ORAL MUCOSAL AND FACIAL MANIFESTATIONS OF HIV/AIDS IN CHILDREN (CAPE PENINSULA, SOUTH AFRICA)

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THIS THESIS IS SUBMITTED TO THE FACULTY OF DENTISTRY, UNIVERSITY OF THE WESTERN CAPE, IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE M.SC. (DENT) IN THE DISCIPLINE OF ORAL MEDICINE.

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DECLARATION

I, Nashreen Behardien, declare that "***Oral Mucosal and Facial Manifestations of HIV/AIDS in Children (Cape Peninsula, South Africa)***", is my own work and that all the sources I have quoted have been acknowledged by references. This thesis has not been submitted for any other degree.

Signed: _____

NASHREEN BEHARDIEN

Date: _____

DEDICATION

This thesis is dedicated to the children affected by HIV. May the findings of this study benefit them.

To the Almighty for his divine guidance in all respects of this project.

My parents, Ebrahim and Fatima, for their support during the course of the study.

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ABSTRACT

ORAL MUCOSAL AND FACIAL MANIFESTATIONS OF HIV/AIDS IN CHILDREN (CAPE PENINSULA, SOUTH AFRICA)

Currently, HIV/AIDS is one of the greatest threats to child survival in South Africa. It is estimated that approximately 6000 newborn babies become infected with the HIV virus monthly i.e. approximately 200 babies per day.

During a 24 month period (October 1999 – October 2001), a descriptive prevalence study of the oro-facial manifestations affecting HIV-positive children was conducted in the Cape Peninsula, South Africa. The study population consisted of 268 vertically infected HIV-positive children. The study was motivated by the lack of data regarding oral mucosal lesions in children with vertically acquired HIV-infection.

The study design was descriptive, and the population included consecutive, vertically infected HIV-positive patients sourced from out-patient clinics, hospital wards and special child-care facilities.

The children were examined once consent was obtained from caregivers. The findings were documented using data capturing sheets. The data was captured on the Microsoft Excel program and analysed using the Epi 2000 program.

The results indicated that a large proportion of HIV-infected children presented with oro-facial manifestations at some stage during the course of HIV-infection. Oro-facial manifestations were observed in 70.1% of the study population. The prevalence of the most commonly observed manifestations were: oral candidiasis, 38.8%; parotid gland enlargement, 10.8%; oral ulceration, 5.6%; molluscum contagiosum, 7.8%; periodontal conditions, 3.4%; and herpes simplex infection, 0.7%.

It can be concluded that in this sample of HIV-infected children, the prevalence of oro-facial manifestations is higher than, and comparable with the findings of similar studies conducted in other regions of the world.

LIST OF ABBREVIATIONS

AC:	**A**ngular **c**heilitis
AIDS:	**A**cquired **I**mmunodeficiency **S**yndrome – a strictly defined human medical condition arising from a profound defect in cell-mediated immunity (T4 lymphocyte depletion) due to infection with the human immunodeficiency virus (HIV).
CDC:	**C**entres for **D**isease **C**ontrol and Prevention (Atlanta, USA)
DNA:	**D**eoxyribose **N**ucleic **A**cid – a constituent nucleic acid of the chromosomes of all organisms except some viruses.
EC:	**E**rythematous **c**andidiasis
HIV:	**H**uman **I**mmunodeficiency **V**irus – a group of lentiviruses which cause T4 lymphocyte depletion and mental deterioration, giving rise to the acquired immuno-deficiency syndrome in human beings.
KS:	**K**aposi's **S**arcoma – most common tumour associated with AIDS
LGE:	**L**inear **G**ingival **E**rythema
LIP:	**L**ymphoid **I**nterstitial **P**neumonitis
MTCT:	**M**other-**t**o-**c**hild **t**ransmission
OPC:	**O**ro-**p**haryngeal **c**andidiasis
PC:	**P**seudomembranous **c**andidiasis
PCP:	***P**neumocystis **c**arinii* **P**neumonia – a pulmonary condition

indicative of AIDS under certain conditions.

RNA: **R**ibo**N**ucleic **A**cid – a group of nucleic acids present in all living cells which serve in the synthesis of protein.

SADC: **S**outhern **A**frican **D**evelopment **C**ountries

WHO: **W**orld **H**ealth **O**rganisation (Geneva, Switzerland)

KEY WORDS

1. HIV
2. AIDS
3. Child
4. Mother-to-child-transmission
5. Immunosuppression
6. Opportunistic
7. Oral mucosal lesion
8. Prevalence
9. Predictor
10. Prognostic indicator

DEFINITION OF TERMS

***AIDS*:**

an acronym for 'acquired immunodeficiency syndrome'.

- Acquired
- Immunodeficiency
- Syndrome

AIDS Syndrome:

The *'syndrome'* comprises the collective opportunistic fungal, bacterial, viral and other infections, consequent to HIV infection, is termed AIDS.

Candidiasis:

Infection of the oral cavity by a fungal organism of the Candida species. (A combination of various clinical manifestations of candidiasis present in the oral cavity have been termed *mixed candidiasis* in this thesis).

***Child**:*

According to the U.S. Centres for Disease Control and Prevention (CDC) 1987, paediatric HIV/AIDS is defined as HIV-infection in children under the age of 13 years. Adolescents older than 13 are considered to have disease patterns similar to those of adults and are included in adult statistics.

The Joint United Nations Programme on HIV/AIDS (UNAIDS), however, defines children as individuals under the age of 15 years and compile their epidemiologic statistics accordingly.

Descriptive Study:

A study which focuses on and is designed to describe the existing distribution of variables, without concern for cause or other hypotheses. In this instance it relates to oro-facial manifestations related to HIV-infection in children.

Epidemic:

An infection simultaneously affecting many people in a defined area.

HIV-infection:

Infection of humans by the human immunodeficiency virus (HIV). Infection by this virus results in suppression of the host's immune system. This increases the susceptibility to opportunistic infections which consequently proliferates.

Hospital-based:

The participants of the study attended a hospital as either an out- or in-patient.

Human Immunodeficiency Virus:

A retrovirus which has affinity for CD4 markers on lymphocytes.

Oral:

The mouth – or related to the mouth

Peri-oral:

Area around the mouth

Prevalence:

The number of instances of a given condition in a given population at a specific point in time.

Retrovirus:

Viruses of the family of the Retroviradae. These viruses contain RNA and have the ability to transcribe its genetic material to host cellular DNA through the action of reverse transcriptase enzymes.

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CHAPTER ONE

INTRODUCTION

HIV-infection globally has reached epidemic proportion. The UNAIDS report (2002) estimates that in excess of 60 million individuals have been infected since the start of the epidemic. It is estimated that ±39.4 million people are currently living with HIV/AIDS *(UNAIDS, 2004)*.

HIV/AIDS is responsible for a large number of deaths in children. Globally, there are approximately 2.5 million children who are HIV-positive *(UNAIDS, 2003)*. Of the 600 000 new infections in children which occurred in the year 2000, 90% were as a result of mother-to-child transmission (MTCT) *(UNAIDS, 2001)*. Sixteen percent (16%) of new HIV-infections (800 000) in 2001, were children *(UNAIDS, 2002)*.

Countries in sub-Saharan Africa continue to bear the brunt of the HIV/AIDS pandemic. Although this region is inhabited by approximately 10% of the world's population *(Laga and Schwartländer, 1994)*, it is estimated that 64% (25.4 million) of the total HIV-infected population reside in this area *(UNAIDS, 2004)*.

Southern Africa, which includes countries such as Botswana, Swaziland, Malawi, Zambia, South Africa, Zimbabwe, Lesotho, Angola and Mozambique, houses less than 2% of the world's population. There appears to be little evidence of a decline in the HIV prevalence in this region, with about 30% of the total infected global population residing here *(UNAIDS, 2003)*. Most of these infected populations will die in the next 10 years *(World Bank Group, 2001)*.

It has also been estimated that 90% of the world's total HIV-infected paediatric population reside in this region *(Henry J. Kaiser Family Foundation, Love Life, 2001)*.

To date, the epidemic has claimed the lives of between 22 and 24 million people in sub-Saharan Africa *(UNAIDS, 2003)*.

The transmission rate in Africa is high. A reason for this may be the fact that the virus is being spread by heterosexual contact. The HIV-1 subtype C virus accounts for half of the infection in the world and is the most prevalent subtype in Southern Africa. This viral subtype is more easily transmissible through vaginal intercourse than any of the other subtypes *(Hensle, 1998)*. It is reported to have the most frightening profile, as it is able to copy its genome and mutate faster than any other subtype (*Wood, 1999*).

South Africa has one of the fastest growing HIV epidemics in the world *(UNAIDS, 2001; Ayo-Yusuf et al, 2001).* The national HIV prevalence at the end of 2002, was 5.3 million, having increased from 47 million the previous year *(Dept. of Health South Africa, 2003; UNAIDS, 2003).* Based on the results of the 2002 antenatal survey conducted by the National Dept. of Health, South Africa; it is estimated that 91 271 babies became infected via MTCT during 2002. The prevalence of HIV-infected women attending antenatal clinics in various provinces in South Africa varies considerably, with KwaZulu Natal (± 37%) almost triple that of women attending antenatal clinics in the Western Cape *(UNAIDS, 2003)*.

The HIV-epidemic represents the worst health crisis known to South Africa in the period 1994 – 2001. The average life expectancy has decreased from 66 years to 47 years *(UNAIDS, 2001).*

The prevalence of HIV-infection for the general population of South Africa is extrapolated from statistics obtained from antenatal clinic surveys. An independent, nationally representative study of HIV/AIDS in South Africa, commissioned by the

Nelson Mandela Foundation and Children's Fund was conducted by the Human Sciences Research Council (HSRC). This study reported that the overall infection rate in the country was 11.4% which is lower than the previously estimated 19% *(Thom, 2002).* Prevalence among 'Black' South Africans was the highest (12.9%), 'Coloured' prevalence was second highest (6.1%) and prevalence among 'Indians' was 1.6%. The infection rate among 'White' South Africans is 6.2%. This is considerably higher than their 'White' counterparts in countries such as America, Australia and France *(Thom, 2002).*

This study focused on the effect of HIV on oral health in a paediatric population.

A large proportion of HIV-infected individuals present with oral lesions. According to Reznik *et al* (n.d.), up to 80% of HIV-infected individuals will present with oral lesions. Approximately 60% of a South African sample of HIV-infected adults presented with oral lesions during the course of infection *(Arendorf et al, 1998).* This translates into approximately 3 million HIV-positive South Africans (60% of 5 million people) that could present for treatment at some point in time, provided that they have access to oral health care. In HIV-positive children, oral mucosal lesions may be more prevalent as a result of their immature and compromised immune systems. Oral manifestations of HIV-infected children have been reported by very few researchers from the African continent. Generally, a large proportion of these infants present with one or more oral lesions *(Ramos-Gomez et al, 1999*).

Currently there is no baseline information of the oral lesions associated with HIV-infection in children in South Africa. This information is necessary in order to determine and implement adequate and effective treatment protocols. It is also important to determine manpower requirements for the training of health personnel

(such as district health nurses), in the early diagnosis of oral lesions and hence HIV - infection.

LITERATURE REVIEW

Oral lesions associated with HIV-infection are reviewed in this chapter. A literature search on the Pubmed website was done in November 2002 using the key words *"**oral, HIV** and **child**"*. Seven-hundred-and-eighty-six articles were listed. The articles focused on different aspects of oral HIV-infection. Some dealt with the management of oral disease, some focused on the effects of oral infection in the adult population, whilst others focused on the effects of oral infection in children. Review articles analysed relevant studies and reported on the accumulated information.

Fifteen articles analysed studies reporting on oral lesions associated with HIV-infection in children (Appendix 1). In addition, 7 articles reviewed available literature and are listed in Appendix 2. Twelve reports (Appendix 3) focused on studies recording oral manifestations in a combined adult and paediatric HIV-infected study population.

This review will focus on:

1.1. The *prevalence* of oro-facial manifestations in paediatric studies;

1.2. The *significance* of oro-facial manifestations in HIV-infection; and

1.3. *Specific oro-facial manifestations* commonly observed in HIV-infection.

1.1. PREVALENCE OF ORO-FACIAL MANIFESTATIONS

The epidemiological studies reviewed in this chapter are descriptive prevalence studies; intergroup comparison studies, and studies which correlate oral lesions with immunological parameters. There is a wide range of prevalence values for oro-facial manifestations in the literature (Appendix 1). Possible explanations for this range are: variable methodological factors, diagnostic criteria, examiner variability, and statistical analyses.

Due to these differences, it is difficult to compare the findings of these studies.

1.1.1. Methodological factors which influence analysis of studies

These include:

a. Study design;

b. Sample size;

c. Bias in sampling (hospitalized subject, out-patient clinic subject, not adequate representation across cultural barriers);

d. Inclusion criteria (mode of infection of study subject, use of antiretroviral drugs)

1.1.1.a. Study design

Variation in study design may be responsible for varying prevalence values. *Longitudinal studies* reflect a higher prevalence of oro-facial manifestations than *cross-sectional studies*. In longitudinal studies the frequency of the lesions irrespective of number of patient visits are recorded. The prevalence of the most commonly observed manifestations in 15 identified studies is compared in Appendix 1.

The differences in prevalence of oral lesions when comparing longitudinal and cross-sectional studies are shown in Appendix 4. There appears to be a large range in the prevalence of the most commonly observed manifestations among the various studies. Longitudinal studies report on cumulative prevalence and tend to reflect a higher value as compared with cross-sectional studies. Although the longitudinal study by Moniaci *et al* (1993) reflects a lower prevalence of its most common lesion, pseudomembranous candidiasis (PC), the reasoning is simply that PC, is a variant of oral candidiasis (OC), which is the most common lesion observed in the cross-sectional study. Hence, its value is likely to be a fraction of the total prevalence of oral fungal infection in that particular study.

1.1.1.b. Sample size

The sample size of a study population is of importance. Too small a sample size will yield unreliable results. For example, if one wants to determine the prevalence of oral lesions in a group of HIV-infected children, a small sample size such as 10 children is more likely to yield unreliable results. If 3 children present with an oral lesion, the prevalence would be 30%. However, if an additional 2 children present with an oral lesion, the prevalence would be 50%. The difference in prevalence is quite significant for merely 2 additional cases. If, however, the sample size was 100 children, a difference of 2 additional cases would not make a significant difference to the prevalence of the condition. Sample size is thus a factor to consider when comparing studies. Some authors choose to report their findings using percentages, whilst others prefer to use numbers. It is not appropriate to compare findings of studies which refer to percentages if the sample size is not known (Appendix 1).

1.1.1.c. Bias in Sampling

Bias in sampling occurs if the sample is not representative of the study population. For example, hospital cases may be more severely ill than cases sourced from the community. The relevance to this study is the fact that patients examined as hospitalised patients are more likely to present with oro-facial manifestations as compared to those who are well enough to be cared for at home. Hospitalised patients are more systemically ill and hence more immune compromised than asymptomatic HIV-infected patients. Since infections with opportunistic pathogens are a measure of immune suppression, it is likely that the prevalence of oro-facial manifestations will be higher in hospitalised patients. A comparison of the prevalence of oro-facial manifestations in HIV-infected children, with similar demographics, but where one sample is hospitalised and the other is ambulatory, may yield different results.

1.1.1.d. Inclusion Criteria

Anti-retroviral drug therapy (ART)

Although the literature on the prevalence of oro-facial manifestations in adult HIV-infection, indicates a lower prevalence of lesions in patients on anti-retroviral therapy, this is not necessarily true for paediatric HIV-infection *(Flanagan et al, 2000)*. These authors reported that highly active anti-retroviral therapy (HAART) does not significantly affect the prevalence of oral soft tissue lesions in HIV-infected children. Del Toro *et al* (1996) however, reported a low prevalence of oro-facial manifestations in a study population on anti-retroviral drug therapy. The available literature on the effects of ART on oral lesions is increasing as more patients have access to drug treatment. Appendix 1 identifies the studies which included children on antiretroviral drug therapy.

Mode of transmission

The participants comprising the study populations in the articles reviewed for this thesis, were selected on the basis that they were vertically infected i.e. mother-to-child-transmission (MTCT). The exceptions were those studies by Barasch *et al* (2000); Fonseca *et al* (2000) and Howell *et al* (1996). Vertically infected children are more severely immune compromised than children who contract HIV-infection later in life e.g. via sexual abuse, contaminated blood products or intra venous drug use. Children who contract the virus later in life already have a degree of immunity.

1.1.2. Diagnostic Criteria

The diagnostic criteria employed affects the prevalence of lesions. The following factors has an effect on the reported prevalence of lesions:

a. The use of microbiology in confirming the clinical diagnosis of certain oral lesions;

b. Reporting on *individual* oral fungal lesions such as pseudomembranous candidiasis (PC), erythematous candidiasis (EC), and angular cheilitis (AC) as opposed to a composite prevalence of *oral fungal infection*; or, reporting on oral candidiasis as a single disease entity and failing to report on its variants;
c. Failure to report on whether more than one variant of oral fungal infection is present in the same mouth at one point in time (combination candidiasis).

Oral candidiasis was by far the most frequently reported manifestation. In the majority of the studies reviewed, it was the most common finding (12 studies). Cervical lymphadenopathy (CL) was the most common finding in 2 studies and plaque induced gingivitis (G) in 1 study.

A possible explanation for a high prevalence of CL and G in so few studies and not in others could be because these lesions may be overlooked in some studies (Appendix 1). Even though it may be common in non-HIV infected individuals, G is not an HIV-associated condition and may thus not have been considered when examining the study populations. Because CL is not an oral mucosal lesion, some examiners do not report on it. There appears to be a large range in the prevalence of OC. The prevalence ranges from 21.6% *(Fonseca et al, 2000)* to 72% *(Katz et al, 1993)*. Numerous factors, as mentioned earlier in this chapter, contribute to this discrepancy.

1.1.3. Examiner Variability

Cruz *et al* (1996) and Hilton *et al* (2001) reported that there are differences in the prevalence of oral lesions when the examination is carried out by a medical practitioner as opposed to a dentist. Medical practitioners were inclined to report oral lesions less frequently and were less able to accurately describe them. Chaloryoo *et*

al (1998) conducted a study on HIV-infected children from an ENT (ear-nose-throat) perspective. Here too, the type of lesion diagnosed by an ENT surgeon differed from that diagnosed by a dentist. Chaloryoo *et al* (1998) reported that upper respiratory tract infections (URTI) were the third most common finding, and otitis media, the fourth most common. This was the only study reporting on these particular oro-facial conditions.

1.1.4. Analysis of Data

Diagnostic criteria is a factor to consider when analysing data. Some authors recognize angular cheilitis as a separate entity whilst others include it as a variant of OC.

1.2. SIGNIFICANCE OF ORO-FACIAL MANIFESTATIONS

1.2.1. Oral lesions as an early sign of HIV-infection

Various studies have demonstrated that oral lesions are more common in persons with HIV-infection than in those who are HIV-negative *(Arendorf et al, 1998; Ramos-Gomez et al, 1996)*. In a Tanzanian study Schiødt *et al* (1990) showed that 85% of the sample who were diagnosed with oral lesions was later confirmed as HIV-infected. Similar studies conducted in Belgium, Greece and Zaire report similar findings *(UCSF AIDS Research Institute, 2000; Laskaris et al, 1992)*. Studies regarding oral HIV-infection as an AIDS-defining condition have been reported *(Klein et al, 1984)*. There seems to be a growing consensus that oral hairy leukoplakia (OHL) and Kaposi sarcoma (KS) in particular, are highly suggestive of HIV-infection *(UCSF AIDS Research Institute, 2000).* These lesions are found in adult HIV-infection. However, prevalence studies on oral lesions associated with HIV-infection in children, do not demonstrate the same lesions which are ranked 'Group 3' (lesions strongly associated with HIV-infection but rare in children) of the Consensus Classification of oro-facial lesions associated paediatric HIV-infection (Appendix 5). During the early stages of the pandemic, when sophisticated diagnostic instruments were not available, oral lesions formed part of the clinical diagnosis (major and minor signs) used to diagnose HIV-infection (Bangui definition, 1986).

1.2.2. Oral lesions as a predictor of disease progression

Oro-facial manifestations are used as predictors of progression of HIV disease to AIDS *(Katz et al, 1993; De Martino, 1994; Tovo et al, 1992; Klein et al, 1984)*. These manifestations may indicate the degree of immunosuppression while some lesions are AIDS-defining conditions *(Klein et al, 1984)*. Appendix 6 presents the prognostic significance of oro-facial manifestations in paediatric HIV-infections. A study by

Barasch *et al* (2000), however, indicated that oral lesions were not necessarily good indicators of immune suppression.

Non-Hodgkins lymphoma, the most common lymphoma of the oral cavity, is suggestive of a declining immune system and has a poor prognosis. The mean CD4+ cell count of patients diagnosed with non-Hodgkins lymphoma is less than 100cells/mm^2, and the mean survival time is between 6 and 9 months *(Lozada-Nur et al, 1996)*.

Oral candidiasis has been associated with immune suppression, a more rapid progression of HIV-infection to AIDS, a more advanced stage of AIDS, and decreased survival *(Flaitz et al, 1999)*.

1.2.3. Oral lesions as markers for clinical drug trials

Oral lesions may be useful during clinical drug trials. They may be used as markers for entry into - or end points, of clinical drug trials *(UCSF AIDS Research Institute, 2000)*.

1.2.4. Oral lesions for disease classification

Oral lesions form part of the criteria for clinical staging of HIV disease (CDC, 1994 - Appendix 7).

1.2.5. Classification of oral lesions in HIV-infected children

During the period March 1994 to May 1995, the Collaborative Workgroup on the Oral Manifestations of Paediatric HIV-infection worked together to develop guidelines for the diagnosis and management of HIV-related oral lesions in children.

In 1999, this group reached consensus and introduced the Consensus Classification for oral manifestations of paediatric HIV-infection.

These proposed guidelines were intended to facilitate early diagnosis of paediatric HIV-infection and effective intervention by dental and medical personnel. The framework was adapted from the EC-Clearinghouse Classification on oral manifestations of HIV-infection. The paediatric classification presents both *presumptive*, as well as *definitive diagnostic criteria for oral and peri-oral mucosal lesions* (Appendix 8). The *presumptive criteria* and diagnostic features applied during a *clinical assessment* of a patient includes the characteristics of a lesion such as *its appearance, colour, texture, localisation, size* and reported *stomatology*. *Definitive criteria* include an *invasive* or *investigative laboratory test to confirm the diagnosis.*

The current classification of oral lesions associated with HIV-infection in children (Appendix 5) is divided into three categories viz.

Group 1 - lesions commonly associated with paediatric HIV-infection;

Group 2 - lesions less commonly associated with paediatric HIV-infection;

Group 3 - lesions strongly associated with HIV-infection but rare in children.

1.3. MOST COMMONLY OBSERVED ORO-FACIAL MANIFESTATIONS ASSOCIATED WITH HIV-INFECTION

The adult and paediatric classification of oro-facial lesions associated with HIV-infection is divided into lesions which are commonly and rarely associated with HIV infection (Appendix 5). The section to follow will describe oro-facial manifestations which are commonly associated with HIV-infection in adults and children.

1.3.1. Oral Candidiasis

Oral candidiasis has been documented as the most prevalent oral lesion observed in adults and children who are infected with the Human Immunodeficiency Virus. Studies of HIV-infected patients have shown a frequency of oral candidiasis ranging from 20% to 93% *(Chan et al, 1994; Dodd et al, 1991)*. The prevalence of oro-pharyngeal candidiasis in sero-positive patients who have not yet developed AIDS ranges from 7% to 48% *(Dreizen, 1984).* With progressive immunodeficiency (as reflected by a decrease in CD4 lymphocytes) the range increases to anywhere from 43% to 93% *(Dunn, as cited in Fonseca et al, 2000)*.

This fungal infection is primarily associated with the proliferation of the organism *Candida albicans*, although other *Candidal* species e.g. *glabrata*, *tropicalis* and *krusei,* have also been isolated from infected areas. *Candida* species may be present as commensals in the oral cavity of healthy individuals. It is estimated to occur in 1% to 37% of normal, healthy children before the age of 6 months *(Feigan, as cited in Katz et al, 1993)*. Infection by this organism is associated with immune suppression and other predisposing factors such as diabetes, antibiotic therapy, radiation therapy and xerostomia *(Cruz et al, 1996).* Oral pseudomembranous candidiasis is not uncommon in healthy newborn babies. Dunn, and Shrand *(cited in Fonseca et al, 2000)* suggest that its occurrence in healthy infants does not exceed 7%. Darwazeh

et al (cited in Fonseca et al, 2000) proved in their studies that *Candida* was present in the normal flora of 48% of children younger than 18 months. In the immune competent child, candidal lesions are often mild, readily amenable to treatment, or they regress spontaneously, and are rarely seen beyond infancy in the absence of predisposing factors.

The mechanism by which the fungus converts from a commensal to a pathogenic form in response to HIV-infection is unclear but the possibilities include: a) increased adhesiveness and invasion; b) acquisition of virulent strains; and c) phenotypic switching *(Agabian et al, 1995)*. It has been suggested that the presence of *Candida* can induce further immune suppression by toxic effects on lymphocytes *(Silverman et al, 1989)*.

The clinical presentation of oral candidiasis is variable. Four types of oral candidiasis have been recognised in HIV-infected adults *(Ketchem et al, 1990).* These included pseudomembranous (PC), hyperplastic, atrophic/erythematous candidiasis (EC) and angular cheilitis (AC). Reznik *et al* (n.d.) and Greenspan *et al*, (n.d.b) only identify 3 variants associated with HIV-infection, namely pseudomembranous candidiasis, erythematous candidiasis and angular cheilitis. Flaitz *et al* (1999) identify 6 clinical variants of oral candidiasis, namely, pseudomembranous candidiasis, erythematous (atrophic) candidiasis, papillary hyperplasia, chronic hyperplastic candidiasis, angular cheilitis, and median rhomboid glossitis. It is unclear why several variants (pseudomembranous, hyperplastic, erythematous) exist and why they manifest differently in different individuals *(Reichart et al, 2000; Dodd et al, 1991)*. An attempt by Reichart *et al* (2000) has been made to clarify the issue with regard to the clinical oral manifestations. They attempted to address the following queries: a) whether histopathologic studies of the variants of candidiasis in immune competent and immune compromised individuals help explain varying manifestations, b) under what

circumstances does oral candidiasis manifest as pseudomembranous rather than erythematous or vice versa, and; c) whether there are differences in immuno-reactivity in closely adjacent mucosae so that the variable presentation of such lesions reflect differences in the local mucosal immune system?

It is known that the host response plays a pivotal role in the pathogenesis of candidiasis. The question as to why several variants occur, sometimes even in the same individual, remains unclear. It is thought that the interplay between both the host and organism play a significant role in modulating the outcome of this clinical entity.

1.3.1.a Oral Candidiasis & HIV-infection in children

Oral candidiasis is ranked as a Group 1 lesion in the classification of *Oral lesions associated with HIV-infection in children (Ramos-Gomez et al, 1999)*. The Consensus Classification for oral manifestations of paediatric HIV-infection has included 3 variants of oral candidiasis.

Candidiasis has been documented as the most frequently occurring oral manifestation in HIV-infected children with a prevalence ranging from 20% to 76% *(Chan et al, 1994)*. Among children who are HIV-positive but symptom free, the prevalence of OC ranges from 11% to 20%, rising to over 70% in those with advanced HIV disease *(Greenspan et al, 1996)*. The median time to death has been reported as 3.4 years among children with oral candidiasis *(Ramos-Gomez et al, 1996)*. Appendix 9 summarises the prevalence of oral candidiasis in paediatric studies. The range for this particular prevalence is very large. Possible reasons or explanations for this could be: difference in sample size, diagnostic ability of the investigator (under-diagnosis of EC), use of confirmatory laboratory tests, mean age of sample, mode of transmission (vertically infected children as opposed to sexual transmission) and the use of medication (anti-retroviral drugs and antibiotics).

Chigurupati *et al* (1996) described the clinical presentation of OC in HIV-infected children as being diverse with manifestations of the pseudomembranous, erythematous and hyperplastic variants as well as angular cheilitis. According to Ketchem *et al* (1990) the two most common types manifesting in children are the pseudomembranous and erythematous variants.

Recurrent candidiasis which is often resistant to conventional antifungal therapy, is a frequent oral manifestation of paediatric HIV-infection/AIDS. Although the organism *Candida albicans* is primarily responsible for the infection, recent cytological and cultural studies have identified a different candidal organism associated with candidiasis in immune compromised patients viz. *C. dubliniensis (Brown et al, 1999)*.

1.3.2. Median Rhomboid Glossitis (MRG)

Median rhomboid glossitis is an oral lesion that has previously been considered a developmental anomaly related to the persistence of an embryonic midline tongue structure known as the tuberculum impar. MRG (central papillary atrophy) of the tongue is characterized by a rhomboid shaped lesion anterior to the circumvallate papillae. The surface of the lesion may vary from being smooth, nodular, fissured, or depapillated *(Flaitz et al, 1999).* The same lesion is now believed to be related to a chronic infection by *Candida albicans (Kolokotronis et al, 1994; Samaranayake et al, 1990; Arendorf et al, 1984; Wright et al, 1981; Van der Waal et al*, *1979).* In 1965 Cornéa and colleagues published the first article relating median rhomboid glossitis to infection by *Candida albicans (Wright, 1978)*. Early in the twentieth century, MRG was considered an inflammatory lesion. The aetiology was then changed from 1934 to about 1970, to a developmental anomaly. Later, in 1975, an article by Cooke implicating *Candida albicans* as an aetiological agent, was published *(Van der Waal et al, 1979).*

Since the recognition of AIDS as a clinical entity in 1981, many varying oral lesions have been recorded. Amongst these lesions, oral candidiasis is one of the most commonly reported associated opportunistic infections *(Kolokotronis et al, 1994)*. Scully *et al* (1994) also recognised this lesion as a specific lesion and not as an erythematous form of candidiasis. To date, the existence of median rhomboid glossitis as a specific variant of candidiasis, as opposed to being included as an erythematous candidiasis, has not yet been established. Some authors (*Kolokotronis et al, 1994)* suggest that median rhomboid glossitis should be included as a clinical form of oral candidiasis in the list of oral lesions associated with HIV-infection.

1.3.3. Oral Hairy Leukoplakia (OHL)

Oral hairy leukoplakia (OHL) appears as a white, non-removable, corrugated ('hairy') lesion, seen on the lateral border of the tongue and occasionally in other areas of the oral cavity. It is caused by the Epstein-Barr virus (EBV), which can be seen on electronmicroscopy and with in-situ hybridization. OHL is one of the most common HIV-associated oral lesions in adults *(Greenspan et al, n.d.c; Chigurupati et al, 1996; Itin et al, 1994)*. However, cases of OHL have been reported in patients with immune suppression other than HIV-infection. Although OHL is seen in all the risk groups for HIV-infection, it is not common in children *(Greenspan et al, n.d.c; Chigurupati et al, 1996; Itin et al, 1994; Leggott, 1992)*. This lesion is used as a predictor of progression of HIV disease, and is not considered to be a pre-malignant lesion *(Greenspan et al, n.d.c).* OHL lesions will regress with antiretroviral therapy and concurrent improvement of cellular immunity, but recurrence is possible after discontinuing treatment *(Chigurupati et al, 1996)*.

Hairy leukoplakia lesions are usually asymptomatic and treatment may be elective. Some patients complain of discomfort, usually due to secondary infection. Lesions

respond to treatment with acyclovir, but they tend to recur when treatment is discontinued *(Ramos-Gomez et al, 1999).*

1.3.4. Kaposi Sarcoma (KS)

Kaposi's sarcoma (KS) is a spindle cell, vascular tumour, that occurs in the skin, lymphoid, respiratory, and gastro-intestinal tract tissue. It is a common tumour in both HIV-positive and HIV-negative persons living in parts of Africa *(Chang et al, 1996).* The HIV sero-negative form of KS is called *'endemic KS*'. KS seen in HIV-positive and HIV-negative individuals is pathologically identical. Endemic KS is generally an indolent tumour in HIV-negative adults, but it also occurs in children where it has a fulminant and often fatal course (*Beral, as cited in Chang et al, 1996*).

The Human Herpes Virus 8 (HHV8) has been identified in the aetiology of KS *(Moore et al, 1995).*

Kaposi's sarcoma is the most common tumour associated with HIV/AIDS, and has been reported in 15% of the AIDS population. These lesions may appear anywhere in the oral cavity and range in appearance from flat to raised, and red to purple lesions.

KS as a manifestation of HIV-infection in children is rare in Western countries. In Kampala, Uganda, KS is being recognized in an increasing number of children. From 1986 to 1990, 25 cases of oral lesions were documented *(Chigurupati et al, 1996).* Detection of the HHV8 genome in KS lesions in pre-pubertal Ugandan children suggests that the transmission of the virus may be non-sexual.

HIV-related cancers occur more commonly in adults than in children. KS is the most common HIV-associated malignancy in adults and frequently presents with oral lesions. Its incidence however, has drastically decreased since the administration of HAART in HIV-infection *(Reznik et al, n.d.)*.

1.3.5. Salivary Gland Disease (SGD)

The term 'HIV-SGD' (salivary gland disease) has been used to designate diffuse enlargement of major salivary glands and/or xerostomia in HIV-infected individuals (*Schiødt et al, 1992)*. Conditions such as parotitis, parotid enlargement and xerostomia may be discussed under this broad heading.

Parotid gland enlargement can occur in both HIV-positive and HIV-negative individuals. In HIV-negative individuals prevalence is low and is usually associated with conditions such as mumps in children, and anorexia nervosa in adults.

Parotid gland enlargement associated with HIV-infection has been found both in adults and in children *(Soberman et al, 1991).* In HIV-infected individuals, parotid enlargement is ranked as a Group 1 lesion in children (Appendix 5) and a Group 2 lesion in adults.

Parotid gland enlargement has been recognized as a distinct feature of HIV-infection in children *(Chigurupati et al, 1996; Leggott, 1992)*. It is prevalent in 0% - 58% of HIV-infected children *(Schøidt, 1992)*. Katz *et al* (1993) reported a figure of 50%, whilst Soberman *et al* (1991) reported that parotid enlargement of varying degrees was seen in 10 % of HIV-children in New York. Parotid enlargement may manifest as unilateral or bilateral swellings. Typically, the enlargement is chronic and the glands are profusely swollen and firm. This manifestation is usually asymptomatic and painless. It is uncertain what the aetiology of the enlargement is, but a computer technology (CT) scan and magnetic resonance imaging (MRI) findings in HIV-infected adults have described benign lymphoepithelial proliferation as the underlying cause of parotid enlargement *(Holiday et al, 1988)*.

Parotid enlargement in children is often associated with lymphoid interstitial pneumonitis (LIP) and diffuse lymphadenopathy, which probably represents a lymphoproliferative stage of HIV-infection in children. It has also been associated with xerostomia. However, it is not certain whether the xerostomia is as a

consequence of concurrent medication, or the parotid enlargement. Studies involving major salivary gland output in HIV-infected individuals have shown a decrease in salivary output *(Yeh et al, 1988; Atkinson et al, 1990).* Some investigators have reported that as many as 13% of HIV-positive patients complain of dry mouth *(Roberts et al 1988)*. Parotid enlargement has been associated with a slower progression to AIDS and is hence a positive prognostic indicator *(De Martino, 1994*). The median time to death has been reported as 5.4 years among those children with parotid swelling *(Ramos-Gomez et al, 1996).*

In adults, the finding of chronic parotid enlargement is significant in that it should suggest the diagnosis of HIV-infection.

Parotid gland enlargement is usually left untreated. In extreme cases however, parotid swelling may be treated with anti-inflammatory agents, analgesics, antibiotics or occasionally, steroids *(Ramos-Gomez et al, 1999)*.

1.3.6. Herpes Simplex virus infection

Infection by the Herpes Simplex Virus (HSV) causes both primary and secondary/recurrent oral lesions. The primary infection is known as herpetic gingivostomatitis and the secondary infection as recurrent Herpes simplex infection. Herpetic gingivostomatitis presents as multiple ulcers on the gingiva, buccal mucosae and tongue while the secondary or recurrent infection presents as a 'cold-sore' on the vermillion border of the lip, or vesicles on the intra-oral mucosa. Lip lesions appear as small vesicles that rupture, ulcerate and then form crusts. The intra-oral lesions appear as small crops of vesicles on the hard palate or gingiva that rupture to produce small painful ulcers. The oral lesions are usually confined to the keratinized mucosa, although lesions may appear on the dorsal surface of the tongue.

Infection by the HSV virus is common in HIV-negative children and young adults.

Recurrent HSV infection affects the lips and intra-oral mucosa of approximately 10% - 25% of people with HIV-infection (*Bartlett, as cited in Reznik, 1999)*.

The reported prevalence for HSV infections in HIV-infected children ranges from 1.7% to 24% *(Ramos-Gomez et al, 1999)*. Leggott (1992) states that Herpes SV-1 is commonly seen in HIV-infected children and recurs more than twice a year. In HIV-infected children, severe, chronic, painful, recurrent lesions may occur on all membranes and may require hospitalization. The lesions appear as crater-like ulcers with well-defined, raised borders and a grey pseudomembrane *(Leggott, 1992)*. Most herpetic lesions, even in HIV- infected children are self-limiting. When lesions do persist however, they can be treated with systemic antiviral agents such as acyclovir. Oral acyclovir may be indicated for treatment of intra-oral lesions and herpes labialis. Foscarnet (trisodium phosphonoformate hexahydrate) has proven to be an effective treatment for resistant herpetic lesions in adults and children. *(Ramos-Gomez et al, 1999)*

1.3.7. Periodontal Disease

Although a study conducted by Sheutz *et al* (1997) does not support the view that there is an association between periodontal conditions and HIV-infection, the EC-Clearinghouse Classification (Appendix 9) and Consensus Classification (Appendix 5), classes periodontal disease as conditions strongly associated with HIV-infection. Gingivitis and periodontitis can occur in both HIV-positive and HIV-negative individuals. There are however, periodontal problems that are unique to HIV infection. Linear gingival erythema (LGE), previously known as HIV-gingivitis and necrotising ulcerative periodontitis (NUP), formerly known as HIV-periodontitis are two such conditions. Periodontal disease in HIV-infected adults, although not clearly defined, has been well described in the literature *(Robinson,1998)*. In a study by San

Martin *(cited in Robinson, 1998)*, 67 children were examined specifically for periodontal disease. The results of this study indicated that 37.3% presented with HIV-G (LGE), 4.5% with HIV-P (NUP) and 58.2% with conventional gingivitis. This study suggests that HIV-G is strongly associated with HIV-infection in children.

1.3.7.a Linear Gingival Erythema (LGE)

Linear gingival erythema (LGE) appears as a profound red (erythematous) band affecting the marginal gingiva along the necks of the teeth. It may vary in width and is disproportionate to the amount of plaque present. It may also be described as a fiery red, linear band 2-3mm wide on the marginal gingiva accompanied by petechiae-like or diffuse red lesions on the attached gingiva and oral mucosa. According to *Greenspan et al (1996),* this lesion was not recognised before the AIDS epidemic. However, *Gomez et al (1995)* reported no difference in prevalence of gingival banding in HIV-infected and non-infected groups. Pain is rarely associated with this lesion *(Ramos-Gomez et al, 1999*). LGE has been classified by the American Academy of Periodontology as a 'gingival disease of fungal origin' *(Lamster et al, 1998)*.

Reports on the prevalence of LGE vary greatly amongst different studies. LGE is strongly associated with HIV-infection in adults and seldom reported in children *(Vieira et al, 1998).* The prevalence of this type of gingivitis varies widely from 0% to 48% *(Ketchem et al, 1990; Moniaci et al, 1993; Valdez et al, 1994; Del Toro et al, 1996; Howell et al, 1996)*. Paediatric studies reporting on this manifestation include: Flaitz *et al*, 2001 (4%); Fonseca *et al*, 2000 (1.96%); Chan *et al*, 1994 (0.0%); and Flanagan *et al*, 2000 (32%).

1.3.7.b Necrotising Ulcerative Periodontitis (NUP)

NUP is a serious oral manifestation that causes pain, spontaneous gingival bleeding, and rapid destruction of bone and soft tissue. Loss of bony support may lead to tooth mobility and even tooth loss.

No unique micro-organisms have been identified. The anaerobic periodontal flora seems similar to that which causes conventional periodontitis.

1.3.8. Oral Ulceration

Ulceration of the oral cavity may be defined as a breach in the epithelial lining of the mouth and its structures. Oral ulceration has numerous aetiologies. It may manifest in both immune compromised, and immune competent individuals. The occurrence of specific oral ulcerations may be a reflection of immune suppression in both HIV-infected and non-infected individuals, or they may be pathognomonic of HIV disease *(Kademani et al, 1998)*. Oral ulcers associated with HIV-infection can be caused by a variety of organisms or processes *(MacPhail et al, 1997)*. These authors also recommend that oral ulcers be categorized into 2 groups on the basis of diagnostic criteria and treatment protocols. The first group consists of ulcers caused by a specific organism (e.g. Herpes Simplex Virus - HSV; Cytomegalovirus - CMV, etc.) or associated with a neoplastic condition (e.g. lymphoma). The second group consists of ulcers which have no identifiable causative organism or process and are histologically 'non-specific'.

To obtain a definitive diagnosis of an oral ulceration, special investigations are necessary. These include: incisional and excisional biopsies with regular or special stains, cultures, and direct or indirect immunofluorescence.

The Human Immunodeficiency Virus has never been isolated from an oral ulcer. The acute seroconversion syndrome of HIV-infection has however been associated with episodes of non-specific ulceration.

There appears to be a strong association between ulceration of unknown origin (recurrent aphthous ulceration - RAU) and immune suppression in HIV-infected individuals.

Haematological disorders such as anaemia and neutropaenia, which are common complication of HIV-infection, causes significant non-specific oral ulceration in the HIV-infected individual.

No study reporting on the oro-facial manifestations observed in children who are vertically infected has been done in South Africa. A study investigating these lesions would be beneficial in assessing its extent and nature.

CHAPTER TWO

STUDY METHODOLOGY

This is a cross-sectional study, which recorded and documented the prevalence of oro-facial lesions and manifestations associated with HIV-infection in a selected group of vertically infected children in the Cape Peninsula area of the Western Cape, South Africa.

The methodology of this study is described and presented in this chapter.

2.1. Aim

To ascertain the prevalence of oro-facial lesions and manifestations observed in vertically infected HIV-positive children who were hospital-based in the Cape Peninsula, South Africa.

2.2. Objectives

To determine the oro-facial manifestations observed in vertically infected HIV-positive children.

To rank the oro-facial manifestations observed in vertically infected HIV-positive children from most to least prevalent.

2.3. Patients and Method

The main study was preceded by a pilot study. The pilot study was used to calibrate the two examiners in the diagnosis of oral mucosal lesions.

2.4. Study design

This is a hospital-based cross-sectional study.

2.5. Site and Sampling

The study population was selected from 4 sites. Consecutive children attending the infectious diseases out-patient clinic for HIV-infected children at Red Cross War Memorial Children's Hospital (Red Cross Hospital); HIV-infected children hospitalised at Conradie and Red Cross Hospital, and orphaned or abandoned children with HIV/AIDS were recruited for the study. Both child-care facilities at which children were examined were affiliated to the hospitals. Participants were not considered for disease stage or reason for visit. None of the examinations were carried out in a dental setting, thus ruling out any bias in the sampling.

2.6. Pilot Study

A pilot study was carried out in October 1999. The study sample included children at a child-care facility which housed orphaned and abandoned children with HIV/AIDS. The children examined in the pilot study were included in the results of the final study as there were no alterations in methodology employed in the pilot study and the main study.

2.7. Inclusion Criteria

The inclusion criteria for this study was:

(1) The children had to be HIV-positive.

(2) The infection had to be as a result of mother-to-child transmission.

(3) The children sourced from special child-care facilities, were treated at a hospital.

2.8. Exclusion Criteria

The exclusion criteria for the study was:

1) Patients on anti-retroviral drugs were excluded from the study.

2.9. Diagnostic procedures and clinical examination

Informed consent (Appendix 10 & Appendix 11) was obtained from parents or caregivers. Standardised protocols were established for registering personal information. Clinical examinations took place between October 1999 and October 2001.

Record taking consisted of intra-oral observations using natural light and an intra-oral light to assist with diagnosis, cytological smears, photographs and documentation of findings (Appendix 12). Diagnosis was made using the presumptive criteria for oro-facial lesions outlined in the Consensus Classification *(Ramos-Gomez et al, 1999)* (Appendix 5*)*.

2.10. Inter-examiner variability

A subset of the total study population was used for the pilot study. Two investigators conducted independent clinical examinations of the children at the child-care facility. The results were then compared. This procedure was subsequently repeated (once only) and an inter-examiner reliability of 95% was established.

2.11. Analysis

Data was analysed according to diagnostic criteria as set out in methodology. For example, angular cheilitis was included as a variant of oral candidiasis and thus formed part of oral candidiasis, combination candidiasis and an entity on its own. Dental caries was noted if present, but did not form part of the prevalence of oro-facial manifestations.

Results were analysed using Epi Info 2000 software package.

2.12. Ethical and legal considerations

Access to patient records was sought from the various institutions by means of a formal letter. Informed consent was obtained from the parent or caregiver either verbally or by means of a consent form. All information recorded remained confidential. Patients and caregivers could withdraw their children from the study at any time. A statement granting ethical clearance was sought and obtained from the University of the Western Cape (Appendix 13).

CHAPTER THREE

RESULTS

The most important demographic details of the study populations are listed in Table 3.1.

TABLE 3.1: DEMOGRAPHIC DETAILS

		CAPE PENINSULA	
		n =268	%
Gender:	Males	149	55.6
	Females	119	44.4
Ethnic group:	Black	237	88.4
	Colou red	30	11.2
	White	1	0.4
Age:	= 11 months	75	28.0
	12 to 23 months	56	20.9
	24 to 35 months	39	14.6
	36 to 47 months	33	12.3
	48 to 59 months	28	10.4
	60 to 71 months	16	6.0
	72 to 83 months	7	2.6
	84 to 95 months	7	2.6
	96 to 107 months	3	1.1
	108 to 128 months	4	1.5

According to the Department of Health – South Africa (2003), the Western Cape had the lowest HIV prevalence (13%) in South Africa.

For this study, only a small region of the Western Cape was included. The study population was restricted to those children attending Conradie and Red Cross War Memorial Children's Hospitals as out-patients. These hospitals are situated in the Cape Peninsula, South Africa. The Red Cross War Memorial Children's Hospital,

which is a major referral centre for HIV-positive children in the peninsula, was the main site for the study. In addition to this site, HIV-positive children residing in two child-care facilities in the Cape Metropolitan area (Nazareth House and Beautiful Gate Ministry) were included. The findings are tabled in Table 3.2.

TABLE 3.2. PREVALENCE OF ORO-FACIAL MANIFSTATIONS

ORO-FACIAL MANIFESTATIONS	HIV-INFECTED CHILDREN	
	n = 268	%
INTRA-ORAL		
Oral lesions	***188***	***70.1***
Oral candidiasis	***104***	***38.8***
Combination candidiasis	22	8.2
Pseudomembranous candidiasis	**98**	**36.6**
Erythematous candidiasis	22	8.3
Hyperplastic candidiasis	5	1.9
Angular cheilitis	13	4.9
Ulceration (NOS)	***15***	***5.6***
Periodontal conditions	*9*	*3.4*
Necrotising stomatitis	2	0.7
Necrotising periodontitis	3	1.1
Necrotising gingivitis	3	1.1
Linear gingival erythema	1	0.4
Molluscum contagiosum	***21***	***7.8***
Herpes simplex virus infection	2	0.7
Xerostomia	8	3.0
Dento-alveolar abscess	5	2.6
EXTRA-ORAL		
Parotid gland enlargement	*29*	*10.8*
Unilateral	2	0.7
Bilateral	27	10.1
Miscellaneous	***21***	***7.8***

The study population consisted of 268 HIV-positive children. Their ages ranged from 1 month to 128 months (i.e. 10 years and 8 months), with a mean age of 31.2 months (std dev = 26.5).

Table 3.2 illustrates the findings of the study. The type of lesion, number, and percentage prevalence are tabled. One-hundred-and-eighty-eight children (70.1%) presented with one or more lesion. A distribution of lesions is presented in Table 3.3.

Oral candidiasis, the most prevalent lesion observed, occurred in its various clinical forms.

Table 3.4 highlights the number of patients who presented with more than one clinical variant.

A total of 345 lesions were observed amongst the 188 children who presented with lesions. Table 3.5 demonstrates the number and proportion of patients who presented with single and multiple lesions.

Dento-alveolar abscesses were seen in 5 of the 189 dentate children.

The oro-facial manifestations observed in this study included fungal, bacterial, viral and other non-specific lesions. Dental caries was recorded as present if a single surface of any tooth was carious. However, dental caries was not included as an oro-facial lesion, and hence is not reflected in the 70.1%. One-hundred-and-two children (38.0%) presented with multiple lesions.

TABLE 3.3 DISTRIBUTION OF LESIONS

LESIONS	n = 188	%
Oral candidiasis	104	55.3
Parotid gland enlargement	29	15.4
Molluscum contagiosum	21	11.2
Oral ulceration	15	8.0
Periodontal conditions	9	4.8
Xerostomia	8	4.3
Herpes simplex virus infection	2	1.0

Oral candidiasis was by far the most prevalent lesion, followed by parotid gland enlargement and molluscum contagiosum.

3.4 NUMBER OF PATIENTS WITH A COMBINATION OF CLINICAL VARIANTS OF ORAL CANDIDIASIS

COMBINATIONS OF CANDIDIASIS	NUMBER OF PATIENTS n = 22
PC + EC	16
PC + EC + AC	2
PC + AC	1
PC + AC + hyperplastic candidiasis	1
PC + EC + papillary hyperplasia	1
PC + hyperplastic candidiasis	1

TABLE 3.5 NUMBER AND PERCENTAGE OF PATIENTS WITH SINGLE AND MULTIPLE LESIONS

NO. OF LESIONS PER PATIENT	NO. OF PATIENTS n=188	PERCENTAGE (%)
One	86	45.7
Two	61	32.4
Three	31	16.5
Four or more	10	5.3

3. Lesions

3.1. Oral Candidiasis

Oral candidiasis was the most prevalent manifestation observed. Approximately 104 patients (39%), presented with one or more variants of this fungal infection. *Pseudomembranous candidiasis* (PC) (Figure 1) accounted for 36.6%, and *Erythematous candidiasis* (EC) for 8.3% of the variants. *Combined candidiasis,* a combination of the variants of oral candidiasis observed in the same mouth, was observed in 9.3% of all oral candidal infections (Figure 2). *Angular cheilitis*, a mixed fungal and bacterial infection was seen in 4.9% of the study population (Figure 3). Other variants of oral candidiasis which were infrequently observed included *papillary hyperplasia* (0.3%) and *hyperplastic candidiasis* (1.9%).

Oral candidiasis was observed in 104 (55.3%) of the 188 children who exhibited oro-facial manifestations.

3.2. Angular Cheilitis

This lesion is recognized as a separate entity. In the analysis however, it has been included as a variant of oral candidiasis. If seen in combination with other oral fungal infections, it was collectively noted as combination candidiasis.

3.3. Oral Ulceration

Ulceration of the oral soft tissues was seen in 5.6% of the study population. The affected soft tissue included the tongue, lips, and buccal mucosae. None of the lesions reported on in this group were biopsied, smeared or cultured for a definitive diagnosis or specific aetiological organisms e.g. HSV and CMV.

3.4. Herpes Simplex lesions

Herpes simplex virus infection was seen in a small percentage of the study population. Only 2 children, seen at their first visit, presented with this infection. A much larger proportion, seen at follow-up visits, presented with herpes labialis, or herpetic gingivostomatitis. For the purposes of the study, only first visit manifestations were recorded so as to obtain a point prevalence of the lesions. It should be noted that opportunistic oral lesions manifest and resolve continuously, are dynamic, and hence may be missed with a once off examination.

3.5. Miscellaneous

Lesions which were not stipulated as a lesion associated with HIV-infection in the Consensus Classification were classed as miscellaneous lesions.

These included lesions such as impetigo, focal epithelial hyperplasia (Hecks disease), peri-oral sores, wart-like lesions, fissured tongue, erosions of the buccal mucosa and petechiae.

3.6. Peri-oral mucosal lesions

These lesions are listed under peri-oral mucosal lesions based on their location. They are found on the lips or around the mouth. Impetigo, angular cheilitis, and herpes labialis constitute the group of lesions referred to as peri-oral mucosal

lesions. Impetigo was observed in 1 child, angular cheilitis in 13 children and herpes labialis in 2 children.

3.7. Dental Caries

Dental caries was not included as an oro-facial manifestation, but was however recorded. It has however been recorded. Ninety-seven of the 189 children who had teeth, presented with one or more carious teeth.

Approximately 30% of the study population did not present with any lesions. There was a trend of a steady increase in the number of lesions per child with increasing age.

CHAPTER FOUR

DISCUSSION

The discussion will deal with the following issues:

Current Literature;

Study Population;

Study Results;

Recommendations

4.1 Current Literature

The recommendations of the Consensus Classification for paediatric HIV infection is based on ***descriptive analysis of various studies***, primarily based in the United States of America and Europe. A few studies were conducted in South America. Differences with regards to the oral manifestations seen in an African population may exist. The epidemic in Africa is mainly of a heterosexual nature with different viral subtypes predominating as compared to that found in more developed areas. An important factor which may alter the presentation and significance of oral mucosal lesions in paediatric HIV-positive patients in South Africa is the fact that the majority of paediatric infection is as a result of MTCT.

Although there are numerous studies specifically reporting on oral manifestations associated with HIV-infection in children, very few are from South Africa. Studies from Thailand, the United States of America and Italy have been published. These include that of Khongkunthian *et al* (2001); Magalhães *et al* (2001); Howell *et al*, (1996); Ketchem *et al* (1993); and Moniaci *et al* (1993). These studies report first visit prevalence values or the point prevalence of oro-facial lesions and are thus of a

similar design to the present study. For comparative purposes, it is appropriate to compare the findings of these particular studies to the present study. Individual lesions will be discussed and compared to other studies in the *Study Results* section below.

4.2 Study Population

The current study consisted of a sample of 268 HIV-infected children. Their ages ranged from 1 month to 128 months (10 years and 8 months). The largest age grouping (28%) was in the under 1 year age group. A possible reason for this is that infants progress to immunodeficiency states faster than adults (Oxtoby, 1990). This would imply that children born with HIV-infection, would have a shorter lifespan than those contracting the virus later in life. Prospective studies document that the highest incidence of AIDS is during the first year of life. In adults the median incubation period is approximately 10 years. However, in infants, it is considerably shorter. This is possibly due to the immaturity of the infants' immune systems at the time of HIV exposure *(Oxtoby, 1990)*.

4.3 Study Results

The prevalence of oro-facial manifestations in this study population of 268 children, was 188 (70.1%). This is higher than other reported point prevalence studies. The findings were however similar to studies by Barasch *et al* (2000) and Flanagan *et al* (2000). They reported a prevalence of 76% and 79% respectively. However, their study designs differed in that they were longitudinal studies and not point prevalence studies. It is thus not practical to compare a point prevalence study to longitudinal studies. A prevalence of 70.1% greatly exceeds the prevalence in studies by Magalhães *et al* (2001); Khongkunthian *et al* (2001) and Howell *et al* (1996). The prevalence rates in these studies were 52.6%, 48.9% and 45% respectively.

Oral candidiasis was found to be the most frequently observed manifestation (38.8%) in this study. The literature reports that the prevalence of OC has ranged from 20% to 76% *(Chigurupati et al, 1996)*. This large range can possibly be explained by the sample size, diagnostic criteria (clinical vs. laboratory), examiner variability, etc.

It is more likely for OC to be underdiagnosed as opposed to being overdiagnosed, as very often the erythematous variant is overlooked. Reporting of OC in the literature is inconsistent. Some studies report individual variants of OC, whilst others combine the variant and report a composite value for OC. Furthermore, not all studies defined angular cheilitis as a variant of OC. In the present study, a diagnosis of OC was made if one or more of the following lesions were observed: pseudomembranous candidiasis, erythematous candidiasis, hyperplastic candidiasis, papillary hyperplasia, and angular cheilitis.

One-hundred-and-four children presented with one or more forms of OC at the time of examination. Combinations of the different variants of this lesion were seen in individual patients. OC has also been the most prevalent in the five studies selected for comparative purposes.

OC was observed as single or multiple lesions within the same mouth. Combination lesions were observed in 22 children. Whether a combination of OC indicates a more suppressed immune system or not, is unclear. Further studies relating CD4+ cell counts and viral load to this combination lesion need to be explored. PC was the most commonly observed individual candidal lesion. This compares favourably with international literature *(Fonseca et al, 2000; Del Toro et al, 1996; Moniaci et al, 1993)*.

Parotid gland enlargement (Figure 5) was the second most common manifestation observed in this study (10.8%). This lesion is suggested to have prognostic

significance. Studies reporting on parotitis or parotid enlargement include Chaloryoo *et al* (1998) (5.2%); Moniaci *et al* (1993) (4.3%); and Flanagan *et al* (2000) (3%). Studies by Yeh *et al* (1988) and Atkinson *et al* (1990) suggest a relation between xerostomia (Figure 6) and parotid gland enlargement.

Molluscum contagiosum (MC) (Figure 7) was observed in 7.8% of the study population. This viral lesion affecting the skin was noted if it affected the peri-oral or facial regions of the children. Flaitz *et al* (2001) reported a prevalence of 3%. The prevalence of this lesion is high in comparison with other studies. This may be due to the fact that a large percentage of the study population lived in child-care facilities where spread of molluscum contagiosum occurs quite easily as facilities such as bathrooms, etc. are shared *(Kauffman et al, n.d* .).

Oral Ulceration (Figure 8)

Lesions of *Herpes simplex* infection are intermittent. These lesions are self-limiting they manifest when conditions are favourable. This results in differences in prevalence values amongst various studies. A true prevalence for this lesion may only be assessed by a longitudinal study.

Although KS is known to be the most common tumour associated with HIV-infection, none of the participants of this study presented with this intra-oral or facial lesion.

4.4 Recommendations

Baseline data on the prevalence of oral mucosal and facial manifestations in vertically infected HIV-positive children for South Africa as well as other sub-Saharan countries are necessary. This will enable us to compile a profile of the oral and facial conditions observed on the African continent and allow for comparison with other parts of the world and hence with other HIV strains.

Prevalence data will also highlight the most frequently occurring manifestations and provide the basis for a similar classification of oral mucosal and facial manifestations associated with HIV-infected children as structured by Ramos-Gomez *et al* (1999). This is of course assuming that the prevalence and type of lesion associated with the HIV subtype C virus found in sub-Saharan Africa, differs to that found in other parts of the world.

A further recommendation would be to focus on specific lesions, in particular, the most common and/or most debilitating ones, and investigate its aetiology and most appropriate management.

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APPENDIX 1

Analyses of studies reporting on prevalence of oro-facial manifestations in children

Author	Sample size	Study design	MTCT	ART used	Prevalence OML	Most common lesion	2nd most common lesion	3rd most common lesion
Barasch, *et al*. 2000	104	Longitudinal	✓ 96.2%	✓ 94%	76%	OC (28%)	LGE (22%)	
Chaloryoo, *et al.* 1998				NR	NR	OC (59.6%)	Lymphadeno-pathy (41.6%)	URTI (39.5%)
Chan, *et al*. 1994	33	Longitudinal	✓	x	NR	CL (54.5%)	OC (42.4%)	Ulceration (3.0%) Petechiae (3.0%) PGE (3.0%)
Costa, *et al*. 1998	41	Case control	✓	NR	NR	CL (53.7%)	OC (29.3%)	AC (9.8%)
Del Toro, *et al.* 1996	28	Longitudnal	✓	✓ 100%	39.3%	PC (17.8%)	MiAU (7.1%)	Parotid swelling (3.6%) Delayed dental development (3.6%)
Flaitz, *et al*. 2001	173	Point prevalence	x	✓ 30%	55%	OC (29%)	Ulcers (15%)	SGD (9%)
Flanagan, *et al*. 2000	38	Longitudinal	✓	✓ 100%	79%	CG (50%)	LGE	OC (24%)
Fonseca, *et al*. 2000	51	Longitudinal	✓ 78.4%	NR	51%	PC (21.6%)	SGD (19.6%)	EC (5.9%)
Howell, *et al.* 1996	60		✓ 91.6%	NR	45%	OC (32%)	CG (45%)	LGE (38%)
Katz, *et al.* 1993	99		✓	NR	NR	OC (72%)	PGE (47%)	Herpes simplex infection (24%)
Ketchem, *et al.* 1993	47	Point prevalence	✓	✓ 2%	NR	OC (25.5)	Dental anomalies 4.3%	G (2%)
Khongkunthian, *et al.* 2001	45	Point prevalence	✓	✓ 33.3%	48.9%	EC (17.8%)	Aphthous ulceration (11.1)	AC (6.7) OHL (6.7) Oral ulceration (6.7)
Magalhaes, *et al.* 2001	38		✓	✓ 81.6%	52.6%	OC (36.8%)	AC (28.9%)	PGE (18.4%)
Moniaci, *et al.* 1993	69	Longitudinal	✓			PC (26%	EC (10%)	AC (5.8%)
Nicolatou, *et al*. 1999	15	Longitudinal, 1st visit findings	✓	✓ 100%	60%	OC (60%)	AC (26.7) Gingivitis (26.7%)	NR

NR = not reported in study
PC = pseudomembranous candidiasis; EC = erythematous candidiasis; OC = oral candidiasis; AC = angular cheilitis; PGE = parotid gland enlargement; OHL = oral hairy leukoplakia; OU = oral ulceration; CL = cervical lymphadenopathy; MiAU = minor aphthous ulceration; CG = conventional gingivitis

✓ = present for column
x = absent for column

APPENDIX 2

Review articles focusing on oro-facial manifestations associated with HIV-infection in children

Author	Title	Reference
Chigurupati *et al* (1996)	Pediatric HIV infection and its oral manifestations; a review	Pediatr. Dent. 18:2 106-113
Grbic *et al* (1997)	Oral manifestations of HIV infection	AIDS Patient Care STDS. 11:1 18-24
Kline (1996)	Oral manifestations of pediatric human immunodeficiency virus infection – review of the literature	Pediatrics. 97:3 380-8
Leggott (1992)	Oral manifestations of HIV infection in children.	Oral Surg Oral Med Oral Pathol. 73:187-92
Silverman *et al* (1989)	Oral manifestations of pediatric AIDS	Pediatrician. 16:185-187
Studen-Pavlovich *et al* (1997)	Oral manifestations in HIV-infected children	Penn Dent J (Phila). 64:2 17-23
Ramos-Gomez (1997)	Oral aspects of HIV infected children	Oral Dis. 3:suppl 1,S31-S35

APPENDIX 3

Oral lesions of adults and children

Author	Title	Reference
Anil *et al* (1997)	Oral lesions of HIV and AIDS in Asia: an overview.	Oral Dis. 3 Suppl 1:S36-40
Arendorf *et al* (1997)	Intergroup comparisons of oral lesions in HIV-positive South Africans.	Oral Dis. 3 Suppl 1:S54-7
Bendick *et al* (2002)	Oral manifestations in 101 Cambodians	J Oral Pathol Med. 31:1 1-4
Chiang *et al* (1998)	Oral manifestations of human immunodeficiency virus-infected patients in Taiwan.	J Formos Med Assoc. 97:9 600-5
De Wit *et al* (1998)	Pharmacokinetics of two multiple-dosing regimens of D0870 in human immunodeficiency virus-positive patients: a phase I study.	Antimicrob Agents Chemother. 42:4 903-6
Hilton *et al* (1997)	Development of oral lesions in human immunodeficiency virus-infected transfusion recipients and hemophiliacs.	Am J Epidemiol. 145:2 164-74
Itula *et al* (1997)	Orofacial manifestations and seroprevalence of HIV infection in Namibian dental patients.	Oral Dis. 3 Suppl 1:S51-3
Navazesh (2001)	Current oral manifestations of HIV infection	J Calif Dent Assoc. 80:4 137-41
Ramirez-Amador *et al* (1998)	Oral manifestations of HIV infection by gender and transmission category in Mexico City.	J Oral Pathol Med. 27:3 135-40
Ranganathan *et al* (2000)	Oral lesions and conditions associated with human immunodeficiency virus infection in 300 south Indian patients	Oral Dis. 6:3 152-7
Schiødt (1997)	Less common oral lesions associated with HIV infection: prevalence and classification.	Oral Dis. 3 Suppl 1:S208-13
Shiboski *et al* (2001)	HIV – related Oral manifestations among adolescents in a multicenter cohort study	J Adolesc Health. 29(3 Suppl):109-14

APPENDIX 4

Comparison of most common lesions in longitudinal studies vs. cross sectional studies.

Author	Study duration	Most common lesion
Howell *et al* (1996)	Cross sectional	OC (32%)
Katz *et al* (1993)	Longitudinal ± 3 years	OC (72%)
Ketchem *et al* (1993)	Cross sectional	OC (25.5%)
Moniaci *et al* (1993)	Longitudinal	PC (26%)

Consensus classification of orofacial lesions associated with pediatric *HIV infection* *(Ramos-Gomez et al, 1999)*

Group 1: Lesions commonly associated with paediatric HIV infection.

- Candidiasis
  - Pseudomembranous
  - Erythematous
  - 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 infection.

- Bacterial infections of oral tissues
- Periodontal diseases
  - Necrotising ulcerative gingivitis
  - Necrotising ulcerative periodontitis
  - Necrotising stomatitis
- Seborrhoeic dermatitis
- Viral infections
  - Cytomegalovirus
  - Human papillomavirus
  - Molluscum contagiosum
  - Varicella Zoster virus
    - Herpes-zoster
- Xerostomia

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

- Neoplasms
  - Kaposis's sarcoma and non-hodgkins lymphoma
- Oral hairy leukoplakia
- Tuberculosis-related ulcers

APPENDIX 6

Prognostic value of oro-facial manifestations in paediatric HIV-infection

Lesion	Comment	Reference
Oro-facial manifestations	Correlation of oro-facial lesions with CD4+ cell counts and clinical staging. P-2 patients had displayed a higher prevalence of oral lesions than P-1 patients (P = 0.04)	Chan *et al* (1994) Del Toro *et al* (1996)
Oral candidiasis	Presence and period of infection may be diagnostic of HIV-infection. Pseudomembranous candidiasis is significantly related to severe immunologic impairment. Oral candidiasis was associated with the most rapid rate of progression to death. Median time from presentation of lesion to time of death was 3.4 years.	De Martino (1994) Moniaci *et al* (1993) Katz *et al* (1993)
Oro-pharyngeal candidiasis	Progression of HIV disease to AIDS	Ramos-Gomez *et al* (1996) Scarlatti (1996) Haitz *et al* (1999)
Parotid gland enlargement	Associated with long-term survival in HIV-positive children. Associated with a less rapid rate of progression to death. Median time from 1st presentation of lesion to death is 5.4 years.	Ramos-Gomez *et al* (1996) Katz *et al* (1993)

APPENDIX 7

CDC (1994) Revised Classification system for Human Immunodeficiency Virus (HIV) infection in Children less than 13 years of age.

Centre for Disease Prevention and Control. 1994.

CLINICAL CATEGORIES

Immunologic Categories	**N: no signs/ symptoms**	**A: Mild signs / symptoms**	**B: Moderate signs/ symptoms**	**C: Severe Signs/symptoms**
No evidence of suppression	N 1	A 1	B 1	C 1
Evidence of moderate suppression	N 2	A 2	B 2	C 2
Evidence of severe suppression	N 3	A 3	B 3	C 3

Children whose HIV status has not yet been confirmed are classified by using the above grid with letter 'E' indicating perinatally exposed, placed before the appropriate classification code.

Clinical categories for children with human immunodeficiency virus (HIV) infection

CATEGORY N: NOT SYMPTOMATIC

Children who have no signs or symptoms considered to be the result of HIV infection or who have only one of the conditions listed in Category A.

CATEGORY A: MILDLY SYMPTOMATIC

Children with two or more of the conditions listed below but none of the conditions listed in categories B and C

- Lymphadenopathy (≥ 0.5 cm at more than 2 sites; bilateral = one site)
- Hepatomegaly
- Splenomegaly
- Dermatitis
- Parotitis
- Recurrent or persistent upper respiratory infection, sinusitis, or otitis media

CATEGORY B: MODERATELY SYMPTOMATIC

Children who have symptomatic conditions other than those listed for category A or C that are attributed to HIV infection. Examples of conditions of clinical Category b but are not limited to:

- Anaemia (<8 gm/dL), neutropaenia (<1,000/mm^3), or thrombocytopaenia (<100,000/mm^3) persisting ≥30 days
- Bacterial meningitis, pneumonia, or sepsis (single episode)
- Candidiasis, oropharyngeal (thrush), persisting (>2 months) in children <6 months of age
- Cardiomyopathy
- Cytomegalovirus infection, with onset before 1 month of age
- Diarrhoea, recurrent or chronic
- Hepatitis
- Herpes Simplex Virus (HSV) stomatitis, recurrent (more than 2 episodes within 1 year)
- HSV bronchitis, pneumonitis, or oesophagitis with onset before one month of age
- Herpes zoster (shingles) involving at least 2 distinct episodes or more than one dermatome
- Leiomyosarcoma
- Lymphoid interstitial pneumonia (LIP) or pulmonary lymphoid hyperplasia complex
- Nephropathy
- Nocardiosis
- Persistent fever (lasting >1 month)
- Toxoplasmosis, onset before one month of age
- Varicella, disseminated (complicated chicken pox)

CATEGORY C: SEVERELY SYMPTOMATIC

Children who have any condition listed in the 1987 surveillance case definition for acquired immunodeficiency syndrome, with the exception of LIP

Conditions included in clinical Category C for children infected with human immunodeficiency virus (HIV)

- Serious bacterial infections, multiple or recurrent (i.e. any combination of at least two culture-confirmed infections within a 2-year period), of the following types: septicaemia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ or body cavity (excluding otitis media, superficial skin or mucosal abscesses, and indwelling catheter-related infections)
- Candidiasis, oesophageal or pulmonary (bronchi, trachea, lungs)
- Coccoldmycosis, disseminated (at one site other than or in addition to lungs or cervical or hilar lymph nodes)
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis or isopsoriasis with diarrhoea persisting

Immunologic categories based on age specific CD4+ T-lymphocyte counts and percent of total lymphocytes.

	Age of child					
	<12 months		1-5 years		6-12 years	
Immunologic category	µL	(%)	µL	(%)	µL	(%)
1: No evidence of suppression	≥1,500	(≥25)	≥1,000	(≥25)	≥500	(≥25)
2: Evidence of moderate suppression	750 - 1.499	(15-24)	500 - 999	(15-24)	200 - 499	(15-24)
3: Severe suppression	<750	(< 15)	<500	(<15)	<200	(<15)

APPENDIX 8

Criteria for Diagnosis of Oral Lesions in HIV infected Children
Ramos-Gomez et al, 1999

FUNGAL INFECTIONS		
	PRESUMPTIVE CRITERIA	**DEFINITIVE CRITERIA**
Pseudomembranous Candidiasis	Multifocal, non-adherent, creamy white papules or plaques that can be wiped off with minimal pressure leaving an erythematous surface. Pinpoint or petechial bleeding may be observed occasionally after removal of the superficial coating. In general, these lesions are widespread and may be located anywhere in the oropharyngeal area.	The patient's response to antifungal therapy is the principal defining criteria for tests for the presence of *Candida spp*. May be helpful, particularly if the patient does not respond to antifungal treatment due to potential resistance.
Erythematous Candidiasis	Multiple, flat red patches of varying intensity, most commonly located on the dorsum of the tongue. Non-adherent, filmy white-to-creamy plaques may be seen concurrently with this form of candidiasis. Median rhomboid glossitis, which is usually a red, smooth, depapillated patch on the mid-dorsal tongue is a variant of this form. Tenderness or a burning sensation may be experienced.	Definitive diagnosis may be assisted by detection of *Candida spp*. In culture or cytologic smear or by the patient's response to antifungal treatment.
Angular Cheilitis	Linear red or ulcerated fissures radiating from the corners of the mouth. Typically the lesions are bilateral, and multiple red papules may be found when the adjacent peri-oral skin is involved. Concurrent intra-oral candidal involvement is a common clinical finding. These lesions are usually tender and slow to heal because of repeated manipulation from opening the mouth.	Definitive diagnosis may be assisted by detection of intra-oral *Candida spp*. In culture or cytologic smear or by the patient's response to antifungal therapies. A staphylococcal or streptococcal co-infection may be present in some cases.

Linear Gingival Erythema (LGE)	A fiery red, linear band 2-3 mm wide on the marginal gingiva accompanied by petechiae-like or diffuse red lesions on the attached gingiva and oral mucosa. The amount of erythema is disproportionately intense given the amount of plaque present. The erythema may be accompanied by bleeding during brushing and, in severe cases, by spontaneous bleeding. It is most notable on the buccal surfaces from cuspid to cuspid. Pain is rarely associated with linear gingiva erythema.	There are currently no known criteria for obtaining a definitive diagnosis of linear gingival erythema. However, linear gingival erythema resists conventional plaque-removal therapies and oral hygiene measures. A similar clinical presentation occurs in neutropaenia. Thus, clinicians should review results of a recent complete blood count and differential analysis of the white blood cells.

VIRAL INFECTIONS HSV infection	Patients will exhibit fever and malaise, swollen and tender lymph nodes, and intra- and peri-oral lesions on the gingiva, hard palate, and vermillion border of the lips. However, any mucosal site may be involved. Initially present as vesicles, these lesions rupture to become painful, irregular ulcers.	Confirmation of a diagnosis of herpetic infection by laboratory methods is available but rarely used. The virus may be isolated in tissue culture. Intact intra-oral vesicles are rare. Cytologic examination reveals ballooning degeneration of infected epithelial cells and nuclear inclusion bodies, but does not permit viral identification. Therefore, DNA hybridization is necessary for a definitive diagnosis. **Note:** Although non-HIV infected children usually recover swiftly and completely from herpes simplex infection, HIV infected children frequently have severe intra-oral lesions that may require hospitalization. Hospitalisation is not routine for HSV infection in children. Moreover, the lesions tend to recur on the oral mucosa and on adjacent facial areas over prolonged periods. Recurrent cases are characterised by extensive lesions and marked crust formations on the vermillion border.
Human Papilloma Virus (HPV)	Raised, irregular, flesh-colored lesions (warts).	Excisional biopsy. However, diagnosis is generally based on clinical appearance. **Note:** Children with HPV infection may develop verruca vulgaris, widespread flat warts, and condylomata acuminata. The presence of condylomata in a child should alert the clinician of the possibility of sexual abuse.

Cytomegalovirus (CMV)	Lesions associated with CMV may mimic a number of persistent oral ulcers, including aphthous ulcers, recurrent herpes simplexvirus infection, necrotising stomatitis, and ulceration NOS. Occasionally this infection may present as a brightly erythematous gingivitis.	A definitive diagnosis can be made through culture and biopsy.
Molluscum Contagiosum	A virally induced lesion of the skin, mucus membranes, and rarely the oral cavity. Lesions are small, discrete and dome - shaped. Their color ranges from pearly white to skin color. In HIV-infected patients, the lesions may number in hundreds.	When the core of the lesion is expressed and stained, molluscum bodies which are virally transformed epithelial cells, can be seen.
Herpes Zoster	Secondary disease or reactivation of latent varicella zoster virus. Herpes zoster is primarily a condition that affects older adults and those who are immunocompromised. Pain and paraesthesia is a prodromal symptom. A well-delineated unilateral maculopapular rash that becomes pustular and ulcerated follows.	Cytologic examination reveals virus-infected epithelial cells. Commonly confused with recurrent herpes simplex virus infections, herpes zoster can be definitively diagnosed through virus antigen typing with laboratory immunologic tests.
Varicella	Primary infection with the varicella zoster virus, one of the herpes viruses. A rash involving the head, neck and trunk may be accompanied by fever, chills, malaise, and headache. The rash becomes vesicular, pustular and, finally, ulcerated. With successive waves of viraemia, successive crops of new lesions appear. When the oral mucus membranes are involved, evanescent vesicles precede multiple shallow ulcers.	Careful attention to history of exposure and type and distribution of lesions usually leads to a clinical diagnosis.

BACTERIAL INFECTIONS		
Necrotising Ulcerative Gingivitis (NUG)	The destruction of 1 or more interdental papillae accompanied by necrosis, ulceration, and/or sloughing. Destruction is limited to the marginal gingival tissues. In the acute stage (ANUG), the gingival tissues appear fiery-red and swollen, and are accompanied by yellowish-grey necrotic tissue that bleeds easily. Patients experience symptoms such as bleeding while brushing, pain, and a characteristic halitosis.	There are no present definite criteria for either NUG or ANUG. Diagnosis must be determined clinically. Responds to systemic antibiotic treatment and local debridement. **Note:** Symptoms may subside gradually over 3-4 weeks, but recurrences are common. NUG may represent an initial stage of necrotising ulcerative periodontitis.
Necrotising Ulcerative Periodontitis (NUP)	Severe soft-tissue necrosis along with destruction of the periodontal	There are no present definite criteria for the diagnosis of NUP. **Note:** Pocketing may be minimal because of simultaneous loss of both hard and soft tissues. Tissue destruction may extend across the muco-gingival junction. NUP is chronic; ulceration will be seen during active periods but may be absent during dormant periods.
Necrotising Stomatitis (NS)	Acute and painful ulceronecrotic lesions on the oral mucosa	Histologic examination reveals the features of non-specific. **Note:** NUG, ANUG and NS each represents a different stage of what appears to be a single disease. Necrotising stomatitis occurs only in the most severe cases.
LGE see fungal		

IDIOPATHIC Parotid Enlargement	Uni- or bi- lateral diffuse soft-tissue swelling resulting in facial disfigurement. May be accompanied by pain, and may be associated with lymphoid interstitial pneumonitis.	No criteria have been established for the definitive diagnosis of parotid swelling.
Minor Recurrent Aphthous Ulcers	A small ulcer less than 5mm in diameter covered with a pseudomembrane and surrounded by an erythematous halo.	A prompt response to steroid treatment confirms the diagnosis of recurrent aphthous ulcers.
Major Recurrent Aphthous Ulcers	Similar to those for minor recurrent aphthous ulceration; however, the mucosal lesions are much larger, sometimes 1-2 cm in diameter and may persist for weeks at a time. Major recurrent aphthous ulcers are painful and may interfere with mastication and swallowing. They tend to occur on the soft palate, buccal mucosa, tonsillar area, and tongue.	Response to treatment with steroid agents. **Note:** Major recurrent aphthous ulcers have recently been associated with the use of HIV antiviral therapies such as ddC (zalcitabine).
Herpetiform Recurrent Aphthous Ulcers	Herpetiform lesions appear as clusters or crops of tiny recurrent aphthous ulcers 1-2mm in diametre, which may coalesce. Like major recurrent aphthous ulcers, herpetiform lesions tend to occur in locations where they hinder eating and speaking, such as the soft palate, buccal mucosa, tonsillar area, and tongue.	Response to treatment with steroid agents.

Seborrhoeic Dermatitis	Erythema and scaling of the scalp, skin behind the ears, and nasolabial folds are particularly characteristic.	No definitive criteria. **Note:** HIV infected children experience a wide variety of mucocutaneous manifestations. Some skin diseases are due to exacerbation of childhood dermatoses (e.g. atopic or seborrheic dermatitis) or are reactions to medications. Viral, bacterial, and fungal infections are most common. Cutaneous Kaposi's sarcoma is extremely uncommon in children.
Xerostomia	Dry mouth and severely reduced salivary flow rates.	No definitive criteria exists for xerostomia. **Note:** Xerostomia is far more common in HIV infected children than HIV infected adults. It may present not only as a result of HIV infection, but also as a result of medications, such as intravenous gamma globulin and antiviral drugs such as didanosine (ddI). However, no discernible difference in the average salivary flow rates has been found between HIV infected and non-infected patients. Xerostomia may appear with or without parotid swelling.

APPENDIX 9

Comparison of prevalence of oral candidiasis in paediatric studies

Author & year	Sample	Country	Prevalence (%)
Ketchem *et al* (1990)	47	USA	25.5
Moniaci *et al* (1992)	69	Italy	35.5
Katz *et al* (1993)	99	USA	72.0
Chan *et al* (1994)	33	Canada	42.2
Valdez *et al* (1994)	*NR	*NR	35.0
Emodi *et al* (1998)	*NR	Nigeria	19.0
Chaloryoo *et al* (1998)	*NR	Thailand	59.6

*NR: Not reported

APPENDIX 10

UNIVERSITY OF THE WESTERN CAPE: FACULTY OF DENTISTRY AND MEDICAL RESEARCH COUNCIL

PAEDIATRIC ORAL HEALTH SURVEY

PARENT INFORMATION LETTER

The University of the Western Cape Oral Health Centre and the Medical Research Council (MRC) is conducting a study to assess the oral health of children infected with the HIV virus (HIV/AIDS).
Oral lesions (mouth sores) associated with HIV infection are common findings in children infected with the virus. Oral lesions may be a source of discomfort and pain. It can affect the general wellbeing and eating behaviour of the child.
To optimise the comfort and quality of life of the child, it is important to decrease mouth infection by proper treatment.

Clinical oral examinations will be performed and a tongue smear may be done. No invasive treatment will be performed. Occasionally, photographs will be taken to record lesions. Treatment required will be referred to the relevant authorities.
If blood tests are required, a separate form will be given to the parent requesting permission.
If you consent to your child participating, you will be required to complete the consent form.

Thanking you in anticipation.

Dr. N. Behardien
(Principal Investigator)

APPENDIX 11

UNIVERSITY OF THE WESTERN CAPE: FACULTY OF DENTISTRY AND MEDICAL RESEARCH COUNCIL

CONSENT FORM

Please print.

I, (father, mother, guardian) _____, herewith grant permission for my child , _____, to participate in the above mentioned study. I have been informed of the procedure s to be performed. I understand that the study is voluntary and that I may withdraw my child at any time. This will not prejudice my child or myself.

Name: _____ Signature: _____

Date: _____

Witness: _____ Signature: _____

Date: _____

APPENDIX 12

University of the Western Cape
&
Medical Research Council

Oral Health Survey: Adapted from WHO recording form.

General :

Date of examination: YYYYMMDD | | | | | | | | |

Clinic/hospital examined at: | |

In-patient/out-patient: In = 1 Out =2 | |

Caregiver: ……. | |

1. Patient Identification

Registration number: | | | | |

Hospital/clinic folder number: | | | | | | | | |

Child's name: _____

Address: _____

_____

_____

_____

Tel #: _____

Birth date: YYYYMMDD | | | | | | | | |

Gender and race (patient coding): ☐

2. Treatment/medication

Is the patient currently (1 month) taking any medication(s) for general HIV infection? 1 = Yes* 2 = No ☐

*If **yes**, please complete:

antiviral 1 = Yes 2 = No ☐

_____

_____

antifungal 1 = Yes 2 = No ☐

_____

_____

antibacterial 1 = Yes 2 = No ☐

_____

_____

Topical corticosteroids 1 = Yes 2 = No ☐

_____

_____

Nutritional supplements 1 = Yes 2 = No ☐

_____

_____

Multivitamins 1 = Yes 2 = No ☐

Salt packets 1 = Yes 2 = No ☐

Other: 1 = Yes 2 = No ☐

_____

Is the child currently on medication(s) for oral problems? ☐
1 = **Yes*** 2 = No

If **yes**, please complete:

Antiviral 1 = Yes 2 = No ☐

_____

_____

Antifungal 1 = Yes 2 = No ☐

_____

_____

Antibacterial 1 = Yes 2 = No ☐

_____

_____

Other 1 = Yes 2 = No ☐

_____

3. Clinical oral examination findings

Oral lesions/conditions present 1 = Yes 2 = No ☐

Candidiasis

Mixed variants present Y = 1 N = 2 ☐

Pseudomembranous Y = 1 N = 2 ☐

Buccal mucosa Y = 1 N = 2 ☐

Soft palate Y = 1 N = 2 ☐

Hard palate Y = 1 N = 2 ☐

Floor of mouth	Y = 1 N = 2	☐
Dorsum of tongue	Y = 1 N = 2	☐
Ventral surface of tongue	Y = 1 N = 2	☐
Right lateral tongue	Y = 1 N = 2	☐
Left lateral tongue	Y = 1 N = 2	☐
Erythematous	Y = 1 N = 2	☐
Buccal mucosa	Y = 1 N = 2	☐
Soft palate	Y = 1 N = 2	☐
Hard palate	Y = 1 N = 2	☐
Floor of mouth	Y = 1 N = 2	☐
Dorsum of tongue	Y = 1 N = 2	☐
Ventral surface of tongue	Y = 1 N = 2	☐
Right lateral tongue	Y = 1 N = 2	☐
Left lateral tongue	Y = 1 N = 2	☐
Median rhomboid glossitis	**Y = 1 N = 2**	☐
Angular cheilitis	Y = 1 N = 2	☐
Hyperplastic	Y = 1 N = 2	☐
Buccal mucosa	Y = 1 N = 2	☐

Soft palate	Y = 1 N = 2	☐
Hard palate	Y = 1 N = 2	☐
Floor of mouth	Y = 1 N = 2	☐
Dorsum of tongue	Y = 1 N = 2	☐
Ventral surface of tongue	Y = 1 N = 2	☐
Right lateral tongue	Y = 1 N = 2	☐
Left lateral tongue	Y = 1 N = 2	☐
Papillary hyperplasia	**Y = 1 N = 2**	☐
Linear gingival erythema	Y = 1 N = 2	☐
Necrotising ulcerative gingivitis	Y = 1 N = 2	☐
Necrotising ulcerative periodontitis	Y = 1 N = 2	☐
Necrotising stomatitis	Y = 1 N = 2	☐

Ulcerations:

Recurrent herpes labialis	Y = 1 N = 2	☐
Recurrent aphthous ulceration	Y = 1 N = 2	☐
Molluscum contagiosum	Y = 1 N = 2	☐
Wart-like lesions	Y = 1 N = 2	☐
Cervical lymphadenopathy	Y = 1 N = 2	☐

Submandibular lymphadenopathy	Y = 1 N = 2	☐
Sublingual lymphadenopathy	Y = 1 N = 2	☐
Dermatitis	Y = 1 N = 2	☐
Dento-alveolar abscess	Y = 1 N = 2	☐

Salivary gland conditions:

Unilateral parotid enlargement	Y = 1 N = 2	☐
Bilateral parotid enlargement	Y = 1 N = 2	☐
Xerostomia	Y = 1 N = 2	☐

Other: _____ Present = 1 Absent = 2 ☐

_____

Unknown lesion 1 = **Yes*** 2 = No ☐

***If unknown**:

Color 1 = red 2 = white ☐

Topography 1 = raised 2 = flat ☐

General Comments:

……

……

……

Dental Hard Tissue Examination

Caries Key:

Primary Dentition

Sound tooth	= 0
Decayed tooth	= 1
Filled tooth with decay	= 2
Filled tooth with no decay	= 3
Tooth missing due to caries	= 4
Congenitally absent tooth	= 5
Erupting tooth	= 6
Unerupted tooth	= 7

Permanent Dentition

Sound tooth	= A
Decayed tooth	= B
Filled tooth with decay	= C
Filled tooth without decay	= D
Tooth missing due to caries	= E
Congenitally absent tooth	= F
Erupting tooth	= G
Unerupted tooth	= H

Dental Status

Max	
17	
16	
55/15	
54/14	
53/13	
52/12	
51/11	
61/21	
62/22	
63/23	
64/24	
65/25	
26	
27	

Mand	
37	
36	
75/35	
74/34	
73/33	
72/32	
71/31	
81/41	
82/42	
83/43	
84/44	
85/45	
46	
47	

Are there any opacities present? Y = 1 N = 2

Are there any hypoplastic teeth present ? Y = 1 N = 2

Patient code:

1 = White male
2 = White female

3 = Coloured male
4 = Coloured female

5 = Indian male
6 = Indian female

7 = Black male
8 = Black female

Caregiver:

1 = Mother
2 = Father

3 = Parents
4 = Grandparent/s

5 = Aunt
6 = Uncle
7 = Institution
8 = Guardian

Red Cross Hospital	= 1
Nazareth House	= 2
Beautiful Gate Ministry	= 4
Conradie Hospital	= 13

Diagnosis of lesions:
Diagnosis of lesions will be made by using the Presumptive diagnostic criteria (Ramos0Gomez FJ, *et al*. 1999). Xerostomia however, will be diagnosed on the basis visibly of dry lips, tongue (glistening) and oral mucosa.

Ethical Statement

Faculty of Dentistry & WHO Oral Health Collaboration Centre
UNIVERSITY OF THE WESTERN CAPE

COMMITTEE FOR RESEARCH ON HUMAN SUBJECTS (MEDICAL)

CLEARANCE CERTIFICATE:	**REGISTRATION N0: 99/8/6**
PROJECT	**Human immunodeficiency virus in children - a clinical investigation of the oral status**
PRINCIPAL INVESTIGATOR	**Dr LXG Stephen**
DEPARTMENT	**Faculty of Dentistry of the University of the Western Cape**
DATE CONSIDERED	**01 August 1999**
DECISION OF COMMITTEE	**Approved unconditionally**
DATE	3/8/99
SIGNATURE:	Roberts

Dr T S Roberts
(Chairperson of the Reseach and Publications Committee)

Mtemoola

Prof H Moola
(Dean\Director)

***Guidelines for "written informed" consent attached where applicable**

ETHICS STATEMENT PROJECT (REF: 99/8/6)

The patient's / guardian's consent would be obtained and the patient / guardian would be informed of the nature of the study. The patient / guardian would have the right to withdraw from the study. Any oral lesions detected during clinical examination, will be treated / referred for treatment. All information will remain strictly confidential.

Tel: -27-21-3704447; Fax: -27-21-3923250; e-Mail: troberts@uwc.ac.za

To be completed in duplicate and ONE COPY returned to the Deans Office, 5th Floor, Oral Health Centre, Mitchells Plain

I\we fully understand the conditions under which I am \ we are authorized to carry out the abovementioned research and I\we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I\we undertake to resubmit the protocol to the Committee.

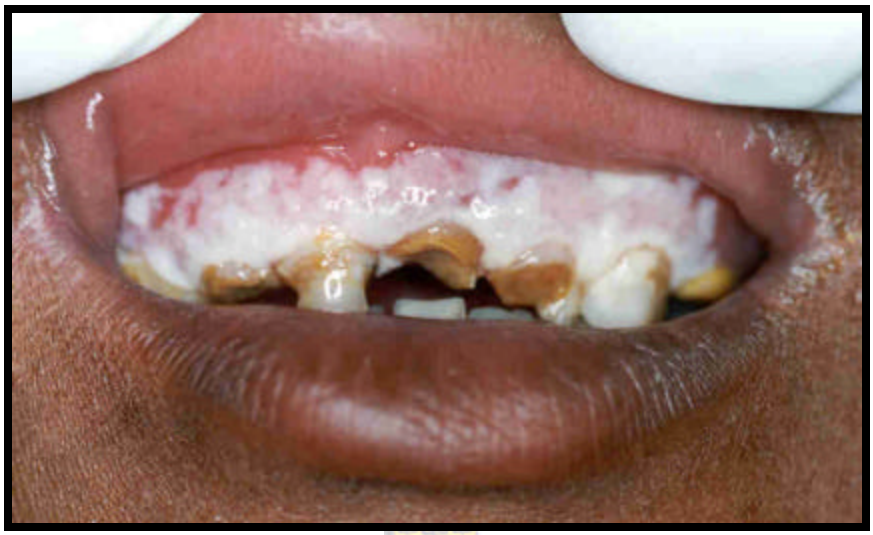
DATE: 1/8/1999 **SIGNATURE:** .....

PLEASE QUOTE THE PROJECT REGISTRATION NUMBER IN ALL CORRESPONDENCE

Tel: -27-21-3704447; Fax: -27-21-3923250; e-Mail: troberts@uwc.ac.za

FIGURE 1

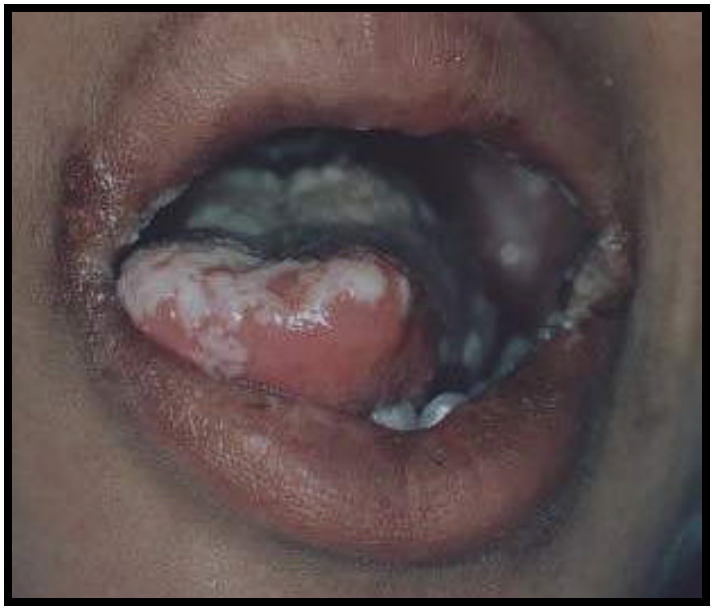
Pseudomembranous candidiasis



Creamy/white plaque covering alveolar mucosa of anterior maxilla, as well as decayed maxillary primary teeth

FIGURE 2

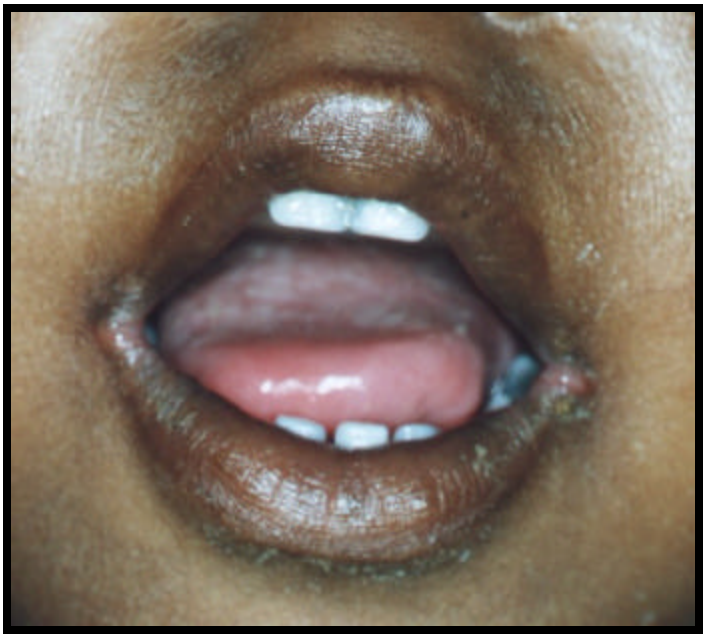
Combined candidiasis



More than one candidal variant seen simultaneously in the mouth

FIGURE 3

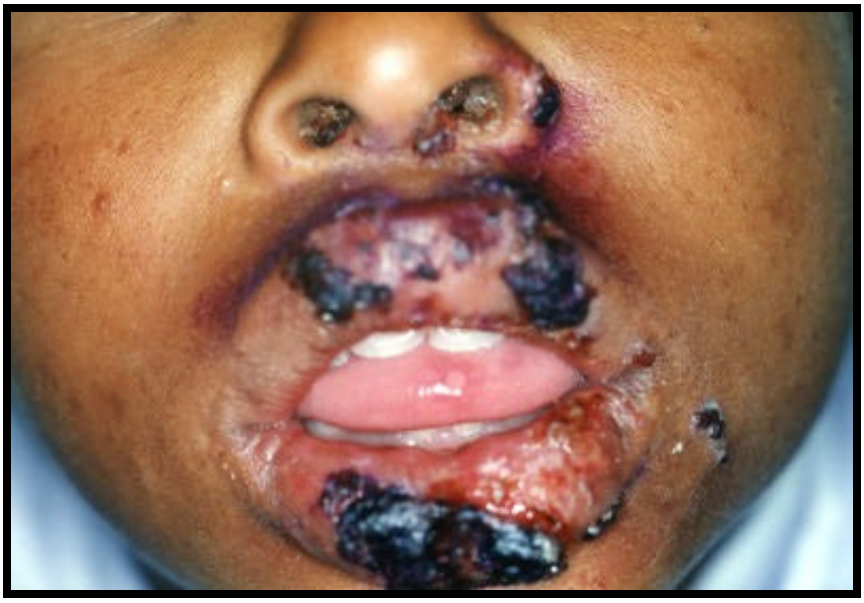
Angular cheilitis



Cracks at the corners of mouth, indicative of angular cheilitis

FIGURE 4

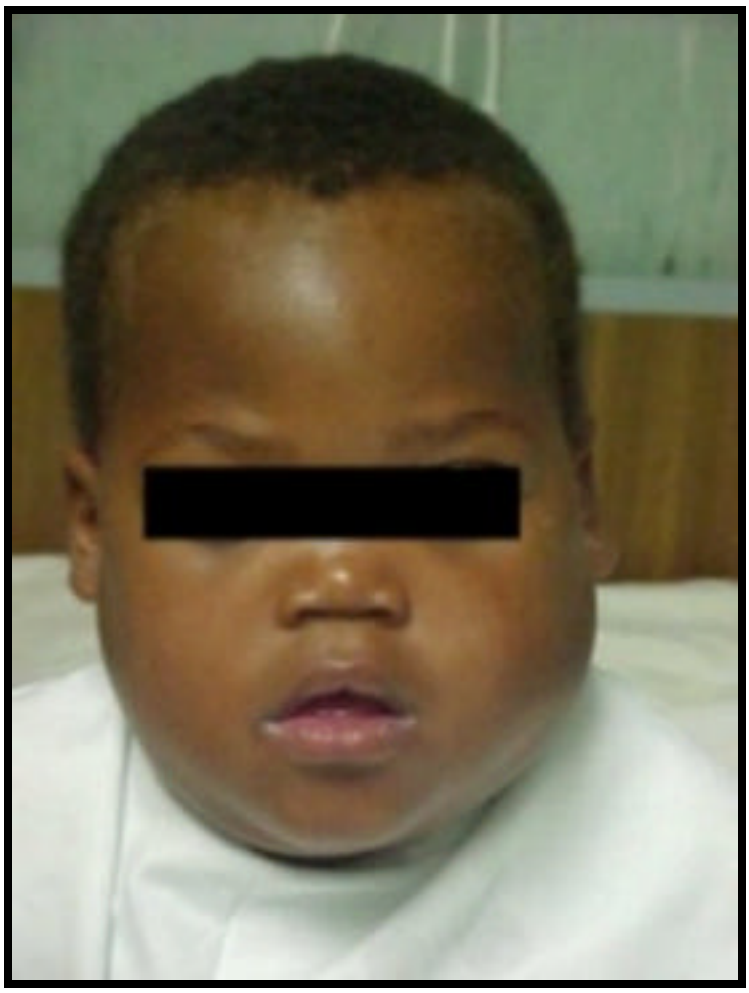
Herpes infection



Healing herpes lesions covered by gentian violet. Ulcerations affect tongue, lips, nose and peri-oral regions.

FIGURE 5

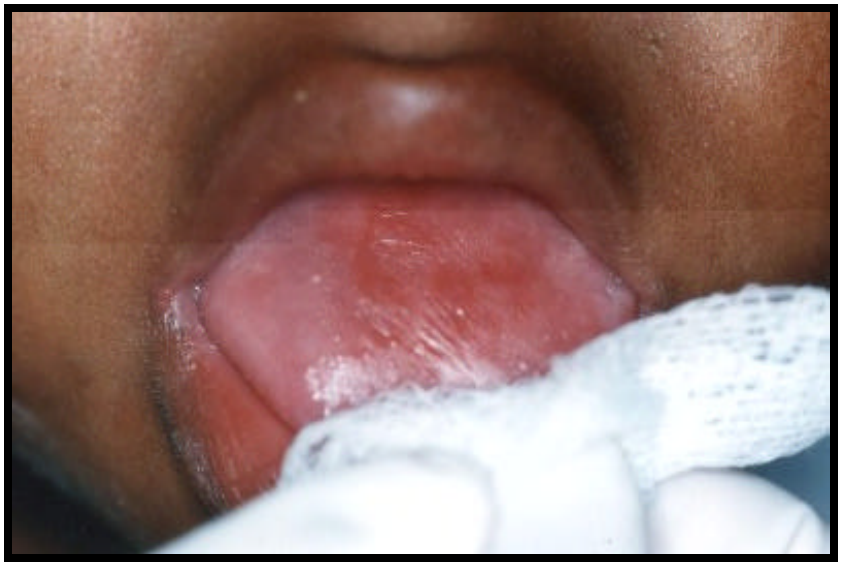
Parotid gland enlargement



Bilateral, parotid gland enlargement, more pronounced on the left

FIGURE 6

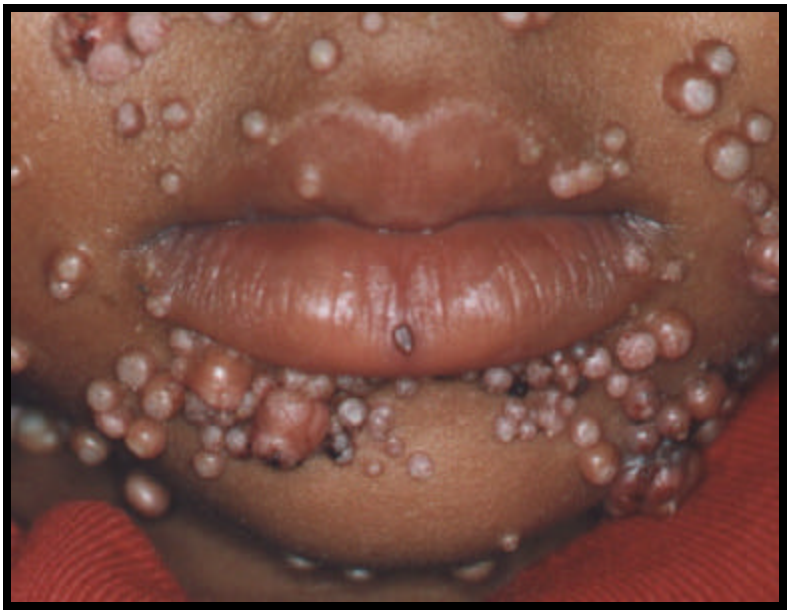
Xerostomia



A dry mouth with a glistening tongue, seen in association with xerostomia

FIGURE 7

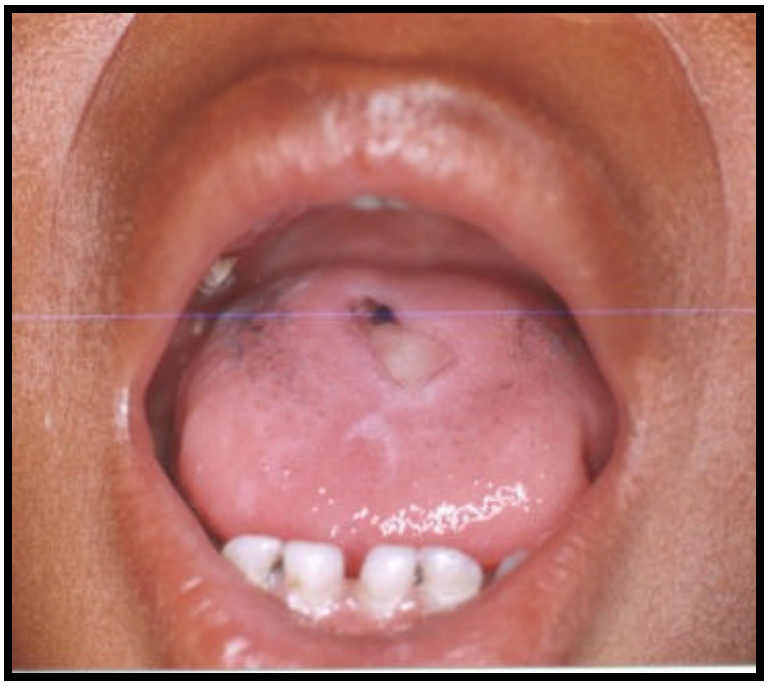
Molluscum contagiosum



Multiple, peri-oral mollusca

FIGURE 8

Oral ulceration



Large ulceration on dorsum of tongue with traces of gentian violet

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