Chikte, 2004).

Some differences are shown in reports from children when compared to the studies from adults - **Salivary Gland Disease**, notably parotid hypertrophy, is present more exclusively in children and others, such as periodontal bacterial infections and kaposi's sarcoma , are lesions that predominate in the adult HIV population (Exposito- Delgado et al, 2004). The salivary gland disease / parotid hypertrophy is being agreed upon within a range of 2% - 50% from the current studies. Reports from the AFRO region (South Africa and

Uganda) inform of prevalence at 50% (Naidoo & Chikte, 2004; Bakaki et al, 2001) whereas a figure of 2% was observed for parotid swelling (Ketchem et al, 1990). In spite of this great disparity, all the authors recognise that the parotid involvement is more specific to the infected pediatric population (Kline MW, 1996; Flaitz et al, 2001; Costa et al, 1998).

9. **DISCUSSION**

9.1 **ADULTS**

After having provided a comprehensive review of the existing literature it is evident that there are limited data available in most parts of the world regarding HIV associated oral lesion and when is available the majority of studies are not recent studies. Most of the published data dates back to several years back in time. Also most of the studies are cross-sectional/descriptive or case studies while longitudinal prospective studies are lacking.

Also the number of subjects involved in studies is quite low which is a barrier to extrapolate it to a larger population/country/region. Women are being under represented in the studies except for a few reports. This is in contrast to the fact that UNAIDS in 2004 has specified that almost 50% of the infected with HIV are females. It indicates the gross under use of health services by women in most parts of the developing world today.

The **prevalence of any HIV associated oral lesion** is quite high in all study groups from all WHO regions. It stresses the strong need for the identification and documentation of oral lesions in HIV infection as they often are the first lesions to be identified, indicate HIV infection, predict progression, symptoms are the entry and end point in therapy and vaccine trials, and they correlate with HIV viral load (Greenspan et al, 2002).

The worldwide reports on oral manifestations of HIV/AIDS indicate that **oral candidiasis** is amongst the most common oral lesions associated with HIV infection. Its very

high prevalence suggests its value in diagnostic and prognostic work in both developed and developing country settings, it can be used as a sentinel marker to assist in diagnosis of HIV infection and to mark disease progression. A study from Zimbabwe (Jonsson et al, 1998) reveals that 72% of Kaposi sarcoma is the best predictor of HIV infection in Zimbabwean adults.

The public health implication of this finding can be enormous as a visual oral examination of mouth and looking for specific oral manifestations like oral candidiasis and can do away with the expensive anti body tests and other cost-prohibitory screening tools.

The health care professionals, clinicians and public health experts can play a very important role in identification and diagnosis of HIV infection. Consequently due to increased case-identification in susceptible populations the general population can be informed and educated as regards modes of transmission, safe sex practices and mother to child transmission of HIV. One very important research implication is for epidemiological studies to evaluate the efficiency of positive predictive value of oral candidiasis and other oral mucosal lesions in relation to HIV in different regions of the world. Such a study was carried out in North California (Patton et al, 2000) which examined the positive predictive value of oral lesions in relation to CD4+lymphocyte count and this study came up with very high percentages for candidiasis – A PPV of 82.2% for Pseudo membranous candidiasis, 73.8 for any form of oral candidiasis, 66.3% for having leukoplakia and 89.3% for oral candidiasis and hairy leukoplakia present concurrently. PPV was defined here as the probability that a patient had a CD4+lymphocyte count < 200 cells mm^{-3} given the presence of a specific oral lesion (Shiboski CH, 2002).

Kaposi sarcoma has been reported from countries in AFRO, AMRO and EURO but not from SEARO region. It may be because in Asian countries, there is no endemic presence of HHV 8 which is associated with Kaposi sarcoma.

Oral Hairy Leukoplakia is found in all regions but in some Asian countries like India, the prevalence is found to be low. OHL is more prevalent in region where MSM (Men having sex with Men) is a common sexual practice. Some earlier studies have a higher prevalence of OHL than the more recent ones (Ramirez-Amador et al, 2002 & 2003). It may be due to the fact that the patients in earlier studies were already in advanced stages of the disease.

Amongst ulcers **Herpes Simplex Viral lesions** were ubiquitous but it has to be examined if it really is associated with HIV as is present endemically in the population. It could also be possible that Herpes Virus lies dormant in the ganglia and gets reactivated under immuno compromised situations due to HIV infection and then shows up more in HIV infected people. The majority of ulcers reported from all regions belong to the non-specified ulcers category. We therefore need more defined diagnostic criteria to distinguish the various ulcers types and classify them epidemiologically.

Also, oral lesion can act as surrogate markers for HIV disease progression and an example is with respect to the prevention of tuberculosis (Shiboski CH, 2002). Tuberculosis is one of the most prevalent causes of death among persons with HIV disease in sub-Saharan Africa (Mokadi et al, 2001) and if we could identify certain oral lesions which predict the progression of HIV infected patient towards Tuberculosis symptoms, we may offer targeted chemoprophylaxis to the high risk groups.

Noma / Cancrum oris is also associated with immuno- suppression. In some HIV infected people, who are poor and malnourished (especially in sub-Saharan Africa), necrotizing diseases of the oral tissues can also predispose to/ present as early signs of noma. So prompt targeted measures should be placed in to prevent an early death of HIV infected malnourished children due to noma. And conversely, all children with cancrum oris should also be serologically tested for HIV infection.

Periodontal and gingival lesions are most prevalent in the AFRO & SEARO regions and there are understandably due to the poor oral hygiene practices, inadequate nutrition and poor access in oral health care in these areas. Standard diagnostic criteria should be established to have a uniform reporting from all over the world and to avoid mixing up of the background periodontal lesions with the HIV associated necrotizing lesions of the oral tissues.

There are certain unique oral lesions reported from certain countries ,for example, in Zimbabwe, a study established a 82% prevalence of **Ranula** to be present in HIV infected patients ( ) and stressed the need for identification of Ranula as another oral lesion to be associated with HIV infection in Zimbabwe.

Likewise **Oral Submucous Fibrosis (OSMF)** has been linked to HIV infection in India but still systematic epidemiologic data is lacking to evaluate the effect of use of areca nut / betel nut chewing in the Indian subcontinent.

Likewise **penicilliosis marneffei & Histoplasmosis** have been said to be very prevalent in South-East Asia (Nittayananta & Chungpanich, 1997; Kerdpon et al, 2004) and are known oral opportunistic infections associated with advanced disease and immunosuppression, but a concrete link between them increased frequency & HIV which is yet to be ascertained.

The majority of **HIV salivary gland disease (HIVSGD)** cases are reported from Africa and a very few from Latin America & EURO region. An explanation given for the high prevalence in the AFRO region may relate to the presence of HLA – DR5 & untreated advanced stage disease in Africans (McArthur et al, 2003).

HIVSGD is often also linked with xerostomia, but xerostomia can also occur due to a variety of other causes including advanced disease radiotherapy and immuno-supression. Oral Pigmentation also seems to be endemic to the Indian subcontinent.

Other oral lesions like **Herpes Zoster & Human Papilloma virus infection / oral warts** fall into the group of lesions lass commonly associated with HIV infection (EC-Clearinghouse, 1993) and have been reported from AMRO and EURO. The increased frequency of oral warts in developed parts of the world could also be a consequence of HAART as it is suggested that HAART increases the frequency of warts in the oral cavity.

The variations and discrepancies in studies reported can be ascribed to many factors like age, gender, race, risk behaviors, geographical location, socio-economic and immune status, duration of HIV infection, medication, diagnostic criteria used and timing of evaluation of subjects (Patton et al, 2000)

9.2 **PAEDIATRIC POPULATION:**

As already stated in the results section, the three most common pediatric HIV associated oral lesions are **oral candidiasis**, **herpetic lesions** & **salivary gland disease**. According to the prevalence of any HIV associated oral lesion , the countries are grouped into three categories of High , Medium and Low prevalence and accordingly assigned red , yellow and green colours (map 2). USA and South Africa fall into the high prevalence zones followed by Brazil, Thailand, and Romania in the yellow colour with India and Italy falling into the low risk category.

The majority of the investigations studied do not take into account whether the children are taking antiretroviral treatment or not. It has great implications and ramifications on the results as a study by Flangan et al (2000) concluded that in children receiving HAART (protease inhibitors, reverse transcriptase inhibitors & fixation and penetration inhibitors),

there is no significant oral implication as compared to children on no therapy or receiving traditional anti-retroviral therapy (reverse transcriptase inhibitors only) (Exposito- Delgrado et al,2004). Also the time period of examination of children is another pivotal factor for the analysis of outcome of such studies.

Nevertheless, the dental practitioner / physician / public health expert can play an instrumental role in the diagnosis, treatment, prevention and control of oral lesions associated with HIV infection which may result in improved quality of life, greater long term survival and lower mortality in HIV infected children.

9.3 **SOCIAL IMPLICATIONS OF HIV ASSOCIATED ORAL DISEASE**

In all affected countries with either high or low HIV prevalence, AIDS hinders development, exacting a devastating toll on individuals and families (US Agency for International Development, 2004). AIDS, on an average, not only lowers the life expectancy by many years but also has a debilitating impact on the already crumbled family economies in the hardest hit countries. In Swaziland , Zambia and Zimbabwe , which lack access to antiretroviral programs , average life expectancy is predicted to drop below the age of 35 (Petersen PE, 2006). The economic burden, on both high and low prevalence countries, has worsened due to the HIV/AIDS pandemic and the living standards are hardly hit. Primary school education has become a victim of the pandemic with the well educated teachers falling a prey to the disease. It is expected to leave behind a future shortage of skilled primary school teachers.

10 **CONCLUSIONS**

This is a comprehensive systematic review of the literature regarding the prevalence of HIV associated oral lesions and grouping of the countries (falling under six WHO regions) according to the prevalence determined by documentation of different studies and reports. The countries are categorised into high, medium and low prevalences and assigned red, yellow and green colours respectively.

Oral candidiasis and Oral Hairy leukoplakia are the most prevalent oral lesions associated with HIV across all WHO regions. Certain lesions like oral kaposi sarcoma are not observed in the countries from SEARO region. HIV associated periodontal lesions like NUG , NUP and LGE are reported from many WHO regions with certain exceptions like that of NUG from SEARO region. Oral ulcers are also ubiquitous with no specific type reported in majority of studies but herpes simplex viral lesions follow closely behind.

Oral submucous fibrosis and oral pigmentation present mostly from the Indian subcontinent.

In certain regions like Zimbabwe , lesions like ranula are argued to be included as HIV associated oral lesion.

In the paediatric population, oral candidiasis, Herpes virus lesions and HIV associated salivary gland disease are the most predominant lesions.

11 **RECOMMENDATIONS**

- Focussed research efforts should be initiated to document the prevalence of HIV associated oral lesions countrywise, especially in the high burden countries of HIV infection.
- The WHO Oral Health Programme has prepared a guide (Melnick et al , 1993) outlining a systematic approach to the implementation of epidemiological studies of oral lesions associated with HIV infection :

To provide guidelines for the collection, analysis, reporting and dissemination of data from such studies; and to facilitate comparison of findings from different studies (Petersen PE, 2006). This guide could be used as a standard reference for the sake of comparison between different studies.

- Continued monitoring of incidence trends and detection of new syndromes associated with HAART are important priorities in the HAART era.

- International collaboration and collective action is needed to ensure that oral aspects of HIV disease are taken into account in medical programmes and to integrate oral health care with the general health care of the patient. It is important that all health care workers receive education and training on the relevance of oral health needs and the use of oral lesions as surrogate markers in HIV infection.

- The health care team should address pain management, nutritional supplementation and stress the importance of oral hygiene. Timely referral to the primary care team is indicated to rule out other systemic opportunistic infections.

- WHO has outlined some basic principles for developing a country – specific approach to capacity building to control HIV / AIDS related oral disease (WHO, 1995). Stress was given on four key areas :

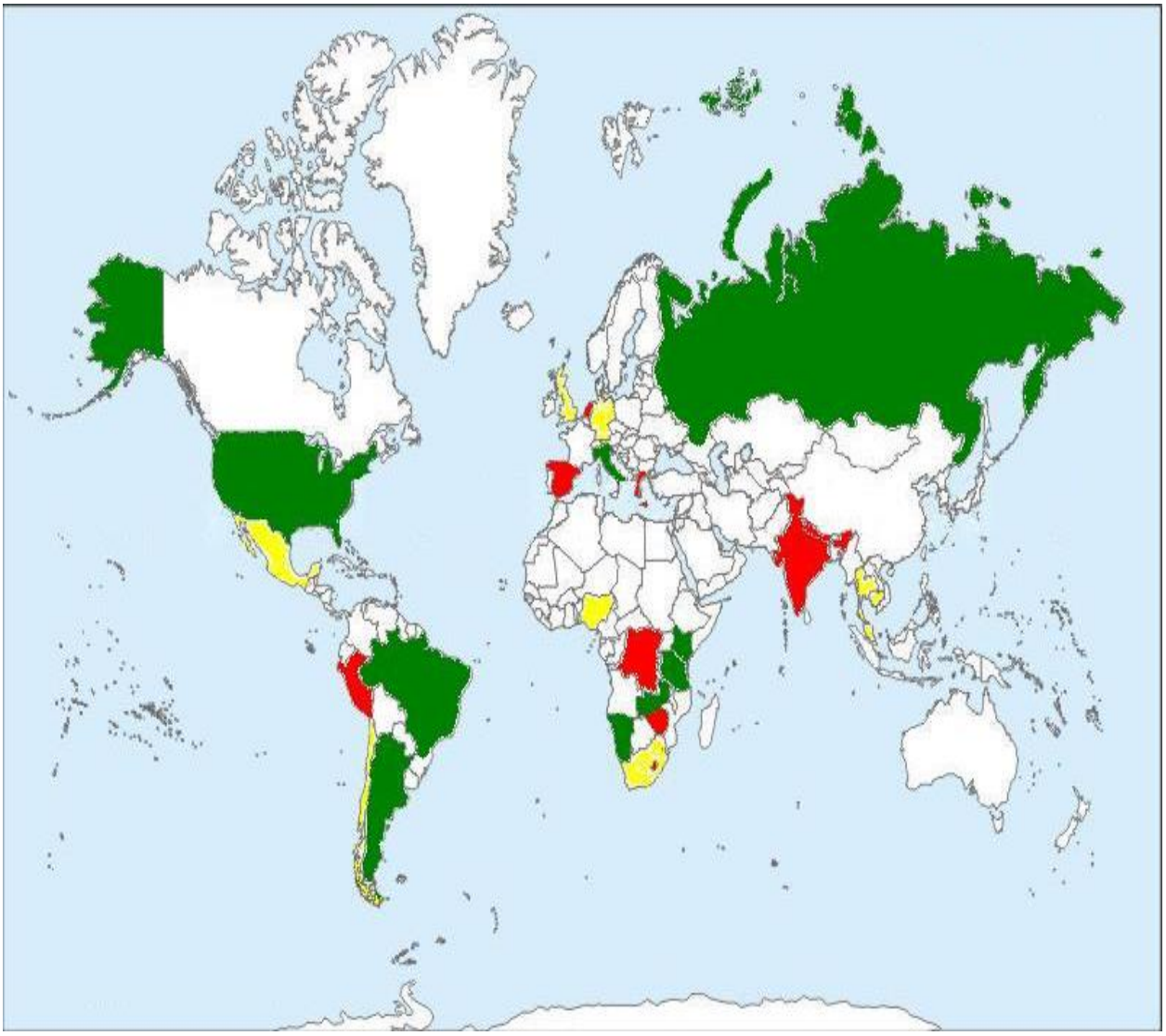
    1. Health promotion and health education
    2. Patient care
    3. Infection control
    4. Epidemiology and surveillance

    So epidemiological surveillance is a very key area to be focus on and needs to be standardised for comparison of result outcomes.

12. **ANNEXES**

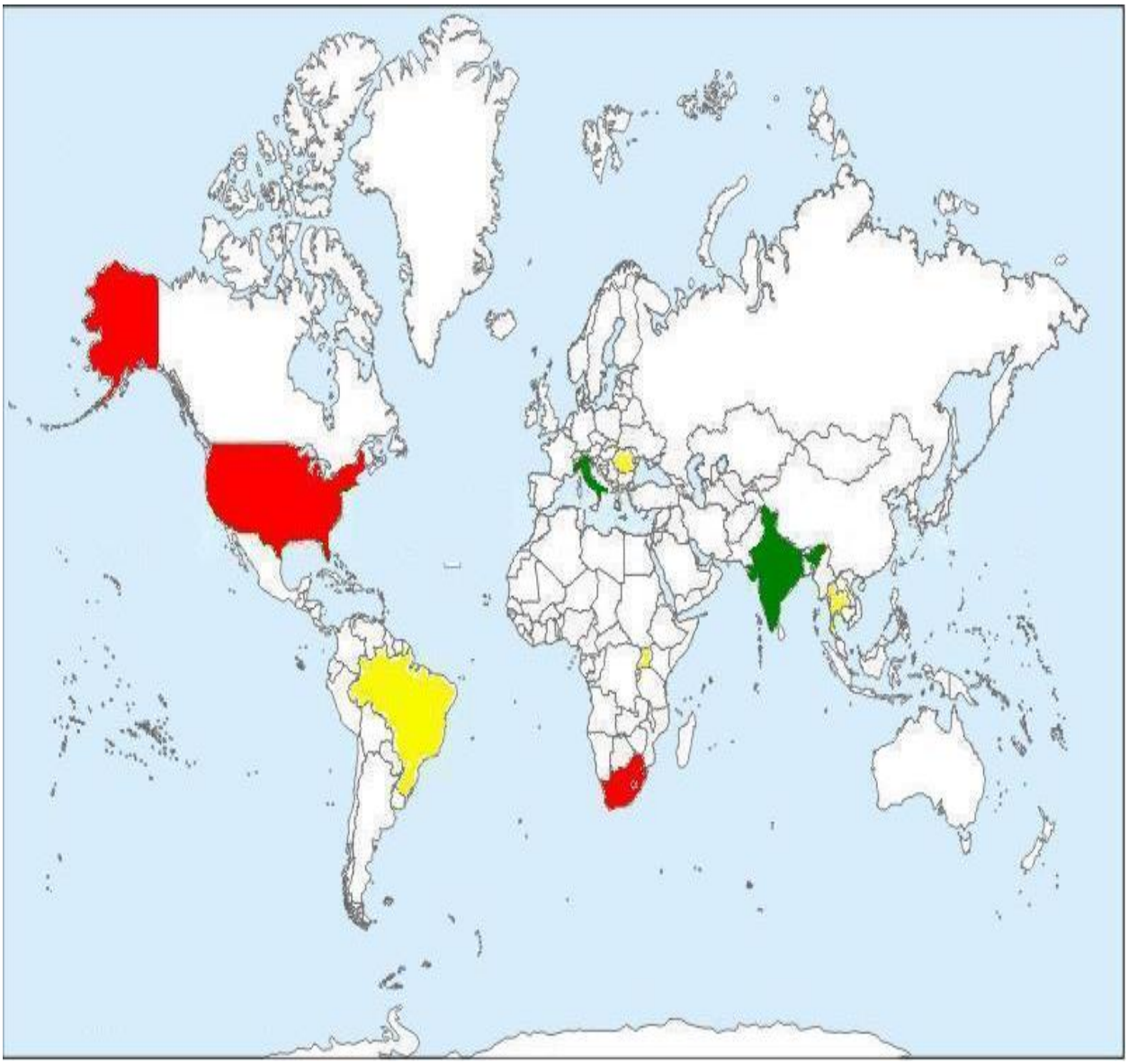
12.1 **LIST OF MAPS**

12.1.1



Global Map depicting prevalence of HIV associated oral lesions in Adults

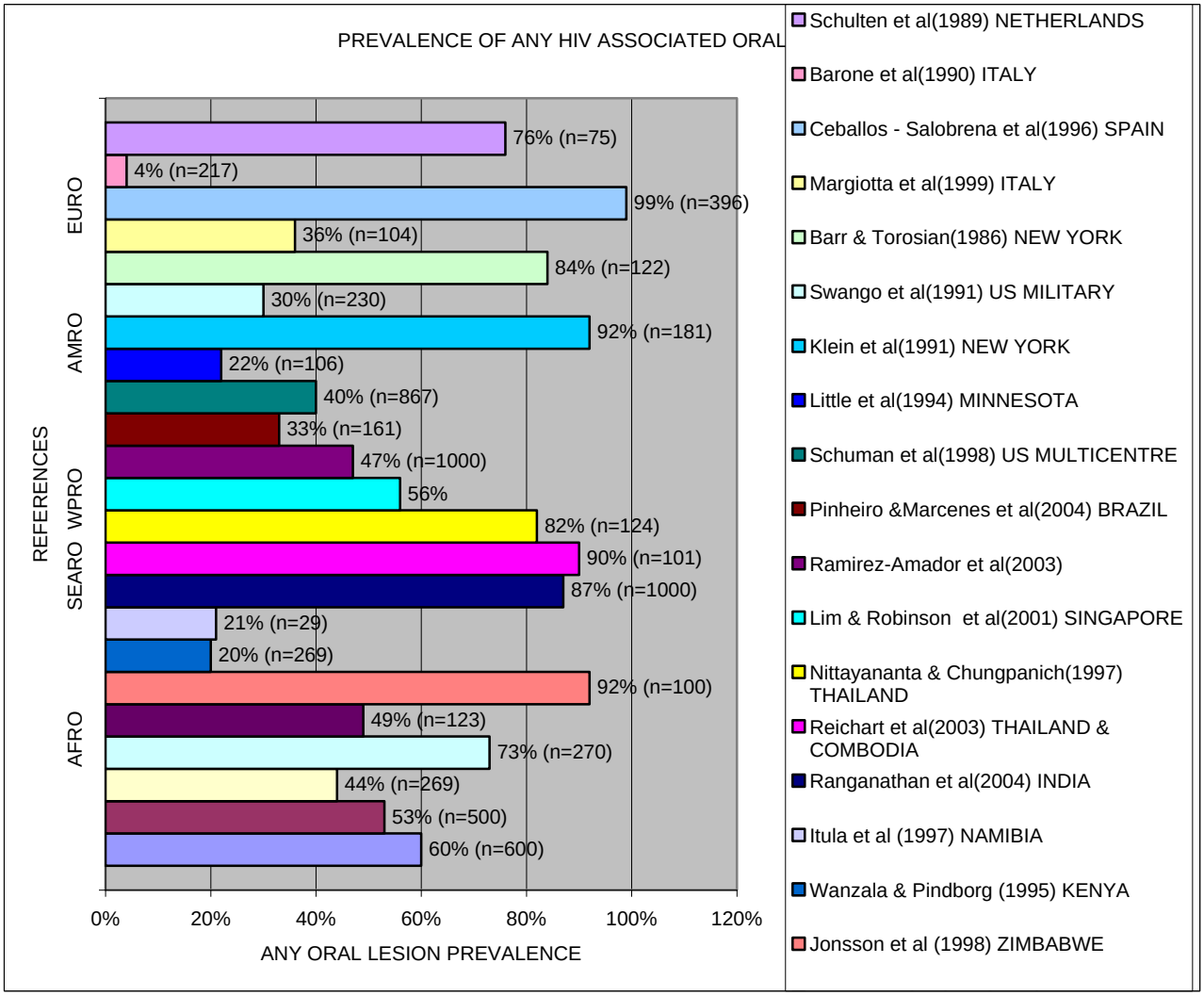
12.1.2



Global Map depicting prevalence of HIV associated oral lesions in Paediatric Population

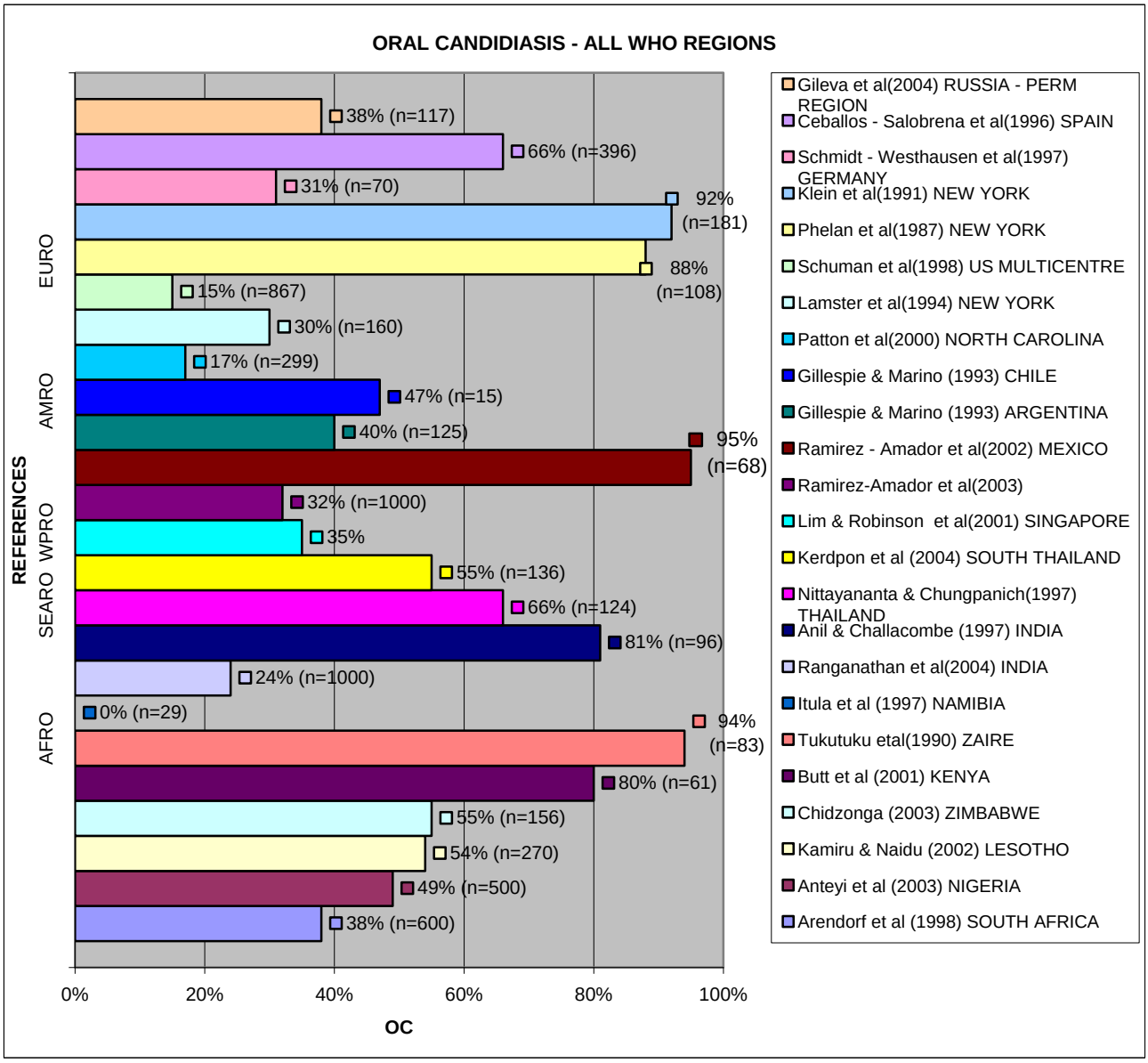
12.2 **LIST OF GRAPHS**

12.2.1



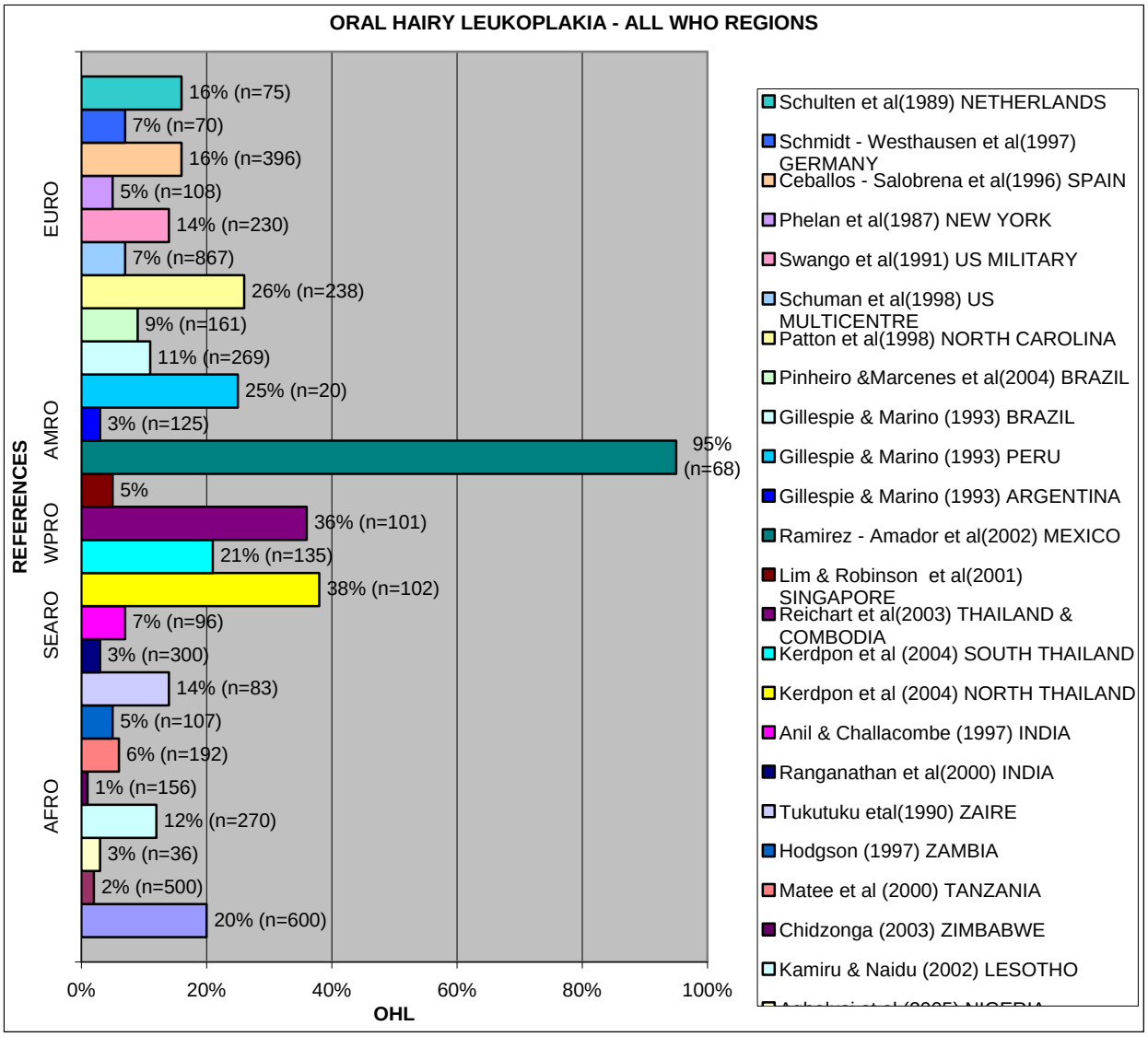
Graph showing prevalence of Any HIV associated oral lesions in all WHO regions

12.2.2



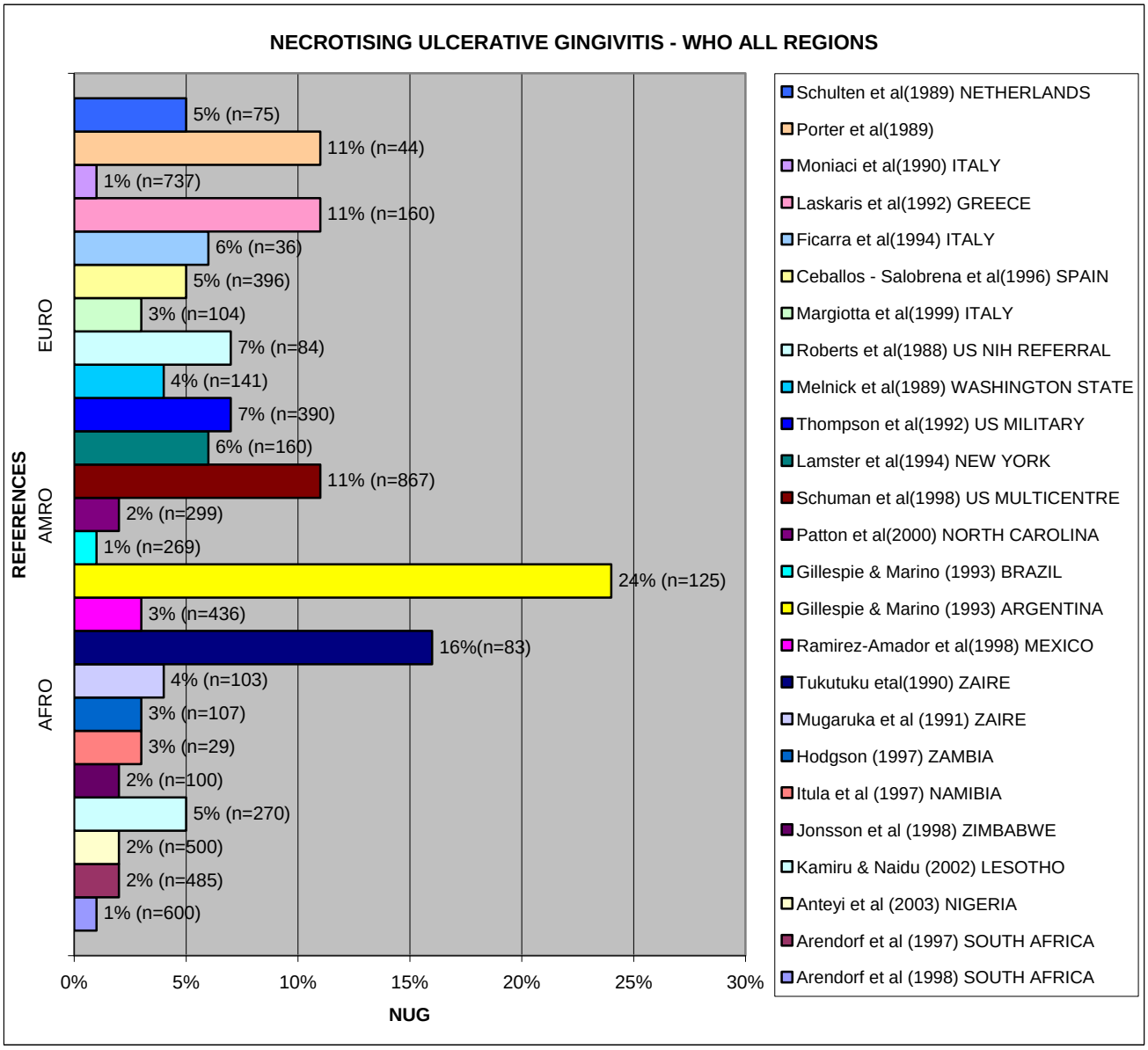
Graph showing prevalence of Oral Candidiasis in all WHO regions

12.2.3



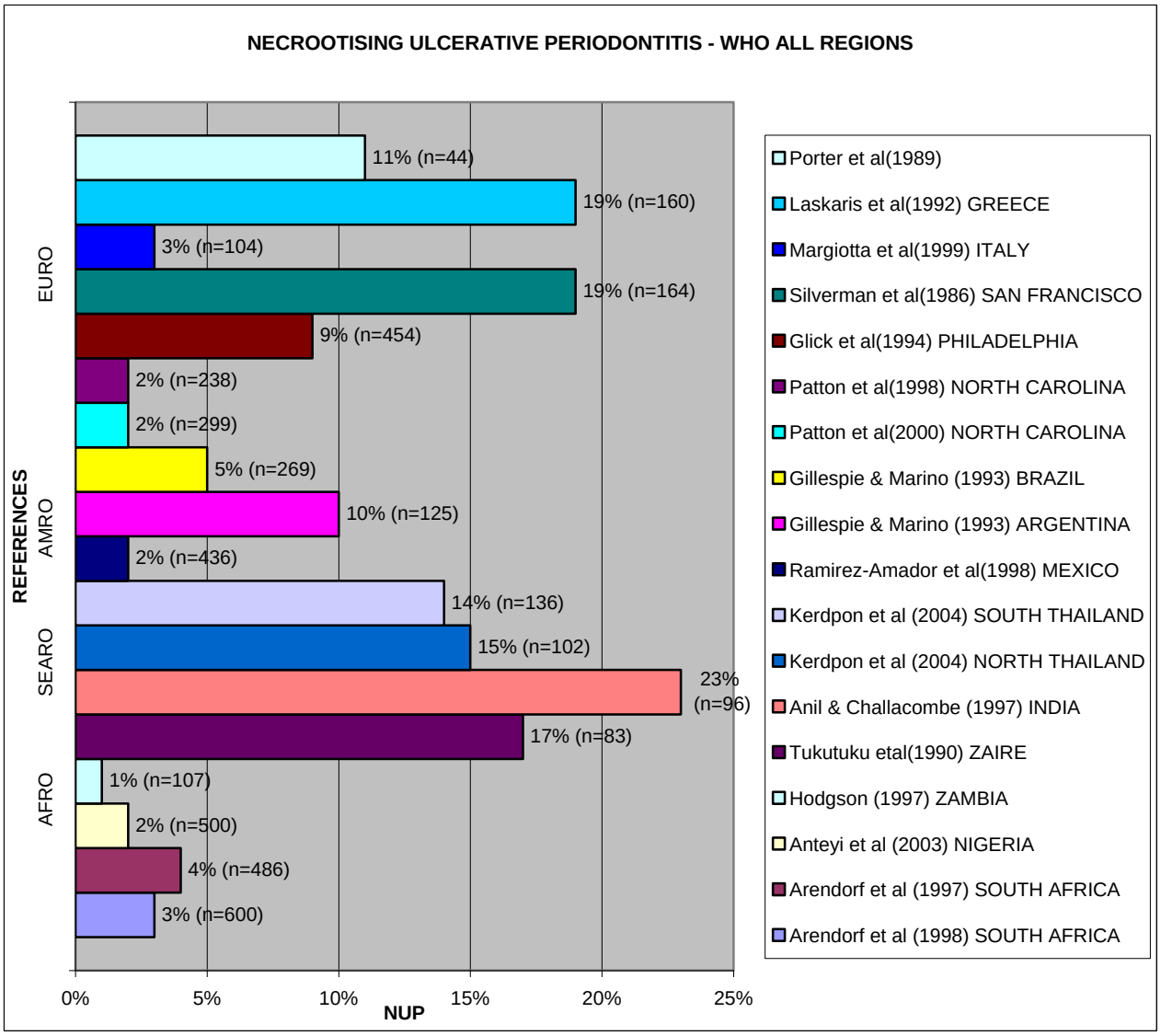
Graph showing prevalence of Oral Hairy Leukoplakia in all WHO regions

12.2.4



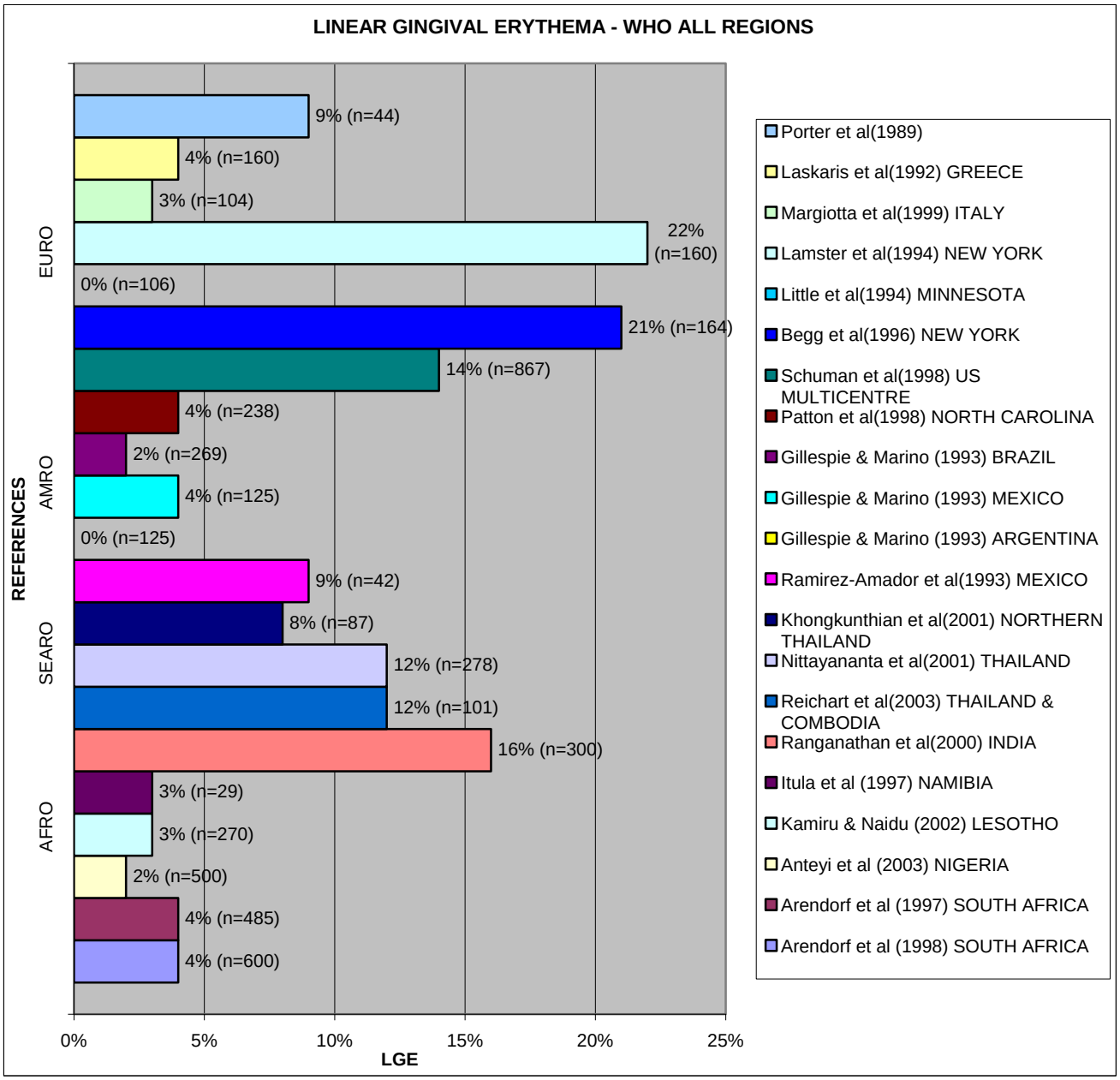
Graph showing prevalence of Necrotising Ulcerative Gingivitis in all WHO regions

12.2.5



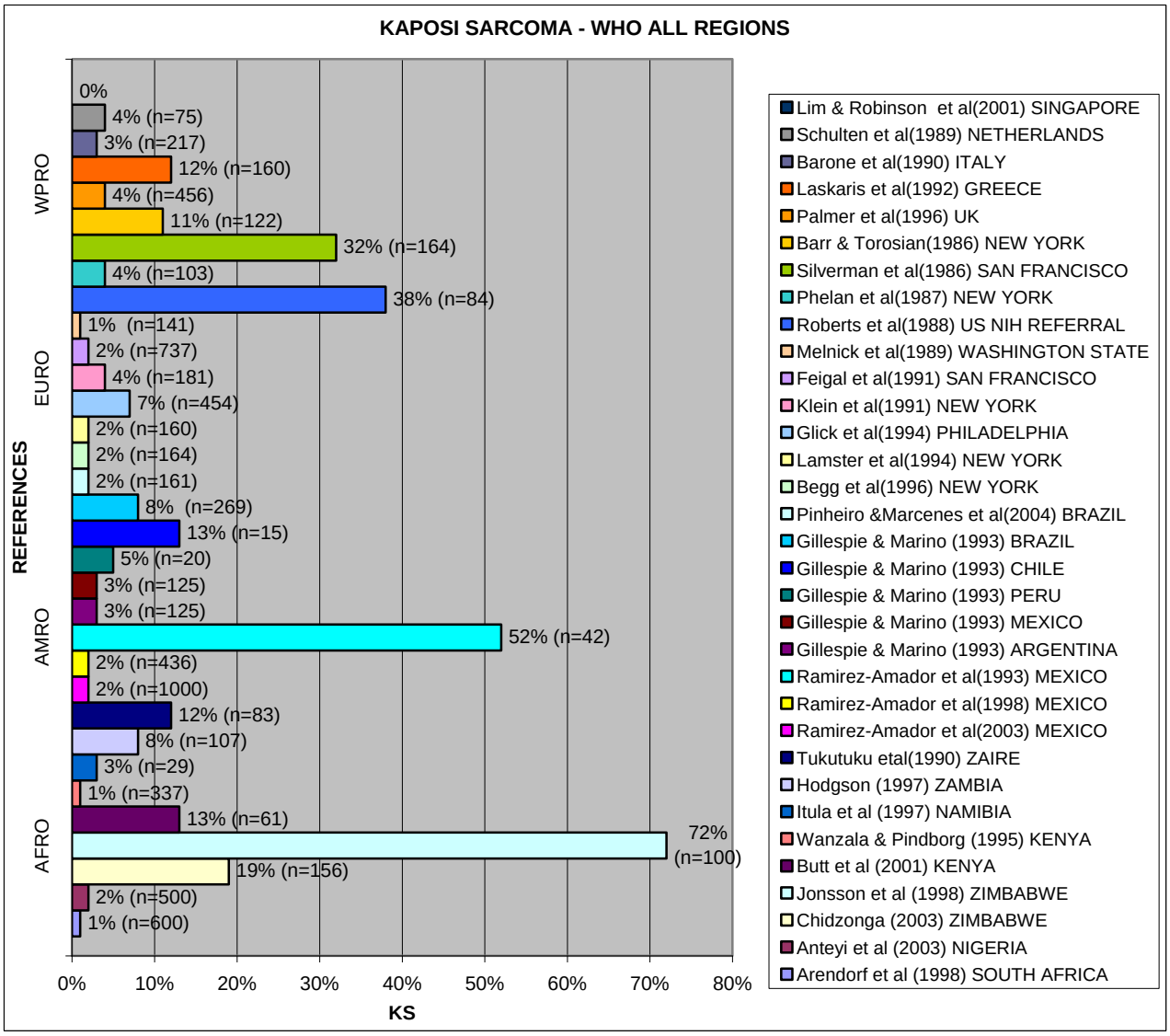
Graph showing prevalence of Necrotising Ulcerative Periodontitis in all WHO regions

12.2.6



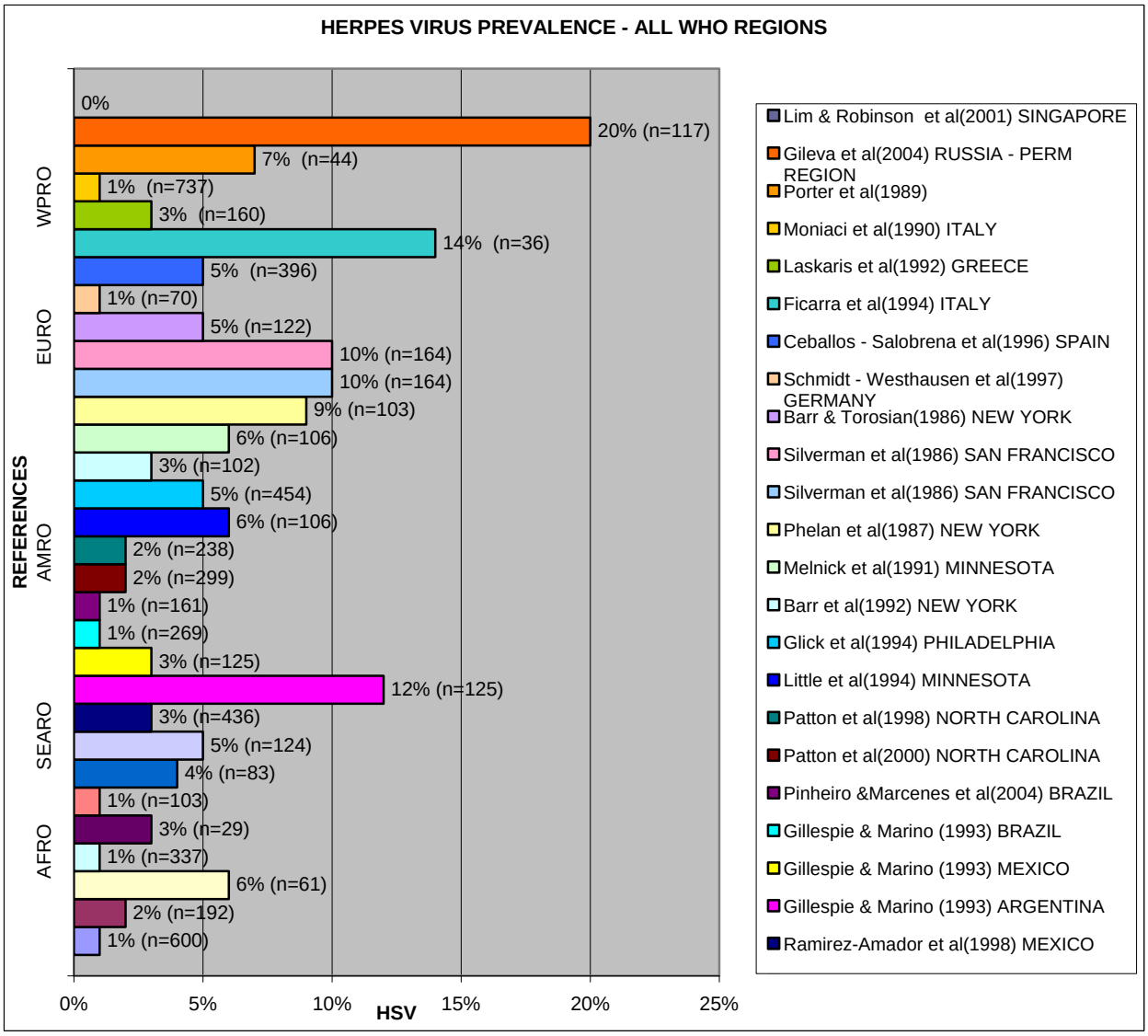
Graph showing prevalence of Linear Gingival Erythema in all WHO regions

12.2.7



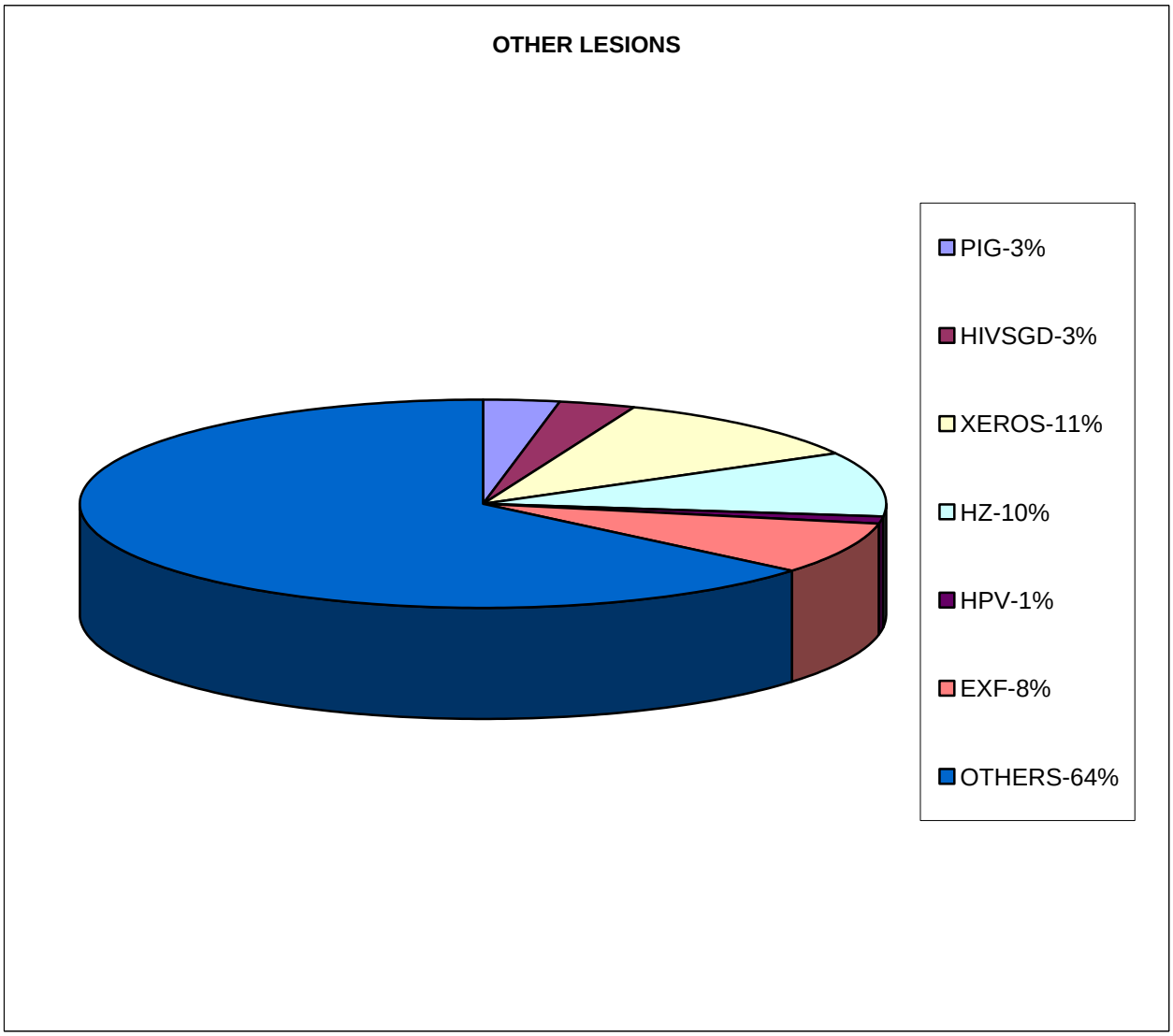
Graph showing prevalence of Oral Kaposi Sarcoma in all WHO regions

12.2.8



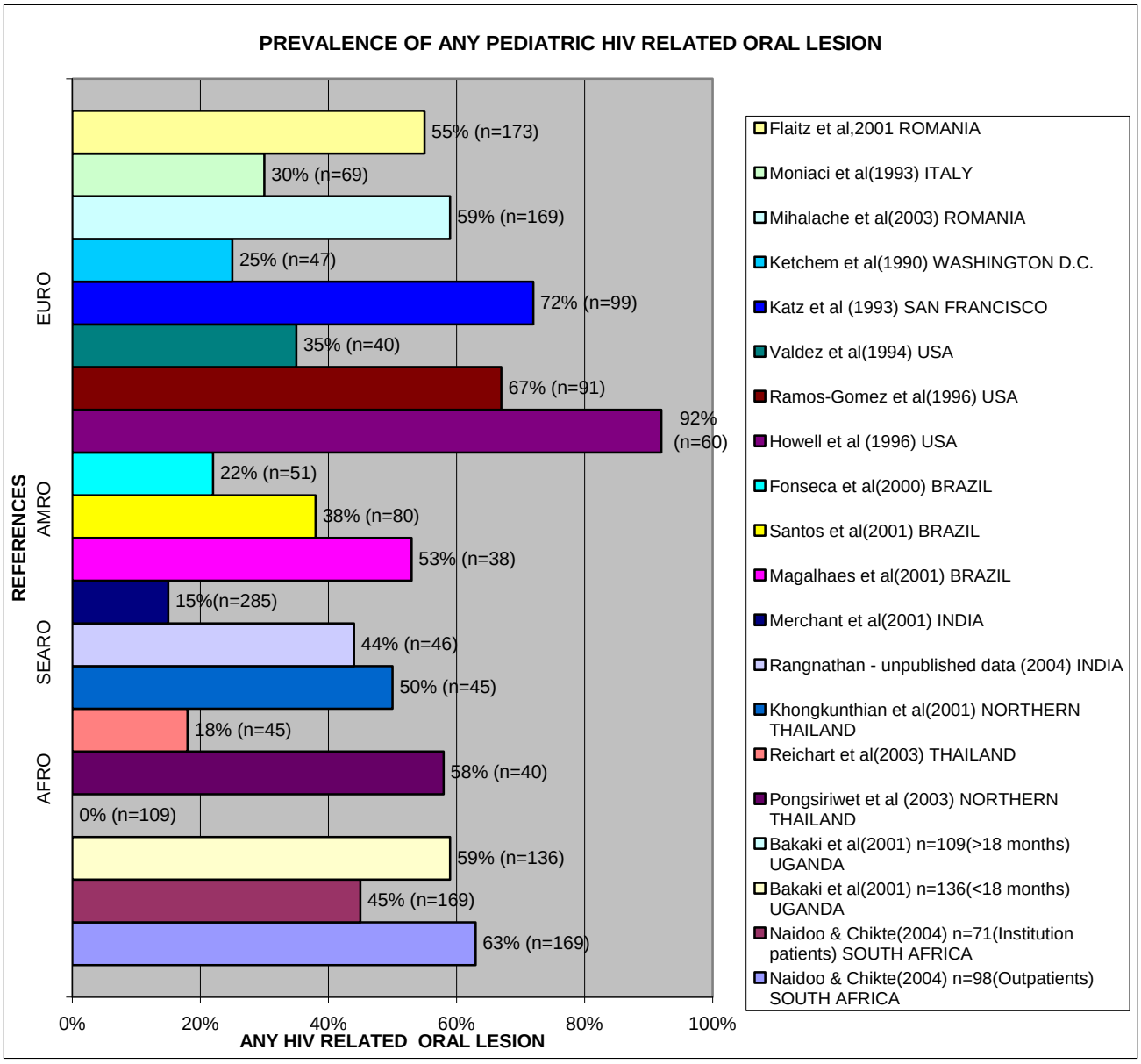
Graph showing prevalence of Herpes Simplex Viral lesion in all WHO regions

12.2.9



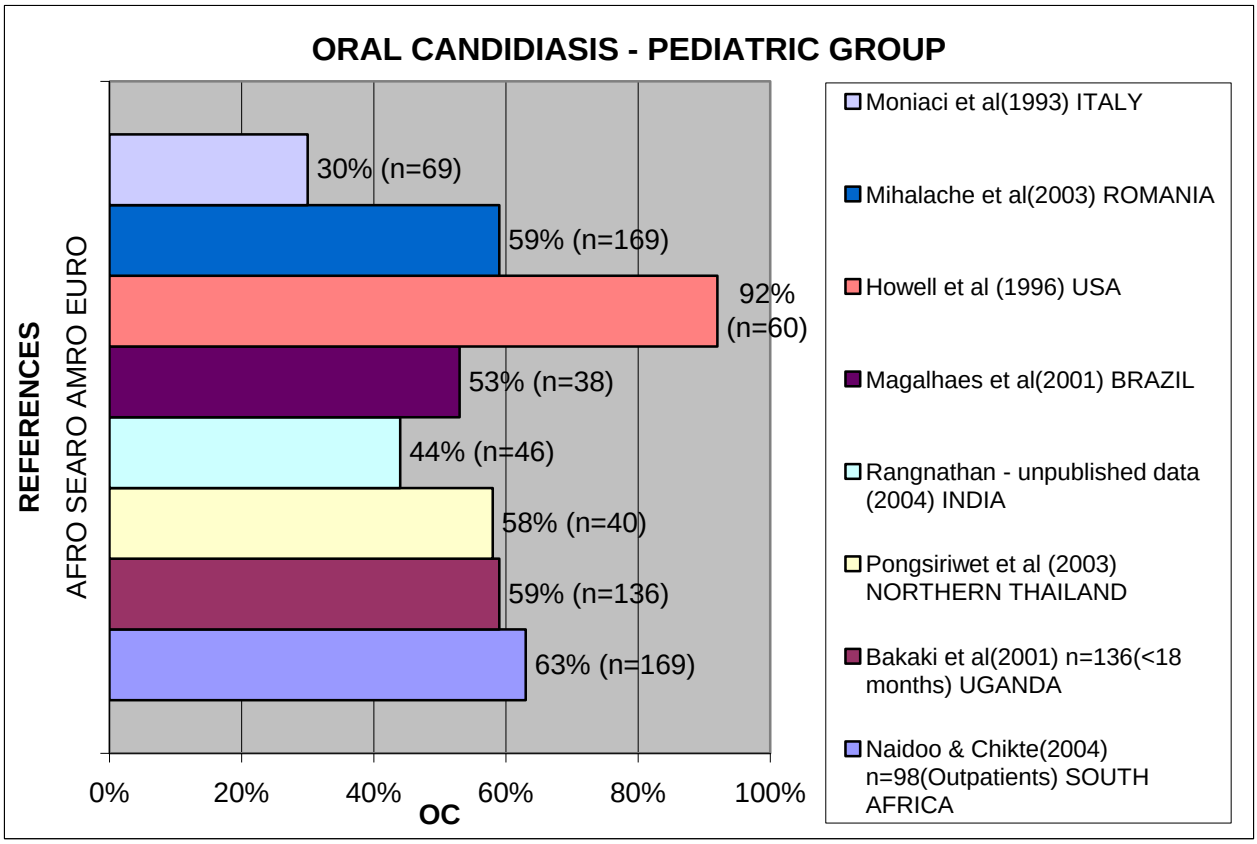
Pie diagram showing miscellaneous / other lesions

12.2.10



Graph showing prevalence of any paediatric HIV associated oral lesions in all WHO regions

12.2.11



Graph showing prevalence of Oral Candidiasis in paediatric population in all WHO regions

12.3 **LIST OF TABLES**

12.3.1

Reference	Country/ Region	No. of subjects	AIDS Cases	%	ANY ORAL LESION	OC	PC	EC	HC	AC	OHL	ULCERS	NEOPLAS MS	HIV Perio /Ging.	OTHERS	ARV Tt
AFRICAN REGIONAL OFFICE (AFRO)																
Arendorf et al 1 (1998)	SOUTH AFRICA	600 (63 %- M)		20	60	38 %	16 %	16 %	16 %		7 %	3 % - NS 20 % 1 % - HSV	1 % - KS	1 %-NUG 3 %- NUP 4 %- LGE	1 %- HIVSGD 1 %-PIG	NA
Arendorf et al 2 (1997)	SOUTH AFRICA	485 (65 %- M)	NA		56 %	35 %	13 %	16 %			6 %	19 % 3 %-NS	0 %	2 %-NUG 4 %NUP 4 %LGE 2 %-NUG	18 % 1 %-PIG	NA
Arteyi et al 3 al (2003)	NIGERIA	500 (55 %- M)	NA		53 %	40 %	44 %	4 %			9 %	2 % 2 %-NS	2 %-KS	2 %-NUP 2 %-LGE	0.4 %- HIVSGD	YES
Taiwo et al 4 al (2005)	NIGERIA	269 (F)	NA		44 %	36	24 %				9.00 %				23 %- HZ	
Agbelusi et al 5 (2005)	NIGERIA	35 (NA)	NA			43 %						3 %			6 %-BM 6 %- FP	
Kamiru & Naidu 6 (2002)	LESOTHO	270 (NA)		0	73 %	54 %	27 %	26 %			14 %	12 % 12 %-NS	<1 %-KS <1 %-NHL	5 %-NUG 3 %-LGE		NO
Onunu & Obuekwe 7 (2002)	BENIN CITY, NIG ERIA	123(NA)	NA		49 % (Fungal)	80 %						10 %- RU 3 %-NRU	12 %-NS	28 %- BACTERI AL	10 %- VIRAL 10 %-HZ	
Chidzonga 8 (2003)	ZIMB ABW E	156 (51 %- M)	NA		NA	55 %	31 %	15 %			10 %	1 %	11 %	19 %-KS 7 %-NHL	12 %- HIVSGD 8 %- NUG+NU P	4 %- CANCRU M 5 %- RANULA	NO
Jonsson et al 9 (1998)	ZIMB ABW E	100 (80 %- M)			92 %	22 %						0 % 26 %-NS	72 %-KS	2 %-NUG 1 %HGS	12 %-HZ 47 %- HIVSGD 1 %-CA	
Matee et al 10 al (2000)	TANZANI A	192 (NA)		38	NA	12 %	12 %	12 %	0		0	4 %-APTH. 6 % 2 %-HSV	0		7 %- 0 OTHERS	NO

Reference	Country / Region	No. of subjects	AIDS Cases	%	ANY ORAL LESION	OC	PC	EC	HC	AC	OHL	ULCERS	NEOPLASMS	HIV/Perio /Ging.	OTHERS	ARV Tt
Butt et al 11 (2001)	KENYA	61(41%-M)	NA		NA		80%				28%	5%	11.5%-NS 6%-HS 5%-HZ	13%-KS	100%-Perio	28%-LAP 6%-PIG 1 CASE-ORAL WARTS	NO
Wanzala & Pindborg 12 (1995)	KENYA	337 (F)	NA			21%		1%	13%	2%	1%	3%	2%-APTH. 1%-HSV	1%-KS	NA		NA
Wanzala et al 13 (1989)	KENYA	269	NA			20%			9%	1%		2%		0%	NA		
Itula et al 14 (1997)	NAMIBIA	29 (55%-M)	NA			21%	0%					3%	3%-HSV	3%-KS	3%-NUG 3%-LGE	3%-LEUKOPLAKIA	NO
Hodgson 15 (1997)	ZAMBIA	107 (42%-F			48 NA		25%	19%	6%			5%	0%	8%-KS	3%-NUG 1%-NUP	5%-HIVSGD 4%HZ	NO
Muganuka et al 16 (1991)	ZAIRE	103 (NA)			95 NA		62%	31%	29%	2%	3%	0%	6%-APTH. 1%-HSV	5%	4%-NUG 12%-NON-NUG	13%-HIVSGD 1%-HPV	NA
Tukutuku et al(1990) 17	ZAIRE	83 (45%)			100 NA		94%	32%	23%	6%	33%	14%	12%-APTH. HSV 4%-	12%-KS	16% NUG 17%-NUP	2%-HIVSGD 8%-LEUKOPLAKIA	NO
SOUTH - EAST ASIAN REGIONAL OFFICE (SEARO)																	
Ranganathan et al(2000) 1	INDIA	300 (68%-M)			37	72%	56%	33%	14%	1%	8%	3%	3%-NS		47%-GIN. 9%-PERIO 16%-LGE	23%-PIG 2%-OSMF 1 CASE LEUKOPLAKIA	NO
Ranganathan et al(2004) 2	INDIA	1000 (77%-M)	NA			87%	24%	16%	3%	1%	8%	2%	3%-NS	0%	72%-GIN 33%-PERIO	26%-PIG. 0.9%-OSMF 1.5%-LEUKOPLAKIA 55-OTHERS	YES

Reference	Country / Region	No. of subjects	AIDS Cases	%	ANY ORAL LESION	OC	PC	EC	HC	AC	OHL	ULCERS	NEOPLASMS	HIV/Perio /Ging.	OTHERS	ARV Tt
Ranganathan-Unpublished data(2003)	INDIA	1700 (74%-M)	NA			82%	21%	13%	2%	1%	8%	2%	3%-NS	71%-GIN. 21%-PERIO	0.7%-OSMF 5%-OTHERS 1%-LEUKOPLAKIA	YES
Anil & Challacombe (1997)	INDIA	96 (59%-M)		44	NA		81%	64%	21%		13%	7%	6%-APTH. 3%-TB	4%-SCC 23%-NUP	4% NON HEALING EXTRACTION WOUND	NA
Kerdpon et al (2004)	NORTH THAILAND	102 (26%-M)		100	NA		25%	15%	18%		3%	38%		15%-NUP	1%-HIVSGD	YES
Kerdpon et al (2004)	SOUTH THAILAND	135 (NA)		0			55%	42%	25%		4%	21%	3%-APTH. 3%-NS	14%-NUP	1%-HISTO 1%-HIVSGD	YES
Reichart et al(2003)	THAILAND & COMBODIA	87 (NA)	NA			48%		10%	7%			12%				NO
Reichart et al(2003)	THAILAND & COMBODIA	45 (NA)	NA		NA				18%			7%				YES
Reichart et al(2003)	THAILAND & COMBODIA	101 (62%-M)	NA			90%		53%	23%		13%	36%		28%-NGP 12% LGE		NA
Nittayananta et al(2001)	THAILAND	278 (83%-M)	NA		NA		40%					26%		12%-LGE	18%-EXFOL.	NO
Khongkunthian et al(2001)	NORTHERN THAILAND	87 (15%-M)		7		38%		10%	7%			12%		0%-NUG 8%-LGE	7%-EXFOL.	NA

Reference	Country / Region	No. of subjects	AIDS Cases	%	ANY ORAL LESION	OC	PC	EC	HC	AC	OHL	ULCERS	NEOPLASMS	HIV/Perio /Ging.	OTHERS	ARV Tx
12 Nittayananta & Chungpanich(1997)	THAILAND	124(73%-M)			100	82%	66%	54%	25%		6%	13%	11%-NS 5%-HSV	5%-NHL	7%-PERIO	4%-HISTO 2%-PENIC 63%-XEROS	NO
AMERICAN REGIONAL OFFICE (AMRO)																
1 Ramirez-Amador et al(2003)	MEXICO	1000 (88%-M)	NA			47%	32%	16%	21%			23%		2%-KS 0.1%-NHL	2%-PERIO		YES
2 Ramirez-Amador et al(2002)	MEXICO	68 (NA)	NA			65%	95%					95%					
3 Ramirez-Amador et al(1998)	MEXICO	436 (87%-M)			79	71%	39%	18%	26%		11%	30%	8%-NS 3%-HSV	2%-KS	3%-NUG 2%-NUP	6%-EXFOL 5%-PIG 3%-XEROS	YES
4 Ramirez-Amador et al(1993)	MEXICO	42 (95%-M)			100	NA		36%	12%		5%	33%	0%	52%-KS	9%-LGE	26%-EXFOL 14%-PIG 9%-XEROS	NA
5 Gillespie & Marino (1993)	ARGENTINA	125 (77%-M)	NA		NA		40%				6%	3%	2%-NS 12%-HSV	3%-KS	24%-NUG 10%-NUP 0%-LGE		NA
6 Gillespie & Marino (1993)	MEXICO	125 (88%-M)	NA		NA		51%	16%	35%		16%	43%	4%-NS 3%-HSV	3%-KS	4%-LGE	5%-ORAL ERYTHEMA	NA
7 Gillespie & Marino (1993)	PERU	20 (100%-M)	NA		NA			70%	25%		55%	25%	30%-NS	5%-KS	0%	25%-ORAL ERYTHEMA	NA
8 Gillespie & Marino (1993)	CHILE	15 (93%-M)	NA		NA		47%	27%	20%			20%	7%-NS	13%-KS	0%		NA

Reference	Country / Region	No. of subjects	AIDS Cases	%	ANY ORAL LESION	OC	PC	EC	HC	AC	OHL	ULCERS	NEOPLASMS	HIV/Perio/Ging.	OTHERS	ARV Tx
Gillespie & Marino 9 (1993)	BRAZIL	269 (85%-M)	NA		NA			42%	12%			11%	5%-NS 1%-HSV	8%-KS 2%-KS	1%-NUG 5%-NUP 2%-LGE		NO
Pinheiro &Marcenes et al(2004)	BRAZIL NORTH	161 (76%-M)	NA			33%	29%					9%	2%-NS 1%-HSV	0.6%-PAPILLOMA	4%-PERIO 2%-NUG/NUP/NUS	1%-XEROS 5%-HIVSGD 4%-HPV	YES
Patton et al(2000) 10	CAROLINA	299 (73%-M)			33	38%	17%					11%	3%-APTH. 2%-HSV	0%-KS 0%-NHL			
Patton et al(1998) 11	NORTH CAROLINA	238 (76%-M)			50	48%	20%	15%	4%		3%	26%	4%-APTH. 1%-NS 2%-HSV	2%-KS 1%-NHL	1%-NUG 5%-NUP 4%-LGE	2%-HIVSGD 2%-HPV	
Schuman et al(1998) 12	US MULTICENTRE	867 (F)			17	40%	15%	12%	3%		4%	7%	3%	0%-KS	11%-NUG 14%-LGE	1%-HPV	
Begg et al(1996) 13	NEW YORK	164 (83%-M)			10	NA	31%					16%	16%	2%-KS	21%-LGE	NA	
Little et al(1994) 14	MINNESOTA	106 (NA)			0	28%	5%					9%	8%-NS 6%-HSV	0%-KS	2%-NUP 5%-NUS 0%-LGE	1%-HPV	
Lamster et al(1994) 15	NEW YORK	160 (83%-M)			10	NA	30%					29%	11%	2%-KS	6%-NUG 22%-LGE	1%-HPV	
Shiboski et al(1994) 16	SAN FRANCISCO,CA	176 (F)			0	22%	14%	11%	4%		2%	10%	3%	0%-KS 0%-NHL	NA	0%-HPV 0%-HIVSGD 8%-XEROS	
Glick et al(1994) 17	PHILADELPHIA	454 (89%-M)	NA		NA		54%					17%	3%-APTH 5%-HSV	7%-KS	9%-NUP	3%-HIVSGD	
Barr et al(1992) 18	NEW YORK	102 (100%-M)			29	36%	17%	9%	6%		2%	20%	4%-APTH. 3%-HSV	2%-KS	NA	NA	
Thompson et al(1992) 19	US MILITARY	390 (97%-M)	NA		NA		9%	8%	1%			9%	NA	NA	7%-NUG	NA	
Klein et al(1991) 20	NEW YORK	181 (57%-M)			100	92%	92%					19%	10%	4%-KS	NA	NA	

Reference	Country / Region	No. of subjects	AIDS Cases	%	ANY ORAL LESION	OC	PC	EC	HC	AC	OHL	ULCERS	NEOPLASMS	HIV/Perio /Ging.	OTHERS	ARV Tx
21 Melnick et al(1991)	MINNESOTA SAN	106 (98%-M)			0	25%	5%					9%	8%-APTH. 6%-HSV	NA	NA	1%-HPV
22 Feigal et al(1991)	FRANCISCO	737 (100%-M)	NA		NA			6%	1%		1%	20%	2%	2%-KS	NA	NA
23 Swango et al(1991)	US MILITARY WASHIN	230 (90%-M)			6	30%	16%	11%	6%		3%	14%	2%-APTH.	0%-KS	NA	NA
24 Melnick et al(1989)	GTON STATE US NIH	141 (NA)	NA			30%	12%					13%	2%-APTH. 0%-HSV	1%-KS	4%-NUG	0%-HPV
25 Roberts et al(1988)	REFERRAL	84 (92%-M)			100	NA	29%					4%	2%-APTH.	38%-KS	7%-NUG	7%-XEROS 9%-XEROS 9%-EXF CHEILITIS 6%-PATCHU DEPAPILLATED TONGUE
26 Phelan et al(1987)	NEW YORK	103 (77%-M)			100	NA	88%	88%				5%	3%-NS 9%-HSV	4%-KS	NA	3%-OTHER
27 Silverman et al(1986)	SAN FRANCISCO	164 (100%-M)			91	NA	87%					21%	7%-APTH. 10%-HSV	32%-KS 2%-NHL	19%-NUP	13%-XEROS 1%-HPV
28 Barr & Torosian(1986)	NEW YORK	122 (100%-M)			66	84%	83%					0%	5%-NS 5%-HSV	11%-KS	NA	NA
EUROPEAN REGIONAL OFFICE (EURO)																
1 Margiotta et al(1999)	ITALY	104 (64%-M)			35	36%		6%	4%			10%	4% APTH.	0%	3%-LGE/NUG /NUP	7%-PIG 1%-HPV

Reference	Country / Region	No. of subjects	AIDS Cases	%	ANY ORAL LESION	OC	PC	EC	HC	AC	OHL	ULCERS	NEOPLASMS	HIV/Perio /Ging.	OTHERS	ARV Tx
Schmidt-Westhausen et al(1997) 2	GERMANY	70 (F)			30	43%	31%	24%	6%		4%	7%	3%-NS 1%-HSV	0%-KS 0%-NHL	0%	3%-HIVSGD	
Ceballos-Salobrena et al(1996) 3	SPAIN	396 (74%-M)			42	99%	66%	38%	24%	7%	23%	16%	1%-NS 5%-HSV	3%-KS 0.25%-NHL	5%-NUG	1%-OTHER 2%-XEROS 2%-PETECHIAE 1%-HIVSGD	
Palmer et al(1996) 4	UK	456 (95%-M)			42	59%		14%	24%		6%	30%	6%-NS 2%-HSV	4%-KS	8%-NUP	1%-HPV	
Ficarra et al(1994) 5	ITALY	36 (100%-M)			22	50%	39%					17%	14%-HSV	0%	6%-NUG	3%-HZ 4%-HPV 26%-XEROS	
Laskaris et al(1992) 6	GREECE	160 (NA)			23	91%	61%	31%	16%	4%	11%	24%	8%-NS 3%-HSV	12%-KS 1%-NHL 1%-SCC 1%-HL	11%-NUG 19%-NUP 4%-LGE	4%-EXFOL 2%-PIG	
Barone et al(1990) 7 8	ITALY	217 (79%-M)			9	4%	31%	9%	18%	1%	4%	19%	1%-HSV	3%-KS	0%	3%-PIG 1%HPV 1%-OTHER	
Moniaci et al(1990) 9	ITALY	737 (73%-M)	NA			40%	24%	7%	11%	1%	2%	10%	3%-NS 1%-HSV	2%-KS	1%-NUG	2%-XEROS 4%-OTHER 5%-FURRED TONGUE	
Porter et al(1989) 10		44 (98%-M)			9	NA		25%	2%	2%	7%	16%	7%-HSV	2%-KS	11%-NUG 11%-NUP 9%-LGE	2%-XEROS 2%-PIG	

Reference	Country/ Region	No. of subjects	AIDS Cases %	ANY ORAL LESION	OC	PC	EC	HC	AC	OHL	ULCERS	NEOPLAS MS	HIV Perio /Ging.	OTHERS	ARV Tft
Schulten et 11 al(1989)	NETHERL ANDS	75 (92%- M)		44	76%	52%	35%	13%	3%	12%	4%-NS 16% 1%-HSV	4%-KS	5%-NUG	5%- PETECHI AE 5%- XEROS 4%- BROWNY HAIR TONGUE 4%-HPV 4%- 3%- OTHER	
Gileva et 13 al(2004)	RUSSIA- PERM REGION	117 (65%- M)		11 NA		38%					20%- HERPETI C LESIONS	3%-APTH.	15%-NUS	4%- CHEILITI S GLANDUL ARIS 27%- LAP 11%- XEROS 2%- PAROTID GLAND SWELLIN G	
WESTERN PACIFIC REGIONAL OFFICE															
Lim & Robinson et al(2001)	SINGAPO RE	81 (NA)	NA		56%		35%				5% 5%-APTH.	1%- LYMPHO MA 0%- KS	16%- PERIO		

* Table showing prevalence of various HIV associated oral lesions in adults in countries falling under six WHO regions. This pattern of table is adapted from the article "Prevalence & Classification of HIV associated oral lesions"- Patton et al, 2002.

Reference	Country / Region	No. of subjects	AIDS Cases %	ANY ORAL LESION	OC	PC	EC	HC	AC	OHL	ULCERS	NEOPLASMS	HIV Perb /Glng.	OTHERS	ARV Trt
AFRICAN REGIONAL OFFICE (AFRO)															
Naidoo & Chikte(2004) n=98(Outpatients)	SOUTH AFRICA	169(NA) (58%Out Pt)	NA	63%	63%	50%		29%		10%	1% 6%-NS			8%-HMSGD	NA
Naidoo & Chikte(2004) n=71(Institution patients)	SOUTH AFRICA	169(42% Inst. Pt)	NA	45%	45%	24%		18%		10%	0% 14%-NS	21%-MC		50%-HMSGD 1 CASE-NOMA	NA
Bakaki et al(2001) n=136(<18months)	UGANDA	136(NA)	NA	NA	59%									7%-HMSGD	NA
Bakaki et al(2001) n=109(<18months)	UGANDA	109(NA)	NA	NA	11%									50%-HMSGD	NA
SOUTH EAST ASIAN REGIONAL OFFICE (SEARO)															
Pongsiriwet et al (2003)	NORTHERN THAILAND	40 (NA)	NA	58%											YES
Reichart et al(2003)	THAILAND	45 (NA)	NA	NA				18%			7%				NA
Khongkunthian et al(2001)	NORTHERN THAILAND	45(NA)	NA	50%				18%			7%			7% GEOGRAPHIC TONGUE	YES
Rajgopalan - unpublished data (2004)	INDIA	46 (54%-M)	NA	44%	37%	24%				9%	7%			2%-PIG	YES

Reference	Country / Region	No. of subjects	AIDS Cases	%	ANY ORAL LESION	OC	PC	EC	HC	AC	OHL	ULCERS	NEOPLASMS	HIV Perb /Glng.	OTHERS	ARV Tt
Merchant et al(2001)	INDIA	285 (NA)	NA		15%										10%-HIVSGD	NA
AMERICAN REGIONAL OFFICE (AMRO)																
Magalhaes et al(2001)	BRAZIL	38(NA)	NA		53%		18%		18%		29%	5%-HSV 3%-APTH.		13%-GIN	18%-HIVSGD 3%-Condyloma acuminatum 24%-Enamel Hypoplasia	NA
Santos et al(2001)	BRAZIL	80(NA)	NA		38%	23%						1% 1%-HSV		18%-GIN	9%-HIVSGD	NA
Fonseca et al(2000)	BRAZIL	51(NA)	NA		NA		22%		6%			2%		2%-LGE 47%-GIN	20%-HIVSGD	NA
Howell et al (1996)	USA		60	NA		92%								54%-PERID		NA
Ramos-Gomez et al(1996)	USA		91	NA		NA		67%				3%-HSV			4%-PAROTID ENLARGEMENT	
Valdez et al(1994)	USA		40	NA		NA		35%								
Katz et al (1993)	SAN FRANCISCO		99	NA				72%				24%-HSV			47%-PAROTID ENLARGEMENT	
Ketchem et al(1990)	WASHINGTON D.C.		47		17 NA			25%						2%-GIN	2%-PAROTID SWELLING	

Reference	Country/ Region	No. of studies	AIDS Cases	%	ANY ORAL LESION	OC	PC	EC	HC	AC	OHL	UCERS	NEOPLAS MS	HIV Perid /Ging.	OTHERS	ARV Trt
EUROPEAN REGIONAL OFFICE (EURO)																
Miliabaile et al(2003)	ROMANIA		169	100	NA	59%						21%-HERPES VIRUS INFECTD NS		5%- NUG/NUP	9%-HIVSGD 1%-HZ 2%-ORAL WARTS	
Fabbet al2001	ROMANIA		173	NA	55%	29%						2%	15%	4%-LGE		
Modaolet al(1993)	ITALY		69	NA	30%											
WESTERN PACIFIC REGIONAL OFFICE (WPRO)																

* Table showing prevalence of various HIV associated oral lesions in paediatric population in countries falling under six WHO regions. This pattern of table is adapted from the article "Prevalence & Classification of HIV associated oral lesions" - Patton et al, 2002.

12.3.3

AVERAGE PREVALENCE BY REGION

ADULTS

ORAL LESIONS	AFRO % (Range)	SEARO % (Range)	AMRO % (Range)	EURO % (Range)	WPRO % (Range)	EMRO % (Range)
ANY LESION	52.7% (21-92)	74.2% (38-90)	43.7% (22-92)	69.6% (43-99)	56%	
OC	54.1% (12-94)	56.7% (25-81)	41.6% (5-96)	47.8% (31-66)	35%	
PC	22.7% (1-44)	39.6(10-64)	34.6(11-58)	23.7 % (9-38)		
EC	15.5% (4-29)	19.8(7-25)	12.7% (3-35)	14.7 % (2-24)		
AC	16.8% (7-33)	7.8% (3-13)	12.7% (2-65)	9.5% (4-23)		
HC	4% (2-6)	1%		3.4% (1-7)		
OHL	7.6% (1-20)	23.3% (7-36)	21% (3-96)	18.2% (7-30)	5%	
HSV	2.2% (1-4)	5%	6% (1-12)	4.7% (1-14)		
APTH	6% (2-12	4.5% (3-6)	4% (2-8)	3.5% (3-4)	5%	
NUG	5% (2-16)		7.7% (1-24)	7.6% (5-11)		
NUP	5.6% (1-17)	17.3% (14-23)	7.4% (2-19)	10.2% (3-19)		
LGE	3% (2-4)	12% (8-16)	10.2% (2-22)	5.35 (3-9)		
HIVSGD	13% (0.4-47)	1%	4% (3-6)	2% (1-3)		
PIGMENTATION	2.6% (1-6)	26%	14%	3.6% (2-7)		
GIN		72%				
PERIO	100%	20% (7-33)	3% (2-4)		16%	
HISTO		2.5% (1-4)		4.6% (2-12)		
KS	13.7% (1-72%)		15.6% (1-62)	0.625% (0.25-1)		
NHL	4% (1-7)	5%	1% (0.1-2)			
CANCRUM	2.5% (1-4)					
OSMF		2%				
SCC	2%	4%		1%		
PENIC		2%				
LEUKOPLAKIA	5.5% (3-8)	1.50%				
XEROS		63%	7.8% (1-13)	8% (2-26)		
NGP		28%				

PEDIATRIC GROUP

ANY LESION	63%	51% (44-58)	72.5% (53-92)	30%	
OC	61% (59-63)	37%	46.7% (23-72)	59%	
PC	50%	24%	22%		
EC	29%	18%	18%		
AC	10%	7%	29%		
OHL	1%		2%		
HSV			10.6% (3-24)		
APTH			3%		
LGE			2%		
PIGMENTATION		2%			
HIVSGD	50%	10%	20%		
GEOGRAPHIC TONGUE		7%			
CANCRUM					
GIN			22.3% (2-47)		
PERIO			54%		

* Table showing average prevalence by region of various HIV associated oral lesions in adults and paediatric population

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