

CHAPTER 1

1.0 INTRODUCTION

There are approximately 40 million people living with HIV/AIDS worldwide and during 2005 almost 5 million new cases were diagnosed (UNAIDS, 2005). Approximately 96% of HIV/AIDS patients live in low and middle income countries with sub-Saharan Africa being the region worst affected. Even though sub-Saharan Africa is home to only 10% of the world's population, almost two thirds (64%) of all patients who are HIV positive reside here (UNAIDS, 2005).

The South African HIV national prevalence rate has been increasing annually since the early eighties and latest results (2005) from the Antenatal Sero-prevalence Survey showed that the HIV infection rate was 30.2% (Department of Health, 2006). Despite numerous awareness campaigns, the uptake of Voluntary Counseling and Testing (VCT) has remained fairly low (Day, Miyamura & Grant, et al., 2003; Kalichman & Simbayi, 2003). Hence many patients remain unaware of their HIV status.

However, patient visits to health facilities (medical and dental) have been increasing and the public sector continues to be burdened with high patient loads and staff shortages (Harkinson & Cleaton-Jones, 2004; Bhayat & Cleaton-Jones, 2003; Wilkinson, Gouws & Sach, et al., 2001).

In the dental setting, it is important to be able to recognise signs and symptoms that are associated with HIV/AIDS so that these patients can be encouraged to attend VCT facilities.

Oral lesions have been shown, as early as 1989, by Pindborg and others (Patton, 2000; Ranganathan, Reddy & Kumarasamy et al., 2000; Pinheiro, Marcenes & Zakrzewska, 2004) to be useful predictors of HIV infection. Furthermore, a number of studies (Ranganathan, et al., 2000; Pinheiro, et al., 2004; Weinert, Grimes & Lynch, 1996 and Arendorf, Bredekamp & Cloete, et al., 1998) have shown that between 35% and 90% of all HIV infected patients present with at least one oral lesion associated with HIV during the course of their diseases. In essence, oral lesions could be included in patient examination protocols as markers to arouse suspicion of potential HIV infection.

In many areas of sub-Saharan Africa, facilities for laboratory diagnosis are limited and inadequate to reliably diagnose HIV/AIDS. Therefore, the World Health Organization (WHO) has proposed a clinical case definition of AIDS. The WHO has also classified specific oral lesions that are prevalent in HIV positive patients but has not promoted their use as a screening tool for diagnosing HIV/AIDS (Patton, Phelan & Ramos-Gomez, et al., 2002). Many studies have shown conclusive evidence that the prevalence of oral lesions in HIV positive patients is high, but no study has used oral lesions as a screening tool in determining the possibility of HIV infection in patients who are unaware of their HIV status. This study will determine the predictive value of oral lesions associated with HIV/AIDS as markers for HIV infection.

1.1 LITERATURE REVIEW

The review examined:

1. The prevalence of group I oral lesions amongst HIV positive patients
2. The use of Group I oral lesions in predicting HIV status
3. The epidemiological tests used for predicting diseases and
4. The sensitivity and specificity of saliva testing for confirming HIV status

1.1.1. Prevalence of group I oral lesions amongst HIV positive patients

There is strong evidence in the medical and dental literature to link the presence of oral lesions to patients' HIV status (Patton, 2000; Begg, Panageas & Mitchell-Lewis, et al., 1996; Begg, Lamster & Panageas, et al., 1997).

As there are more than 40 oral lesions associated with HIV (Greenspan & Greenspan, 1996; Weinert et al., 1996), the EC-Clearinghouse on Oral Problems related to HIV Infection and WHO Collaborating Centre on Oral Manifestations of the Immunodeficiency Virus have established a classification system for these lesions (Patton, et al., 2002). The EC-Clearinghouse classification of September 1992 (EC-Clearinghouse, 1993) is accepted internationally as the classification for oral lesions associated with HIV. Oral lesions associated with HIV can be divided into 3 groups:

Group I – Lesions strongly associated with HIV infection

Group II – Lesions less commonly associated with HIV infection

Group III – Lesions seen in HIV infection

Group I lesions are those that occur most frequently in HIV/AIDS patients. These lesions are: Oral Candidiasis (OC), Oral hairy leukoplakia (OHL), Kaposi's sarcoma (KS), Non-Hodgkin's lymphoma (NHL) and periodontal disease [such as linear gingival erythema (LGE) and necrotising ulcerative gingivitis (NUG) and periodontitis (NUP)].

Table 1 provides details of the current literature reporting on the prevalence of Group I oral lesions in HIV positive patients. This table shows that between 30% and 90% of HIV positive patients present with at least one of the Group I oral lesions. Oral candidiasis was the most common oral lesion diagnosed in all of these studies.

Table 1. Studies reporting on the prevalence of Group I oral lesions in HIV positive patients

	Author/s	Participants	Study design	Sample Size	Prevalence of oral lesions	Results (prevalence rates)	Setting
1	Ranganathan et al 2004	HIV positive patients over 18 years old. 77% Males and 23% Females	Cross sectional analytical study	1000	86.6%	OC- 24%, AC-7.9%, OHL-2.1%	ASIA South India
2	Nittayananta et al 2002	HIV positive patients between 16-65 years old who attended a public facility 83% Males and 17% Females	Cross sectional analytical study	278	Sample group consisted of patients with oral lesions only (Not Applicable).	OC-40%, OHL-26%	ASIA Thailand
3	Ranganathan et al 2000	HIV positive patients between 7 months and 72 years who attended a public facility 68% Males and 32% Females	Cross sectional analytical study	300	72%	OC-56%, AC-8%, OHL-3%	ASIA South India
4	Anil and Challacombe 1997	HIV positive patients over 18 years old	Cross sectional analytical study	96	Sample group consisted of patients with oral lesions only (Not applicable).	OC-81%, AC-13%, OHL-7%, NUP-23%	ASIA India
5	Matee et al 2000	HIV positive patients over 18 years old 78% females and 22% males	Cross sectional study	192	Not Applicable	OC-12%, OHL-6%	AFRICA Tanzania
6	Arendorf et al 1998	HIV positive adults	Cross sectional study	600	60%	OC-38%, AC-7%, OHL-20%, NUP-3%, NUG-1%, KS-2%	AFRICA South Africa
7	Arendorf et al 1997	HIV positive adults 225 Blacks, 191 Coloureds and 69 Whites	comparative inter-group cross sectional study	485	56%	OC-35%, AC-6%, OHL-19%, NUG-2%, NUP-4%	AFRICA, South Africa
8	Mugaruka et al 1991	HIV positive adults	Cross sectional study	103	Not Applicable	OC-62%, AC-3% NUG-16%, KS-5%	AFRICA, Zaire

9	Ramirez-Amador et al 1998	HIV positive adults 60% Females and 40% Males all study sample were Mexican	Cross sectional analysis study	436	71%	OC-39%, AC-11%, OHL-30%, NUP-2%, NUG-3%, KS-2%	SOUTH AMERICA Mexico
10	Schuman et al 1998	HIV positive woman over 18 years who attended a multi centre health facility 100% Females	Longitudinal cohort study	867	40%	OC-15.3%, AC-4.2%, OHL-6.8%	U.SA Detroit Providence
11	Klein et al 1991	HIV positive patients over 18 years 43% Females and 57% Males	Cross sectional study	181	92%	OC-92%, OHL-19% KS-4%	USA New York
12	Silverman et al 1986	HIV positive patients over 18 years 100% white homosexual males	Longitudinal cohort study	164 (all males)	Not applicable	OC-87%, OHL-21%, NUP-19%, KS-32%	USA San Francisco
13	Margiotta et al 1999	HIV positive patients over 18 years Both males and females, all subjects were Italian	Cross sectional study	104	36%	OC-6%, OHL-10% NUP/NUG-3%	EUROPE Italy

KEY: OC = oral candidiasis; AC=angular cheilitis; NUG =necrotising ulcerative gingivitis; NUP =necrotising ulcerative periodontitis; OHL = oral hairy leukoplakia; KS=Kaposi's sarcoma

Some generalisations can be made from the data presented in Table 1. The most common oral lesion that was diagnosed was oral candidiasis. The majority of studies were cross sectional study in design and comprised of known HIV positive patients over 18 years old. These studies were carried out in all parts of the world in different types of settings. The sample size of the study population varied between the different studies. The prevalence and type of oral lesions varied in the different studies. Possible reasons for the variations in the prevalence and type of oral lesions included:

1. the cohorts were in different stages of the HIV disease with variable CD4 counts
2. some sample groups were hospitalised while others were ambulatory patients
3. some cohorts were convenience samples while others were randomly selected and
4. there was no standardised calibration of the examiners for diagnosing of oral lesions according to the EC clearinghouse criteria (Patton, et al., 2002).

1.1.2. The use of group I oral lesions in predicting HIV status

Oral lesions have been used to predict the HIV status and progression of the disease in numerous studies both locally and internationally. A study done in Cape Town by Badri, Martins & Wood in 2001 concluded that the presence of Oral Hairy Leukoplakia (OHL) and Oral Candidiasis (OC) provided prognostic information, and could be used as a cost effective tool for screening patients in resource limited settings. This prospective study was done on a cohort of 772 HIV positive patients who had attended adult HIV clinics in Cape Town. It was carried out over a six year period extending between 1992 until 1997. Of the sample group, 205 (27%) presented with Oral Hairy Leukoplakia (OHL) and or Oral Candidiasis (OC). Furthermore, patients who presented with OHL and OC simultaneously, were significantly ($p<0.05$) more likely to be associated with the diagnosis of AIDS and the possibility of death. These results confirmed the value of OHL and OC in predicting the HIV status of patients.

A similar study done by Shangase, Feller & Blignaut (2004) correlated the presence of necrotising ulcerative gingivitis (NUG) and periodontitis (NUP) to the HIV status of patients in Garankuwa, South Africa. In this study 86 patients were diagnosed with NUG/NUP and advised to have a blood test done in order to determine their HIV status. Of these, 56 consented and 39 (70%) of them tested positive for HIV. This yielded a strong correlation between the HIV status and the presence of NUG/NUP with a predictive value of 70%. The authors therefore recommended that patients with either of these two

conditions should be encouraged to undergo testing for HIV which could assist in early referrals and management.

These results have been supported by the findings of Ranganathan, Umadevi & Saraswathi, et al. (2004) who reported on a study carried out in India on 1000 patients. This study also showed that multiple oral lesions were much better predictors of HIV/AIDS compared to single oral lesions. The study population comprised of consecutive HIV seropositive patients that attended a non-governmental clinic in Chennai, South India. There were three times more males than females in the study population and 95% of them had acquired HIV through heterosexual contact. The majority of patients (87%) were between 21 and 40 years old. Their results showed that almost 87% of all patients presented with group I oral lesions. The researchers concluded that group I oral lesions played an important role in determining the immune status of individuals and in the management of HIV/AIDS. Hence, they recommended that a comprehensive oral examination would play a vital role in both the management and follow up of these patients.

A study done in Thailand by Nittayananta, Chanowanna & Winn, et al. (2002) showed that HIV positive patients with group I oral lesions were more likely to have Tuberculosis (TB) compared to patients without these oral lesions. The aim of this study was to determine whether any relationship existed between oral lesions and opportunistic infections amongst HIV infected patients. A sample of 278 (230 males and 48 females) patients were examined. The authors reported a positive predictive value of 87% for any group I oral lesion in predicting TB. They therefore concluded that the presence of group I oral lesions in HIV positive patients could be used with confidence as a clinical marker for TB. Hence, health care providers need to examine the oral cavity thoroughly to detect possible oral lesions and perform necessary laboratory investigations in order to diagnose TB. These providers could also use the oral lesions for monitoring possible infections and provide prophylaxis against opportunistic systemic infections.

Patton (2000) examined the sensitivity, specificity, odds ratio and positive predictive value of oral lesions in adults with HIV. Her study was carried out in the United States of America (North Carolina) and consisted of a single observational cohort of 606 HIV positive patients who were followed over a five year period (1995 to 1999). All of the oral examinations were done by one oral medicine trainer who was calibrated according to the EC- clearing house (1993) criteria. Her results showed that specific Group I oral lesions

were strongly associated with immune suppression and could serve as potential clinical markers of HIV. The odds ratios were relatively low and ranged between 1.9 (0.9-4.0) and 7.5 (3.9-14.8); this showed that there was a weak correlation between the immune suppression state of the patients and their HIV status.

However, a weakness of most of these studies (including the Patton study) was that the patients HIV status was known and this could have led to bias in the diagnosing of oral lesions. Another weakness of all of these studies was that the clinical diagnosis of oral lesions was not confirmed by histological evidence (biopsies). This could have led to an over or under estimate of the actual oral lesions.

An African study done by Schiodt, Bakilana & Hiza, et al. (1990) in Tanzania correlated the association between two Group I oral lesions (oral candidiasis and oral hairy leukoplakia) and the patients' HIV status. The sample consisted of 186 patients who presented with serologic signs of HIV infection but who were unaware of their HIV status. Within this cohort, 39 were suspected of having AIDS, 44 were medical patients who were non suspected AIDS patients, 53 were dental out patients and the remaining 50 patients had a confirmed sexually transmitted disease. The oral examination was carried out without the clinician being aware of the patients HIV status. The authors reported that more than half of all confirmed HIV positive patients presented with some form of group I oral lesions compared to 6% of those who tested negative for HIV. The most common forms of oral lesions were oral candidiasis and oral hairy leukoplakia. It was therefore concluded that the presence of group I oral lesions had a high predictive value for the presence of AIDS criteria as well as for the presence of HIV infection in that hospital setting. Hence, it was recommended that all patients have a thorough oral examination and the presence of these lesions should warrant testing for HIV infection.

The authors unfortunately did not use sensitivity or specificity tests in detecting the probability of the patients' HIV status.

1.1.3. Epidemiological tests used to determine the predictive value of oral lesions

The positive (PPV) and negative (NPV) predictive value, sensitivity, specificity and likelihood ratio tests have been used to determine the accuracy of various diagnostic tools in health care. Studies by Gallant, et al. (1992); Keou, et al. (1992) and Colebunders, Mann

& Francis, et al., (1987) have used sensitivity, specificity, NPV and PPV tests to evaluate the accuracy and reliability of the WHO clinical staging in diagnosing HIV/AIDS.

These tests (sensitivity, specificity, NPV and PPV) have also been used to compare oral lesions and a combination of CD4 counts and immune suppression in HIV positive and negative patients (Patton, 2000; Begg, et al., 1997; Begg, et al., 1996 and Schiodt, et al., 1990). While Patton (2000) and Begg, et al., (1996) examined known HIV positive patients, Schiodt et al (1990) confined his sample to patients who were suspected of being HIV positive.

Schiodt, et al., (1990) only used the positive predictive value while Begg, et al., (1997) and Patton (2000) used sensitivity, specificity, odds ratios and negative and positive predictive values to correlate the group I oral lesions to the patient's CD 4 cell count as an indication of the patients immune suppression.

Even though the composition of the cohorts used by the above studies differed in their HIV status, gender ratios and ethnic and cultural backgrounds, all of them reported similar high positive predictive and specificity values for group I oral lesions in detecting immune suppression (which was as a result of HIV infection). These authors also reported low odds ratios which indicated a weak correlation between the HIV status and the immune status of these patients.

Schiodt, et al., (1990) examined the association between group I oral lesions and the HIV status. Oral lesions were present in 52% of HIV infected patients compared to 6% of patients without HIV infection. These authors reported that amongst patients with AIDS, 36% were diagnosed with hairy leukoplakia and 23% with pseudomembranous candidiasis. They reported that patients who presented with oral lesions (oral candidiasis and hairy leukoplakia) had a significantly higher ($p < 0.01$) positive predictive value (PPV) for HIV infection within their hospital setting compared to those patients who did not have these oral lesions.

Begg, et al., (1997) whose cohort consisted of known HIV positive patients, correlated the presence of group I oral lesions to the progression of HIV to full blown AIDS. These authors used oral lesions as clinical markers to detect the transition from HIV to AIDS using the World Health Organisations' (WHO) criteria. Their results showed that combined oral lesions (oral candidiasis, hairy leukoplakia and necrotising ulcerative gingivitis) had a significantly higher ($p = 0.018$) predictive value compared to any single

oral lesion. They further noted that the prognostic value of the core lesions (oral candidiasis and hairy leukoplakia) was significantly enhanced ($p=0.036$) by the addition of linear gingival erythema (LGE). They therefore concluded that the prognostic value of oral candidiasis and hairy leukoplakia had increased significantly by the addition of other group I oral lesions such as necrotising ulcerative gingivitis and linear gingival erythema and these lesions should be used in the staging systems of HIV in order to improve the current WHO AIDS staging criteria.

Patton (2000) showed significantly higher ($p<0.01$) positive predictive and specificity values for oral candidiasis and oral hairy leukoplakia in predicting patients with low CD4 counts (<200 cells/mm³) or immune suppression (Table 2). Patton concluded that specific Group I oral lesions (candidiasis and hairy leukoplakia) were strongly associated with immune suppression and could serve as potential clinical markers for HIV disease. The reasons for the low sensitivity values were due to low prevalence rates amongst the cohort. However, the high specificity and positive predictive values (PPVs) indicated that those patients who presented with these oral lesions were significantly more likely to have CD4 counts below 200 cells/mm³ and hence more likely to have full blown AIDS compared to patients without these specific oral lesions. The combination of oral hairy leukoplakia (OHL) and oral candidiasis (OC) yielded an odds ratio (OR) of 12 which showed a strong correlation between the presence of these oral lesions and the HIV status of the patients. Kaposi's sarcoma (KS) had an undefined OR since there were no patients who were diagnosed with KS and had a high CD4 count (≥ 200 cells/mm³).

Table 2. Results of epidemiological tests performed by Patton (2000)

	Oral lesion/s	Sensitivity (%)	Specificity (%)	PPV	NPV	OR	P value
1	OC	30	92	74	63	4.8	<0.01
2	OHL	26	90	66	61	3.3	<0.01
3	KS	2	100	100	57	∞	0.04
4	OHL and OC	10	99	89	59	11.9	<0.01

Key:	OC=Oral Candidiasis	OHL=Oral Hairy Leukoplakia	KS=Kaposi's sarcoma
	PPV=Positive Predictive Value	NPV= Negative Predictive Value	OR=Odds Ratio

After an extensive literature search (Pubmed 1970 to 2006), no published data correlating the sensitivity, specificity, odds ratios, positive and negative predictive values of group I oral lesions to the presence of HIV antibodies was found.

The Likelihood Ratio (LR) is another epidemiological test used to determine the probability of a person having a disease if he or she presents with certain conditions. In other words, it is defined as the probability of a particular test result for a person with the disease divided by the probability of that result for a person without the disease (Greenberg, Daniels, & Flanders, et al., 2001). The LR has been often used in medicine since it is much more accurate and is independent of the prevalence of a disease. This is unlike the other tests such as PPV and sensitivity and specificity values which are dependent on the prevalence (Greenberg, et al., 2001).

Although the test has proven to be a more accurate and reliable method of determining the likelihood that a person may or may not have a disease, the LR has not been used frequently in published data. Some of the reasons given by Greenberg and his co-workers (2001) for its limited use include:

- It is a relatively new and unknown epidemiological test
- It is difficult to compare new and old studies since older studies have not used the LR
- Focussed on a lesion/condition and not on a diagnostic test or tool

The Likelihood ratio is calculated as follows:

$$\text{Likelihood Ratio} = \frac{\text{Sensitivity}}{1 - \text{Specificity}}$$

The **sensitivity** is defined as the percentage of persons with the disease who tested positive while the **specificity** is defined as the percentage of persons without the disease who have tested negative. Sensitivity and specificity values are calculated using the information in Table 3 and the formulae which follow thereafter.

Table 3. Formulae to calculate the Likelihood Ratio

	HIV positive	HIV negative	Total
Oral lesion present	A	B	A+B
Oral lesion absent	C	D	C+D
Total	A+C	B+D	A+B+C+D

$$\text{Sensitivity} = \frac{A \times 100}{A + C}$$

$$\text{Specificity} = \frac{D \times 100}{B + D}$$

The Likelihood ratio is interpreted as follows:

If the LR is 1, it indicates that there is no value in the test in separating persons who have the disease from those who do not.

If the LR is between 1 and 10, it indicates that the test is useful in determining whether individuals who have a positive result actually have the disease. However, the association is weak and should be used with caution.

If the LR is large (>10), it means that there is a strong association between having a positive result and having the disease of interest.

This interpretation framework provides a useful tool in determining the strength of the association between a lesion/condition and the presence of a disease. Since most diseases are multifactorial in aetiology, this test has not been used frequently in medicine and dentistry as compared to the behavioural and social sciences (Greenberg, et al., 2001).

Gallagher (1998) examined the relevance and usefulness of the likelihood ratio test. He noted that sensitivity and specificity were limited since it represented an inversion of customary clinical logic and hence failed to highlight the important clinical findings. In contrast, he showed that the predictive values, although provided relevant and requisite information depended on the prevalence rates and was therefore unstable. The likelihood ratio test, in contrast, combined the stability of the sensitivity and specificity tests with the usefulness of the predictive tests to be one of the most stable and robust epidemiological tests in disease probability. He confirmed this conclusion with a simple equation which is listed hereunder:

Clinically estimated pre-test odds of disease X likelihood ratio = post-test odds of disease. This simple equation illustrated a concordance between the mathematical properties of likelihood ratios and the central strategy underlying diagnostic testing, the revision of disease probability.

Pearl, a year later (1999), reviewed the various epidemiological tests and described a hierarchical classification system for diagnostic assessments. Using various clinical end points including diagnostic accuracy, therapeutic effect and clinical outcomes amongst others, he rated the likelihood ratio as one of the more robust and accurate epidemiological tests for medical conditions. He confirmed Gallagher's' (1988) results and concluded that the likelihood ratio was useful in the medical setting in determining different disease probabilities.

Dominicus, Skrondal & Gjessing, et al., 2006 used the likelihood ratio in a clinical setting to assess the genetic and environmental influences on the variation within individual traits. They found the test to be easy to calculate and robust since it used a chi-square distribution and is not dependent on the prevalence of specific factors. This ensured that even rare factors within either the environment or the genetic make up was equally weighted and provided significant and realistic p values.

There have been no published dental studies that have used the likelihood ratio as an epidemiological test in a clinical setting.

1.1.4. The sensitivity and specificity of saliva testing for confirming HIV status

HIV/AIDS diagnosis continues to be a problem especially in resource poor countries where the prevalence rates continue to rise (Major, Read & Coates, et al., 1991). Modern immunodiagnosis is characterized by at least some of the following criteria: convenient access of the patient to primary health care professionals, collection of a specimen with disposable instruments, rapid specimen transport in cooled containers, specimen processing by automated analyzers in highly specialized, centralized laboratories, well-researched reference and control protocols, and establishment of feedback loops between test results and treatment regimens. Unfortunately, such criteria cannot be met by many countries in the world. There is an urgent need for methods which facilitate specimen collection and analysis while the patient is present at the testing site (Major, et al., 1991).

Several requirements must be satisfied in order to perform on-site analysis. One of which being a less invasive specimen collection technique (e.g., by use of saliva). It has been shown that antibodies to HIV from the oral cavity (saliva) can be detected with a

sensitivity and specificity that are essentially identical to those of tests from serum (Bhore, Sastry & Patke, et al., 2003; King, Wynter & Bain, et al., 2000; Granade, Phillips & Parekh, et al., 1998 and Emmons, 1997). The use of saliva in diagnosing HIV/AIDS has become equally feasible, when all the relevant protocols are appropriately modified and applied (King, et al., 2000).

The saliva test is an immunochromatographic test for the detection of antibodies. It consists of a soft flat pad which is porous and is placed in contact with the gums. The pad absorbs the saliva and is then placed into a vial containing a pre measured amount of developer solution and allowed to develop. The saliva gets transmitted onto a test strip. As it migrates across the strip, it mixes with a red colored reagent dye. If any IgG antibodies are present it mixes with the dye and forms a line. The presence of the line would indicate the presence of IgG antibodies specific to HIV (Major, et al., 1991).

There have been numerous studies (Mortimer & Parry, 1994; Hunt, Connell & Christofinis, et al., 1993; Major, et al., 1991 and Parry, Perry & Mortimer, 1987) which have shown the validity of saliva testing for the HI Virus. According to all of these authors, the possibility that saliva could be used for HIV screening and diagnosis has been known since 1986. However, despite the obvious advantages over venepuncture of ease of collection, safety, compliance and cost, interest in salivary testing has grown relatively slowly. Several studies have demonstrated that salivary anti-HIV testing can be highly accurate, particularly if specimen collection procedures are optimal (Mortimer & Parry, 1994).

It must be noted that saliva tests do have limitations. The saliva test is not recommended for patients under 12 months old. Antibodies can be transmitted from the mother during birth and breast feeding, and therefore will be present in the infants' saliva even though the child may not be infected (Mortimer & Parry, 1994 and Hunt, et al., 1993). Hence although they would test positive for antibodies, it is possible that they would actually still be HIV negative (test false positive).

Ongarbaev, Avazova & Mustafaeva, et al. (2004) used the saliva samples and sera of 81 HIV-infected and 99 presumably non-infected patients to investigate the sensitivity and specificity of the "OraQuick" HIV saliva test kit. The data obtained from the saliva test was compared with the results of the gold standard, Enzyme-Linked Immunosorbent Assay

(ELISA)-based serum testing. The sensitivity of the "OraQuick" test was 95% and the specificity was 100%. The authors concluded that the test was appropriate for HIV screening procedures.

Hunt and his co-workers (1993) evaluated the reliability of the saliva test on 534 patients in London during 1993. Their results showed an overall sensitivity of 96.2% and a specificity of 100%. None of the saliva tests were falsely positive for HIV-1 antibodies. They concluded that saliva tests can be reliably used in HIV screening and testing.

Another study by Major et al., (1991) compared the effectiveness of the saliva test against the Enzyme-Linked Immunosorbent Assay (ELISA). Of the total 548 patients that were screened, the saliva test accurately identified 117 out of 119 HIV positive patients (sensitivity of 98.3%) and all of the 429 HIV negative patients (specificity 100%). The authors concluded that saliva specimens can be easily collected and provide a valuable alternative to testing blood for HIV sero-prevalence rates.

Other studies (Akanmu, Akinsete & Adesemoye, et al., 2001; Gallo, George & Fitchen, et al., 1997 and Grant, Piwowar & Katongole-Mbidde, et al., 1996) have also evaluated the reliability of saliva testing for HIV against blood specimens. All of these studies have shown sensitivity and specificity values greater than 96% and 99% respectively. All of the authors have agreed that saliva tests are both reliable and accurate for HIV detecting and can be used with confidence in routine screening and epidemiological studies.

Various other studies done throughout the world (Bhore, et al., 2003 in India; King, et al., 2000 in Jamaica and Granade, et al., 1998 in Bahamas, Trinidad and Tobago) have confirmed the reliability of saliva tests against the ELISA test. Even though these studies were done in different parts of the world with different cohorts in various stages of the HIV disease, all of them have shown that saliva tests are effective and safe to use for HIV screening and testing. These studies have all shown a specificity of between 99% and 99.87% and a sensitivity of between 75% and 96%.

A South African study (Webber, Swanevelder & Grabow, et al., 2001) reported that the saliva test strip results correlated 100% to the gold standard (blood test). This was a prospective pilot study which screened a total of 153 patients including HIV-positive and negative individuals, children (>1 year) and medico-legal cases from Gauteng, South

Africa. Whole blood specimens were taken from every individual and medico-legal case (total study population 153) while saliva specimens were taken from 76 selected cases. All the results from the saliva tests were correlated with the currently recommended anti-HIV assays. The whole blood test strip results correlated 100% with the traditional diagnostic results. Only two saliva test results tested false-negative. Both of these were from marasmic and severely dehydrated babies.

The authors concluded that the saliva test for HIV/AIDS was rapid, reliable and easy to perform and interpret. The saliva specimens could be readily collected from any individual, and there was a reduction in hazard risk for the health professionals.

Therefore the authors recommended Anti-HIV saliva testing for South Africa, particularly in high-risk situations such as the pediatric and forensic medicine settings.

The “OraQuick” HIV-1/2- Rapid HIV-1/2 Antibody Test®, was tested and evaluated by Major et al., 1991 and Bhore et al., in India during 2003 when they tested pregnant woman attending an antenatal clinic. The results from this study showed a specificity of between 96 and 100% and sensitivity between 75 and 94%. These results were similar to those reported by Major et al. (1991) who showed a specificity of 100% and a sensitivity of 98.3%.

All of the authors have concluded that saliva tests for HIV antibodies can be used for screening purposes. The authors listed some of the advantages of the saliva kit as being user friendly and easy to interpret and perform. Patients reported less fear and were much more willing to participate compared to studies using blood samples. Some of the disadvantages as listed by the authors included the cost of the kits, access to the kits and suspicion by some sectors within the health services.

In summary, a review of the literature on the prevalence and predictability of oral lesions, the epidemiological tests available and the use of saliva tests to determine the HIV status of patients have shown the following results. Oral candidiasis was the most common oral lesion diagnosed in HIV positive patients. Group I oral lesions have been shown as useful predictors in patients who are HIV positive and the presence of multiple lesions are almost indicative of a patient testing positive for HIV/AIDS. Most of these studies have used sensitivity, specificity, odds ratio and positive and negative predictive values in assessing the reliability of oral lesions in detecting HIV positive patients. No study has used the

Likelihood Ratio test (a more robust and reliable test) to screen possible HIV positive patients using oral lesions as clinical markers. Lastly, saliva testing for HIV has been used for over ten years and has been shown to be extremely sensitive and specific (96-100%) when diagnosing HIV patients.

Therefore the authors have opted to use the saliva test in this study to determine the HIV status of all participants. The study will also utilise the Likelihood and Odds ratios to correlate the patients' HIV status to the presence of oral lesions.

1.2 AIM

The aim of this study was to determine the predictive value of Group I oral lesions for HIV infection among patients attending Primary Health Care (PHC) facilities during April and May 2005 in Gauteng, South Africa.

1.3 OBJECTIVES

The specific objectives of the study were to determine the:

1. Prevalence of HIV among attendees at two Primary Health Care (PHC) facilities in Gauteng
2. Prevalence of group I oral lesions in patients attending curative care services at these facilities
3. Predictive value of group I oral lesions in detecting HIV infection using the sensitivity, specificity, negative and positive predictive values the odds ratio and the likelihood ratios.

CHAPTER 2

2.0 STUDY DESIGN

This was a cross-sectional analytical study. It formed part of a larger surveillance study that was undertaken by the Gauteng Department of Health (DOH) to measure the burden of illness that HIV patients presented at Primary Health Care (PHC) facilities in the Province. The investigators had coordinated the surveillance studies at two PHC sites: Khutsong Main Primary Health Care (PHC) facility and Heidelberg PHC facility. These 2 facilities were chosen for the following reasons:

1. They were the 2 feeding facilities to the larger hospitals that were randomly selected, viz. Heidelberg and Carletonville Hospitals.
2. The PHC facilities were located in different geographical regions within Gauteng Province. Khutsong PHC is located in Region A while Heidelberg PHC is in region B.
3. The management and staff at these 2 PHC facilities were much more eager and willing to participate in the study compared to other clinics. These attitudes were identified in workshops held between management and the Department of Health prior to the initiation of this study.

Khutsong PHC facility

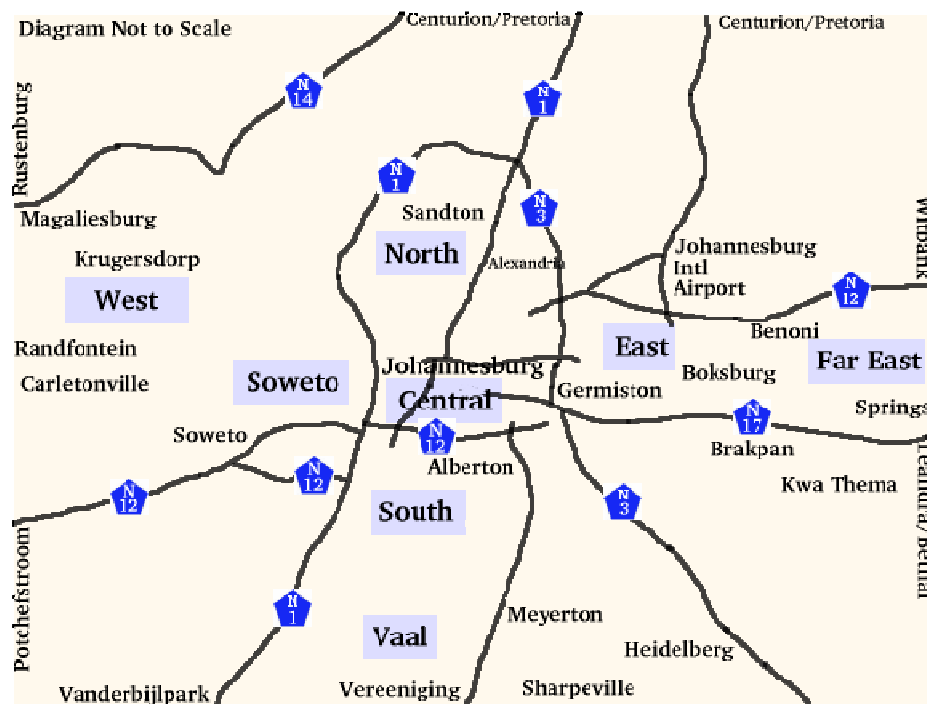
Khutsong is approximately 90km West of Johannesburg (see Figure 1) and is situated in the Merafong (the Sesotho word meaning “mining place”) local municipality. Merafong, together with Randfontein, Carletonville, Mogale City and Westonaria forms part of the West Rand District. The West Rand district is one of 5 districts within Gauteng Province in South Africa. Khutsong is situated in the heart of a mining territory and is also a developing agricultural area. The demographic profile of residents in Khutsong is consistent with a low socioeconomic status, high unemployment rate, low educational status and predominantly migrant labor force. Given these circumstances, Khutsong is suspected of having a high HIV prevalence rate (Municipality of Khutsong, 2006).

Heidelberg PHC facility

Heidelberg is situated approximately 60 km south of Johannesburg in the Lesedi (the Sesotho word meaning “light”) municipality (Figure 1) which is part of the Sedibeng District.

There are 2 other municipalities in this district; namely Emfuleni and Midvaal. Heidelberg has many residents who commute to surrounding areas (Johannesburg) for employment while others are involved in agriculture and small business holdings. The residents have a similar demographic profile compared to Khutsong residents in terms of employment, socio-economic status and education levels. However, there are not many resident migrant labourers, mines and mining hostels compared to Khutsong (Sedibeng District, 2006).

Figure 1. Map of Gauteng Province



2.1 STUDY POPULATION

All patients who had attended the two PHC facilities for curative/acute care services (i.e. presenting with an illness) over the study period were included in the study population. Curative or acute care patients were defined as all patients who attended the PHC facilities with signs and symptoms indicating ill-health. In other words, patients had to have a complaint relating to ill health. The study period comprised one full week (Monday to Saturday) at each of the two participating PHC facilities. The study was carried out during

the first week of April 2005 (Khutsong PHC) and the second week of May 2005 (Heidelberg PHC).

Inclusion criteria

- All patients who provided written consent to being part of this study
- All patients who attended the PHC facility for curative care
- Only patients older than 12 months of age were included in the study as the saliva test has shown false positives for children under this age. The reason for these false positives is the fact that HIV positive mothers would pass on their antibodies to the children even though the children might be HIV negative.

Exclusion criteria

- Patients attending for follow-up chronic disease care and management e.g. hypertensive and diabetic patients.
- Children less than 12 months of age
- Pregnant females attending the Ante-Natal Clinic (ANC), this group was excluded as they were not attending the clinic for acute/ curative treatment.
- Patients who did not provide written consent.

2.2 STUDY SAMPLE

There was an average attendance rate of 1800 patients per month in total at the Khutsong PHC facility while the Heidelberg PHC facility attended to approximately 1000 patients per month (as per register records at the clinics). These are the total attendance figures at each facility. The target sample size for Khutsong PHC was calculated to a minimum of 300 patients per week while Heidelberg PHC required a minimum of 250 patients per week. This sample size was calculated using the assumed prevalence of 50% (from pilot surveillance study) and power (95%) to detect differences over time of 5-10% (at 95% confidence intervals).

2.3 INFORMED CONSENT

Informed consent was done in a 3-stage process. Firstly, all patients were addressed in the waiting room by the clinic nurse or lay counsellor at each facility informing them of the presence of the research team and the aims and objectives of the study.

Secondly, all patients who attended for curative care received a subject information sheet (Appendix A1 and 2). The information sheet was translated into three languages; viz.

English, Tswana and Zulu, and patients were allowed to choose the language they preferred. The patient was then seen by a lay counsellor who further explained the procedures, aims and objectives involved in the study and the issues of consent (Appendix B 1 and 2). Lastly, those that were interested in being part of the study and provided signed informed consent then underwent a short interview, were provided with Voluntary Counselling and Testing (VCT) and were shown to a separate room for an oral examination and saliva collection for HIV testing. Those participants who were under the age of 18 years required consent from their parents and/or guardians. The oral health examination results were collected using an examination form (Appendix C).

2.4 MEASUREMENT

The measurement procedure consisted of two stages. The first stage comprised the clinical oral examination of the patient while the second consisted of the saliva test to determine the patients' HIV status.

The oral clinical examination was done in a well-lit room (overhead light and sunlight) with the patient seated with his/her head tilted slightly backwards to ensure adequate visibility. The examination kit consisted of a mirror and gauze.

Infection control measures were adequately maintained by placing used instruments back into their individual packs after use and by the regular changing of gloves and facial masks after every patient. The used examination packs were placed in larger containers for transport back to the dental faculty where the instruments were then autoclaved. All of the used gauze, gloves, gowns and masks were disposed in medical waste bags.

2.4.1. Calibration of examiners

All clinical oral examinations were performed by two calibrated dentists and clinical diagnosis of oral lesions was determined by consensus. The dentists attended an international workshop, "Calibration of Oral Lesions in HIV Disease Workshop", that was held at the University of the Witwatersrand on the 11th and 12th of January 2005. This workshop, which was facilitated by Professor Challacombe, the chairman of the International Steering Committee on Oral Health and Disease in AIDS, ensured that the examiners were calibrated in diagnosing oral lesions associated with HIV at an international level.

The examiners were unaware of the patients' HIV status (blinded) since the HIV results were only confirmed twenty minutes after the oral examination was complete. This was

due to the duration of time required to read the results of a patient's HIV test (as per manufacturer's instructions) and hence determine his/her status.

2.4.2. Group I oral Lesions

The Group I oral lesions were diagnosed using the EC-Clearinghouse criteria (EC-Clearinghouse, 1993). The diagnoses from the oral examination were recorded on an oral examination form (Appendix C). The presumptive criteria that were used in diagnosing the oral lesions strongly associated with HIV (Group I lesions) were:

1. Candidiasis

A. Erythematous Candidiasis- red area without removable white spots or plaques. It is usually located on the palate and dorsum of the tongue but occasionally on the buccal mucosa.

B. Pseudomembranous Candidiasis- white or yellow spots or plaques which may be located in any part of the oral cavity and can be wiped off.

C. Angular Cheilitis- characterised by soreness, erythema and fissuring unilaterally or bilaterally at the angles of the mouth.

2. Hairy leukoplakia

A bilateral whitish-grey lesion on the lateral margins of the tongue. They are not removable and exhibit vertical corrugations. Lesions may extend onto the ventral surface of the tongue, when they are usually flat, and the dorsal surface, when they are usually patchy. In addition, lesions may occur on the buccal mucosa.

3. Kaposi's sarcoma-

One or more erythematous, slightly bluish or violaceous macules or swellings with or without ulceration. Predominantly seen on the palate or gingival.

4. Periodontal disease

Linear gingival erythema- any gingival discolouration which presents as a distinct fiery band along the margin over more than two teeth. No ulceration is present and there is no evidence of pocketing or attachment loss. The amount of erythema is disproportionately intense for the amount of plaque seen.

Necrotising ulcerative gingivitis- localized or generalised destruction of the interdental papillae. In the acute stage of the process ulceration, necrosis and sloughing may be seen.

Necrotising ulcerative periodontitis- periodontitis characterized by soft tissue loss as a result of ulceration or necrosis. Exposure, destruction or sequestration of bone may be seen. Pain may be a prominent feature.

5. **Non-Hodgkin's lymphoma**

A firm elastic, often somewhat reddish or purplish swelling, with or without ulceration. The gingiva and the palatal mucosa are sites of predilection.

2.4.3 The saliva test

The second stage of the examination involved taking a saliva specimen using the saliva kit. One of the two examiners took a saliva sample using the Oraquick Rapid HIV ½ Antibody Test kit ®. This test has been used for both surveillance and screening procedures internationally (Parry et al, 1987; Major et al, 1991). The saliva test is completely non-invasive and has no side effects (e.g. pain, bleeding trauma etc) for the patient. The procedure that was used to **collect the saliva specimen** was as indicated by the manufacturer (Appendix D) as follows:

1. Open foil pouch containing the test device and developer vial. Uncap the vial and place into stand holder
2. Remove the test device without touching the collection pad.
3. Swab the collection pad around the outer gums by gently wiping the porous flat pad across the upper and lower gums one time around.
4. Place the pad end of the collection device into the vial. Start the timer and ensure the window is facing forward for ease of reading.
5. Read results in 20 to 40 minutes.

Interpretation of the results

Non-reactive (HIV negative)

Only the control line appears. The line appears adjacent to the “C” triangle. This shows an absence of antibodies to the HI virus (Figure 2).

Reactive (HIV positive)

Two lines appear adjacent to the “T” and “C” triangles. This shows the presence of anti-HIV antibodies (Figure 2).

Invalid

No line appears in the area adjacent to the “C” triangle and the test must be redone.

Figure 2. Interpretation of the saliva test. The dipstick on the left is non reactive while the one on the right is reactive.



The results were read (between 20 to 40 minutes) and confirmed by consensus between the 2 examiners. The result was then entered onto the data capturing sheet (Appendix C). Both the specimen and data capturing sheet was labelled with the same bar code and no names were recorded thus protecting the identity of the patient.

Patients who wanted to know their HIV status were referred to the Voluntary Counselling and Testing (VCT) nurse who then performed the routine HIV test for them. Since there were no names recorded, all results were anonymous, unlinked and confidential.

2.5 TESTS USED TO DETERMINE THE PREDICTIVE VALUE OF ORAL LESIONS

The positive (PPV) and negative (NPV) predictive value, sensitivity, specificity, odds ratio and likelihood ratio tests were used to determine the reliability of oral lesions in predicting the HIV status. These tests were calculated using the information in the table below (Table 4) and the subsequent formulae (Katzenellenbogen, Joubert & Abdool Karim, 1997):

Table 4. Formulae to calculate the epidemiological tests

	HIV positive	HIV negative	Total
Oral lesion present	A	B	A+B
Oral lesion absent	C	D	C+D
Total	A+C	B+D	A+B+C+D

Sensitivity

It is defined as the percentage of persons who test positive for HIV and who present with oral lesions. As the sensitivity gets closer to 100%, it means that patients who are HIV positive are more likely to present with the lesion. The sensitivity was calculated as follows:

$$\text{Sensitivity} = \frac{A \times 100}{A+C}$$

Specificity

The specificity is defined as the percentage of persons who test negative for HIV and do not present with oral lesions. As the specificity gets closer to 100%, it indicates that patients without the specific oral lesions are less likely to be HIV positive. All specificity values were calculated as follows:

$$\text{Specificity} = \frac{D \times 100}{B+D}$$

Positive Predictive Value (PPV) of oral lesions

The PPV can be defined as the percentage of persons who present with oral lesions and who actually test positive for HIV. A PPV close to 100% for any one or more oral lesion will indicate that if patients present with that lesion, they are likely to be HIV positive. All PPV values were calculated using the formula below:

$$\text{PPV} = \frac{A \times 100}{A+B}$$

Negative Predictive Value (NPV)

The NPV can be defined as the percentage of persons who do not present with oral lesions and do not test positive for HIV. A NPV close to 100% for any one or more oral lesion will indicate that if patients do not have the lesion, they are most likely going to test negative for the disease (HIV)

All NPV values were calculated using the formula below:

$$\text{NPV} = \frac{D \times 100}{C+D}$$

Likelihood Ratio (LR)

The LR is defined as the probability of a particular test for a person with the disease divided by the probability of that test for a person without the disease. If the LR value is high, it is more than likely that a person having an oral lesion would test positive for HIV.

The formula is
$$LR = \frac{\text{Sensitivity}}{1 - \text{Specificity}}$$

Odds Ratio (OR)

The OR is defined as the chance of testing positive for HIV if a person is diagnosed with a specific lesion compared to a person who tests positive for HIV and does not present with that lesion. It is calculated as follows:

$$\frac{AD}{BC}$$

It is the only epidemiological test from those described above that includes a Confidence Interval (CI) range of 95% and has a p-value which is used to calculate the statistical significance.

2.6 ETHICAL CLEARANCE

Ethical clearance was obtained from the Wits Ethical Committee- M050302 (Appendix E).

2.7 DATA COLLECTION

The data was captured by the examiners and collected on a daily basis. Once all the data was collected, the data was captured over a one month period onto the Epi-Info version 3.2 software package.

2.8 DATA ANALYSIS AND STATISTICAL TESTS USED

All analysis was done using the Epi-info version 3.2 software package. Descriptive statistics, logistic regression analysis and sensitivity, specificity, predictive values and likelihood ratios of the HIV prevalence and group 1 oral lesions were performed. The odds ratios and likelihood ratios were reported using a CI of 95% for the association between the oral lesions and the HIV status for specific oral lesions. The Mantel-Haenszel P values were utilised and a 2-tailed Fisher exact test P value was used when the prevalence of oral lesions in any one category was zero. The significance value was set at $P < 0.05$.

2.9 LIMITATIONS

Due to financial and time constraints, only one week of screening per PHC facility could be performed. As a result of the short duration, these results must be interpreted with caution and longer follow up studies done to determine trends.

Due to ethical and financial reasons, the examiners could not obtain the sample patient's CD4 counts. If the CD4 counts were available, it could be linked to the type and prevalence of the group I oral lesions. This then could be compared to other similar studies.

CHAPTER 3

3.0 RESPONSE RATE

All 657 patients who had attended at the two clinics over the two week study period for curative care agreed to participate in the study which gave a 100% response rate.

At Khutsong PHC facility, a total of 403 (61%) patients were examined while 254 (39%) patients were examined in the Heidelberg PHC facility. The daily attendances and variations are shown in Table 5. Heidelberg PHC was busiest on Wednesday and Thursday while Khutsong PHC was busiest on Monday and Tuesday. Both clinics were relatively quiet on Saturdays.

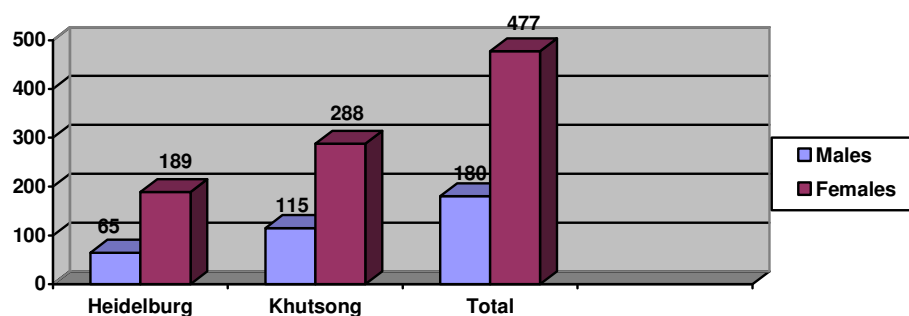
Table 5. Daily attendances at the two PHC facilities.

	Heidelberg PHC		Khutsong PHC	
Day	n=254	%	n=403	%
Mon	48	18.9	75	19
Tue	46	18.1	92	23
Wed	60	23.6	66	17
Thur	52	20.5	48	12
Fri	30	11.8	69	17
Sat	18	7.1	53	13
Total	254	100	403	100

3.1 GENDER

There were 477 (72.6%) female patients and 180 (27.4%) males. There were significantly more females than males ($p < 0.05$, CI 95%). Figure 3 shows the distribution of respondents as per clinic and gender. Both facilities had similar attendance patterns in terms of the gender distribution with more than 70% of the total number of patients being female.

Figure 3. Gender distribution according to the PHC facility, n=657.

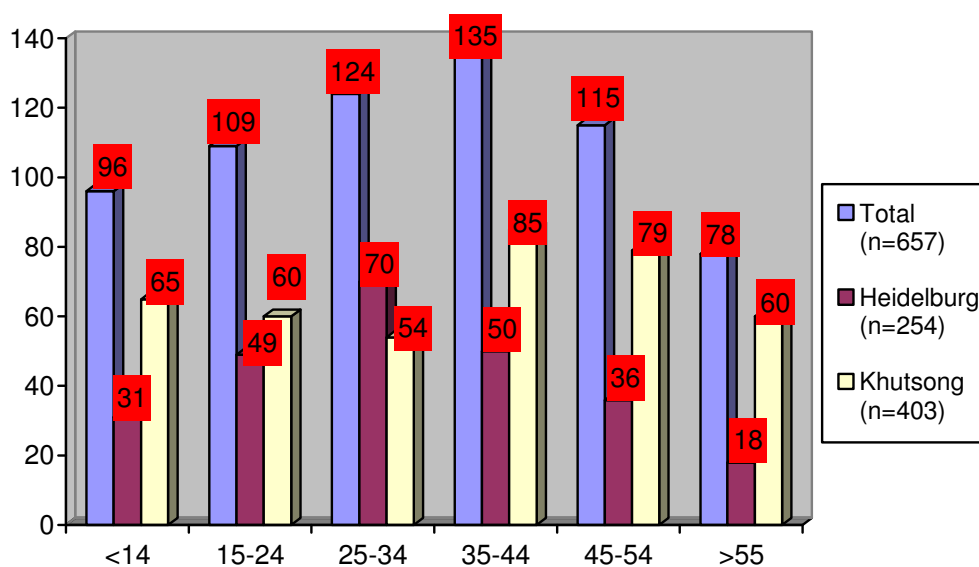


3.2 AGE

The combined mean age was 33.95 years with a standard deviation of 17.82. There was a wide age range (1-94 years) with a median of 34 years and a mode of 28 years (n=657).

This can be seen in Figure 4. More than half of all patients (56%) were between the ages of 15 and 44 years old. There was no significant difference ($p>0.05$) between the ages of patients attending the two PHC facilities.

Figure 4. The total number of patients per age group per facility (N=657)



3.3 HIV STATUS

There was a total of 227 (34.6%) patients who tested positive for the HI virus with a significant number ($p=0.015$) of respondents being female (78%). Table 6 displays the HIV status of all respondents in relation to their gender. Although Heidelberg PHC facility had a slightly higher prevalence rate of (36%) versus Khutsongs' (34%), there was no significant difference ($p=0.58$) between the two PHC facilities.

3.3.1 Gender

In Table 6 the overall HIV prevalence rates for males was 27% (49 out of 180) compared to the 37% (178 out of 477) amongst females. There was no significant association between the HIV status of males and females amongst the respective gender groups ($p=0.32$).

However, of the total 227 patients who tested positive for HIV, 49 (22%) were males and 178 (78%) were females. This difference between male and female subjects was statistically significant ($p=0.015$) and showed that the prevalence of HIV amongst females was considerably higher compared to males.

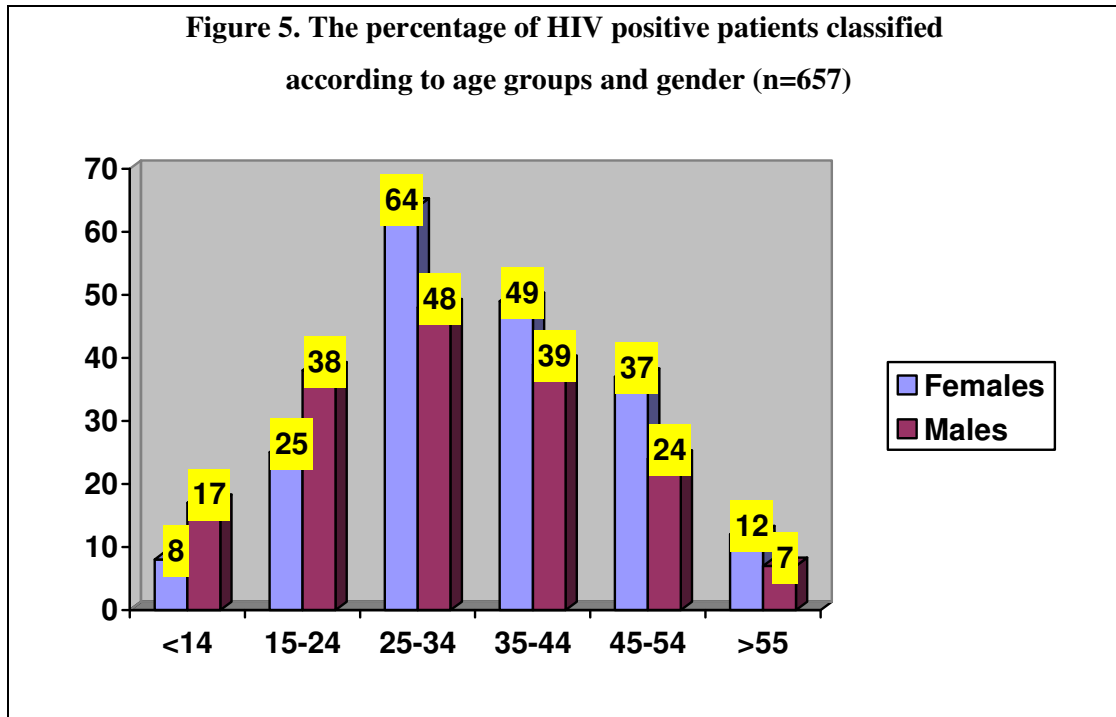
Table 6. Distribution of patients according to their gender and HIV status.

Gender	HIV positive [N=227(%)]	HIV negative [N=430 (%)]	
Males	49 (22)	131(30)	180
Females	178 (78)	299 (70)	477
Total	227 (100)	430 (100)	657

3.3.2 Age and gender of HIV positive patients

Of the total 657 patients, the majority of HIV positive patients were between 25 and 34 years old (Figure 5). In this specific age range, almost two thirds of all females (64%) and almost half of all males (48%) tested positive for HIV. this was followed by the 35 to 44 year age group in which 49% of all females and 39% of males tested positive for HIV. There was a statistical correlation between four of the age groups and the HIV status. The 15 to 24, 25 to 34, 35 to 44 and 45 to 54 year age groups all yielded a statistically significant correlation with a positive HIV status ($p<0.05$, $r^2=0.14$). There were more males who tested positive for HIV than females in the under 25 year age groups. This was

reversed for the rest of the age groups in which more females tested positive compared to males. This can be seen in Figure 5.



3.4 TYPES OF ORAL LESIONS DIAGNOSED

The types of oral lesions that were diagnosed in the total sample of patients are shown in Table 7. This table classified the lesions according to the patients' HIV status and the facility that the patient attended.

A total of 187 (28%) patients (both HIV negative and positive) presented with Oral Candidiasis (OC). A considerable number of those who tested positive for HIV (46%) presented with some form of OC. Both facilities had high prevalence rates of OC amongst the HIV positive group of patients (Heidelberg (40%) and Khutsong (50%)).

The most common type of OC diagnosed was Pseudomembranous Candidiasis (PC). This was seen in 37% of those who tested HIV positive. The other prevalent lesions that were diagnosed in those who tested HIV positive were Erythematous Candidiasis (EC) (25%), Oral Hairy Leukoplakia (OHL) (19%) and Angular Cheilitis (AC) (6%). It was noteworthy that both clinics had similar prevalence rates of oral lesions amongst the HIV positive group. There was no significant difference between the prevalence of oral lesions between the two clinics ($p=0.89$).

Table 7. The prevalence of Group I Oral lesions in the study population (N=657).

		No and (%) present in HIV +			No and (%) present in HIV -			Total (%)
	Types of lesions	Heidelberg	Khutsong	Total	Heidelberg	Khutsong	Total	
1	Oral candidiasis (all forms)	36 (40)	68 (50)	104 (46)	36 (22)	47 (18)	83 (19)	187 (28)
2	Pseudomembranous Candida (PC)	32 (35)	52 (38)	84 (37)	31 (19)	40 (15)	71 (17)	155 (24)
3	Erythematous Candida (EC)	25 (27)	31 (23)	56 (25)	9 (6)	12 (4)	21 (5)	77 (12)
4	Angular Cheilitis (AC)	5 (6)	8 (6)	13 (6)	0	2 (1)	2 (0.5)	15 (2)
5	Combined Candida (PC+EC+AC)	3 (3)	3 (2)	6 (3)	0	0	0	6 (1)
6	Oral Hairy Leukoplakia (OHL)	15 (16)	28 (21)	43 (19)	2 (1)	1 (0.4)	3 (0.7)	46 (7)
7	Kaposi's sarcoma (KS)	0	1 (1)	1 (0.4)	0	0	0	1 (0.2)
8	Necrotizing Ulcerative Gingivitis (NUG)	0	1 (1)	1 (0.4)	0	0	0	1 (0.2)
9	Necrotizing Ulcerative Periodontitis (NUP)	0	1 (1)	1 (0.4)	0	0	0	1 (0.2)
10	Non Hodgkin's Lymphoma (NHL)	0	0	0	0	0	0	0
11	Linear Gingival Erythema (LGE)	0	0	0	0	0	0	0

3.5 The prevalence of oral lesions in relation to the patients' HIV status

The number of oral lesions and its relationship to the HIV status is shown in Table 8. Of the 31% (206) who presented with 1 or more oral lesions, more than half (53%, n=121) were HIV positive. From the total number of patients who were diagnosed with 2 or more oral lesions, 83% (59 out of 71) tested positive for HIV. These results showed that patients who tested HIV negative were significantly unlikely to present with more than 2 oral lesions ($p=0.001$, CI=95%, $\chi^2=106.1$).

Table 8. The prevalence of oral lesions in relation to the patients' HIV status

Presence of oral lesions	HIV +ve	HIV -ve	Total N (%)
Patients with no lesions present	106	345	451 (69)
Patients with 1 or more lesions present	121	85	206 (31)
Patients with 2 or more lesions present	59	12	71 (100)

3.6 Strength of the association between oral lesions and HIV status

The prevalence of the group I oral lesions were analysed in relation to the patients' HIV status using a logistic regression analysis. Table 9 shows the results that were obtained. All p-values below 0.05 were statistically significant, the Confidence Interval (CI) was set at 95% and the Correlation Coefficient (CC) was 0.18.

Each of the lesions was tested individually using a logistic regression analysis against a constant -the HIV status. Four of the Group I oral lesions, pseudomembranous candidiasis (PC), erythematous candidiasis (EC), angular cheilitis (AC) and oral hairy leukoplakia (OHL), were significantly associated ($p<0.05$) with a positive HIV status. That meant that patients who presented with these lesions were significantly more likely to test positive for HIV compared to patients who did not have them.

Linear Gingival Erythema, Hodgkin's Lymphoma and Hyperplastic Candidiasis were excluded as none of these lesions were seen in the sample group.

Further analysis were limited to the 4 oral lesions (**PC, EC, AC and OHL**) that were significantly associated ($p<0.05$) with the presence of HIV. The remaining oral lesions were excluded from the sensitivity, specificity, likelihood ratio, odds ratio and negative and positive predictive value tests as they were either not diagnosed in any of the patients or were not significantly associated with the presence of HIV. If statistical tests were

performed on these lesions, it would not have showed any significant results nor be able to correlate their presence with the positive diagnosis of HIV.

Table 9. The association between the HIV status and the presence of oral lesions using logistic regression

	Variable	Odds ratio	Confidence Interval (95%)	P-Value for logistic regression
1	NUG (Yes/No)	∞	-	0.948
2	NUP (Yes/No)	∞	-	0.945
3	AC (Yes/No)	7.1	1.5-34.6	0.015
4	PC (Yes/No)	2.0	1.3-3.0	0.002
5	EC (Yes/No)	3.3	1.8-6.1	0.000
6	OHL (Yes/No)	19.5	5.8-65.2	0.000
7	KS (Yes/No)	∞	-	0.968
	<i>CONSTANT (HIV STATUS)</i>			

LEGEND:

NUG=Necrotising Ulcerative Gingivitis

NUP=Necrotising Ulcerative Periodontitis

OHL=Oral Hairy Leukoplakia

PC=Pseudomembranous Candidiasis

KS=Kaposi's sarcoma

EC=Erythematous Candidiasis

AC=Angular Cheilitis

3.6.1. Positive Predictive Values (PPV), Negative Predictive Values (NPV) Sensitivity (SEN), Specificity (SPEC), Odds Ratio (OR) and Likelihood Ratios (LR)

Table 10 shows the results of the various statistical tests that were performed on the 4 oral lesions that were statistically significant ($p < 0.05$) in predicting the HIV status of individuals. In general, the PPVs, specificities and LR were high for specific single (AC and OHL) and multiple (AC+PC+OHL, PC+OHL and EC+PC+AC) oral lesions. The PPVs ranged between 54% and 100%. Single lesions had PPVs of up to 93 (OHL) compared to multiple lesions which had a PPV of 100 (EC+PC+AC, EC+PC+OHL and AC+EC).

The specificity values were also high and ranged between 84% (PC) and 100% (AC, OHL, EC+OHL). This was expected since the sensitivity and specificity values are reciprocal of each other. In other words, if the sensitivity was high the specificity should be low and vice

versa. Since these tests are reciprocal and depend almost entirely on the prevalence of the condition within the population, they are not considered to be as robust and very informative.

Alternatively, the likelihood ratio (LR) is not totally dependent on the prevalence and has no reciprocal test and is therefore considered much more accurate, reliable and robust. All but one single oral lesion, OHL, had relatively low LR values (11 and below). Oral Hairy Leukoplakia had a LR value of 19 which was considerably higher than the others. The likelihood ratios for some of the combinations of multiple lesions (PC+OHL; EC+PC+OHL and AC+EC) were extremely high and indicated that the presence of these lesions were diagnostic for HIV. The combination of all four lesions however yielded a very low sensitivity even though all of the patients who presented with all four lesions tested positive for HIV. This was due to the low prevalence of patients presenting with a combination of four oral lesions. The LR was also low due to the sensitivity being very low and the specificity being very high. This is a limitation of the LR test in that if the prevalence of a lesion/s is extremely low, the LR loses its robustness and accuracy.

The odds ratios (OR) s were high for all single lesions and ranged between 3.0 for PC to 33.3 for OHL. The multiple lesions also yielded high results with the combination of PC and OHL yielding an OR of 53.1. Of the multiple lesions, six of them yielded undefined results since all of the patients who were diagnosed with these lesions tested positive for HIV. This was one of the weaknesses of the OR test and proved that when the lesion is non-existent within the cohort, the OR should not be used.

The confidence intervals (CI) for most of the lesions (both single and in multiple combinations) were large and this meant that these results must be interpreted with caution. However, it was noteworthy that the OR and LR demonstrated similar results and therefore either of these tests could be used to correlate the presence of the lesions and the patients' HIV status.

In general, the sensitivity and NPVs remained low compared to the PPVs, specificity, OR s and LRs.

Table 10. Statistical analysis performed on specific oral lesions

	Lesion	PPV (%)	NPV (%)	SEN (%)	SPEC (%)	OR (95% CI)	P Value	LR
1	PC	54	72	37	83.5	3.0 (2.1-4.3)	<0.05	2.24
2	EC	73	71	25	95	6.4 (3.7-10.9)	<0.05	5
3	AC	87	67	5.7	99.5	13.0 (2.9-58.1)	<0.05	11.4
4	OHL	93	70	19	99	33.3 (10.2-108.6)	<0.05	19
5	EC+PC	73	68	12	97.7	5.9 (2.7-13.3)	<0.05	5.4
6	EC+OHL	100	68	10	99.9	∞	-	10
7	AC+OHL	100	66	1.3	99.9	∞	-	13
8	AC+PC	90	66	4	99.8	17.7 (2.3-375.7)	<0.05	20
9	AC+EC	100	66	3.5	99.9	∞	-	35
10	PC+OHL	96	68	11	99.8	53.1 (7.6-1060.6)	<0.05	55
11	EC+PC+AC	100	66	2.6	99.9	∞	-	26
12	EC+PC+OHL	100	67	4.8	99.9	∞	-	48
13	EC+PC+AC+OHL	100	66	0.9	99.9	∞	-	9

LEGEND:

PPV=Positive Predictive Value	NPV=Negatives Predictive Value	SEN=Sensitivity	SPEC=Specificity	OR=Odds ratio
LR=Likelihood Ratio	AC=Angular Cheilitis	PC= Pseudomembranous Candidiasis	EC=Erythematous Candidiasis	OHL=Oral Hairy Leukoplakia

CHAPTER 4

4.0 RESPONSE RATE

This study yielded a 100% response rate which was unique for an HIV related study that deals with prevalence of HIV status. This could be attributed to a number of factors including; the efforts of the counsellors, the fact that these counsellors had gained/earned the trust from the patients and the community, the 'buy in' or cooperation from the management at these facilities, the strict anonymity and unlinked data that was coded and collected and the use of the user friendly, non invasive saliva tests that were used to test the HIV status and the clear explanation that was given to the patients.

4.1 GENDER

More females had attended the two PHC facilities than males. This was similar to other studies which examined attendances at health facilities (South African Demographic Health Survey (SADHS) 1998; Gift, 1997). The SADHS (1998) showed that more than two thirds of attendees at public health facilities (both Primary Health Care facilities and hospitals combined) were females compared to males. Hence the attendance patterns at the two Primary Health Care facilities in this study were in keeping with both international and SA patterns.

4.2 HIV PREVALENCE

There were a total of 227 (34.6%) patients who tested HIV positive at both of the facilities. This high prevalence rate was even higher than the 30.2% reported in the most recent National Antenatal Sero-prevalence (ANC) Survey of 2005 (Department of Health, 2006). The difference between the national prevalence rate and the prevalence that was recorded at these 2 PHC facilities could be attributed to several factors:

- The national figures are an estimate of the general population derived from antenatal clinic data. The sample in this PHC study comprised patients attending for acute illnesses and was not extrapolated for any specific community or population and therefore was expectedly higher than the national figures.

- The national figures are obtained from ante-natal facilities throughout the country while the PHC study was focussed on 2 Gauteng PHC facilities only. Gauteng does have a relatively high HIV prevalence rate (Department of Health, 2006) compared to other provinces and this may have attributed to the higher rates that were reported at these two PHC facilities.

Nevertheless, the results from the PHC study are similar to the national figures reported by the ANC survey of 2005 (Department of Health, 2006).

An unexpected result was the higher prevalence rate, although not statistically significant ($p > 0.05$), that was recorded at Heidelberg (36%) compared to the Khutsong (34%) PHC facility. Khutsong, being a mining town was expected to have a higher HIV prevalence rate compared to Heidelberg.

This study has confirmed the results of other similar South African studies (SADHS, 1998 and Arendorf, 1998) which have reported that most of the HIV positive patients were female (78%) and between 25 and 44 years old (64%). The large number of females who tested HIV positive amongst all female attendees, almost 80%, was substantially higher than the results reported by the UNAIDS (UNAIDS, 2005) update (57%). However, the UNAIDS report combined the sub-Saharan Africa countries and this may have contributed to the lower prevalence of HIV amongst females.

The UNAIDS report also showed that the highest prevalence rate (almost 40%) of HIV occurred in the 25 to 29 year old age group. This was similar to the results that were obtained from the PHC study in which the highest prevalence rate (36%) was within the 25 and 34 year age group. The second and third highest prevalence rates were also similar in this study compared to the UNAIDS report of 2005.

The high HIV prevalence rate (35%) that was recorded at the two primary health care facilities and the young age groups that were most severely affected indicate that the treatment and medication requirements (Antiretroviral therapy as well as antibiotics for opportunistic infections) may increase and this will increase the burden on the health services. Thus good planning and adequate allocation of resources will need to be done in order to address these problems. The Gauteng Department of Health will need to examine

staffing ratios and predict the future increased demands. The burden that HIV/AIDS has placed and will be placing in the future on the health services needs to be critically examined and appropriate measures need to be implemented in order to deal with these demands.

The Actuarial Society of South Africa released a document in 2004 projecting the prevalence of HIV/AIDS and its impact in South Africa (Darrington, Bradshaw, Johnston and Budlender, 2004) and predicted that the prevalence rate would be approximately 29.2% of the total population. The results that were obtained from the PHC facilities seem to support this scenario.

4.3 PREVALENCE OF GROUP I ORAL LESIONS

Oral candidiasis (OC) was the most common oral lesion diagnosed (46%) in HIV positive patients. Pseudomembranous candidiasis (PC) was the most prevalent form of OC (37%), followed by erythematous candidiasis (EC) (25%) and angular cheilitis (AC) (6%). The remaining number of patients were diagnosed with more than one type of OC. The prevalence of OC varies in different studies and ranged between 15% to more than 80% (Holmes & Stephen, 2002). The wide ranging results could be explained by the range of diagnostic techniques that were used and that many studies had not differentiated between the clinical forms of the disease, making direct comparisons difficult. Comparisons were further complicated by differences in study groups, HIV disease stage, ethnicity, socio-economic status, diet and access to health care (Hodgson & Rachanis, 2002).

Studies in South Africa by Arendorf, et al., (1998) have shown prevalence rates for PC and EC to be around 16%. However, the prevalence rate of OC in general was reported to be at 38%, which was lower than the 46% that this study has shown. The sample group in the Arendorf study was limited to HIV positive dental patients only and this could explain the variations in the prevalence rates. The HIV positive patients who presented at the PHC facilities were generally ill and therefore probably had lower CD4 counts compared to the dental patients. This could explain the higher prevalence rates of OC amongst the PHC attendees.

The prevalence of AC (6%) amongst HIV positive patients concurred with two South African studies, both done by Arendorf, et al., in 1997 and 1998. Arendorf and his colleagues reported a prevalence of 6% in 1998 and 7% in 1997.

The result amongst PHC attendees was also similar to other studies; Ranganathan et al (2000) who reported an 8% prevalence amongst HIV positive patients presenting at a government organisation in India.

This variation of prevalence rates may be attributed to diagnostic criteria, the age group of the cohort and the different staging (CD4 counts) of volunteers in the study sample.

The prevalence of OHL in this study (22%) was similar to Arendorf et al (1997 and 1998) who reported 20% and 19% prevalence respectively. However, their results and those found in this study were much higher compared to other studies done in Africa in which the prevalence varied between 0% and 14% (Patton, et al., 2002). OHL prevalence values described by Holmes and Stephen (2002) ranged between 0% amongst Tanzanians to 20% in South Africans.

The wide variation in the prevalence of OHL could be due to the frequent coexistence of oral candidiasis, often presenting as a white lesion, which can be mistaken for, or mask OHL. Clinical judgement may be unreliable because it is difficult to distinguish OHL from candidiasis. It must be noted that the clinicians involved in this study underwent an international calibration workshop by Professor Challacombe at the University of the Witwatersrand. This calibration exercise and the confirmed diagnosis by consensus between the two clinicians have ensured that the diagnosis is accurate and in accordance with the international EC-Clearing house criteria (2003). The appearance of one or both oral lesions either signals that a relatively advanced stage of immunosuppression has been reached or heralds an impending rapid AIDS progression (Teo, 2002).

KS is generally not a common finding and was only seen in one (0.5%) individual. KS was either not seen or had a low prevalence of 2% in the early South African studies Arendorf 1997, 1998). There was no KS diagnosed in the Thai and Indian studies (Holmes & Stephen, 2002). Since KS has been found to be more common amongst HIV positive homosexual men (Ramirez-Amador et al, 1998), and given the profile of HIV positive patients in South Africa; it is not unusual to find such a low prevalence of KS in the sample of patients. There has also been a declining prevalence trend in KS associated with HIV as a result of active antiretroviral therapy, which effectively reverses the otherwise inexorable destruction of the immune system by HIV (Teo, 2002). Although the number of patients in this sample who were on antiretroviral treatment was not determined, it is possible that this factor could have contributed to the lowered prevalence of KS. The presence of KS was

not found to be statistically significant ($p>0.05$) in relation to the persons HIV status. In general, KS is usually associated with late stages of HIV ($CD4<200$ cells/mm³) and full blown AIDS (Teo, 2002). In the later stages of HIV/AIDS the patient is often admitted to a hospital or specialised health care facility and unlikely to attend a PHC facility.

In the current study, unlike many others (Patton, et al., 2002), no patients were diagnosed with Linear Gingival Erythema (LGE). Only one case of Necrotising Ulcerative Gingivitis (NUG) and one case of Necrotising Ulcerative Periodontitis (NUP) were diagnosed and therefore no further analysis was done.

LGE was shown to be present in up to 16% of patients in developing nations and up to 22% in the USA in particular (Patton, et al., 2002). In the studies by Arendorf no LGE were reported. It is possible that due to the nature of LGE, it is often mistaken for gingivitis in patients with poor oral hygiene and this could account for the low prevalence rates that were reported.

Necrotising ulcerative gingivitis and necrotising ulcerative periodontitis were reported to be present in up to 16% and 17% of patients in Africa respectively, and a 23% prevalence of necrotising ulcerative periodontitis has been reported in India (Patton, et al., 2002). The patients that were examined at the PHC facilities reported much lower prevalence rates which was consistent with the results of another study done by Shangase et al (2004) in Garankuwa, South Africa. This Garankuwa study showed a prevalence of 0.7% amongst 12159 out patients that were treated at the MEDUNSA Oral Health Centre.

It must be noted that for clinicians to be able to accurately diagnose these group I oral lesions, some form of calibration exercise must be undertaken. This would ensure that the diagnosis is standardised and the results can be compared to other studies. This calibration would require sending oral health staff and PHC nurses on courses and multiple workshops which would prove to be costly, time consuming and creating a staff shortage at these facilities. These factors need to be borne in mind when deciding on training or upgrading current staff in the diagnosis of oral lesions. It is therefore suggested that PHC nurses and medical doctors receive training on the diagnosis of oral lesions during their training so that once qualified they would be able to apply this knowledge in diagnosing oral lesions.

4.4. Predictive value of single Group I oral lesions

4.4.1. Sensitivity

The sensitivity values in the present study were probably low because the prevalence of oral lesions amongst the total sample (31%) of patients was relatively low. Since the sensitivity is dependent on the prevalence of the condition (lesions), the sensitivity test is a less reliable diagnostic tool for diagnosing HIV using oral lesions.

For the three types of candidiasis [erythematous (EC), pseudomembranous (PC) and angular cheilitis (AC)], the sensitivity values were relatively low (25%, 37% and 5.7% respectively). This was not surprising as the prevalence of these lesions was low. Erythematous (EC) and Pseudomembranous (PC) candidiasis can also occur in patients without HIV/AIDS since many patients with immune suppression present with oral candidal lesions. Immune suppression can occur in a number of diseases such as tuberculosis, cancer, pneumonia (not uncommon in the South African population), transplant patients etc and therefore EC and PC alone or combined was not a strong indicator for HIV status.

The sensitivity values for oral hairy leukoplakia (OHL) (19%) and for the presence of multiple lesions (1-11%) was considerably lower and could be attributed to its low prevalence rate amongst the total sample.

4.4.2. Specificity

The specificity for EC, PC and AC was 95%, 84% and 99.5% respectively. The specificity for a combination of all types of OC yielded a value of 99.9%. These high values indicated that patients who tested negative for HIV were almost certain not to have EC, AC or a combination of the three types of OC.

The OHL specificity value was high (99%) and meant that patients who tested negative for HIV would almost never be diagnosed with OHL.

4.4.3. Positive Predictive Values (PPVs)

The PPV for PC was relatively low (54%) compared to that of EC (73%) and AC (87%). This meant that patients who presented with EC or AC were more likely to test positive for HIV compared to patients with PC.

The PPV for AC was one of the highest single lesion results (87%). It showed that 87% of patients who presented with AC tested positively for HIV.

OHL in this study had the highest PPV of 93%. This meant that almost everyone who was diagnosed with OHL tested positive for HIV. The PPV was much higher than in studies done by Patton (2000), Begg, et al., (1996) and Glick, et al., (1994) who reported PPVs of 66.3%, 55.6% and 70.1% respectively. This difference could be attributed to the fact that all of the later three studies were done on known HIV positive patients with relatively low CD4 counts.

The PPVs for multiple lesions were much higher than those for single lesions and ranged between 96% and 100%. The reason for the increasing PPVs for multiple lesions compared to single lesions was due to the fact that those with increasing numbers of oral lesions were more likely to test positive for HIV compared to those with fewer lesions. All of those who had 3 or more lesions tested positive for HIV and therefore the PPV was 100%. Since the PPV test is measured as the number of people with oral lesions and HIV in relation to patients with oral lesions and who test negative for HIV, oral lesions that can occur in HIV negative patients would yield low PPVs. Therefore, lesions such as PC and EC, which often occur in HIV negative and positive individuals yielded lower PPVs. Alternatively, lesions such as AC and OHL, which are do not occur routinely in HIV negative patients, yielded much higher PPVs.

4.4.4. Negative Predictive Values (NPVs)

The NPVs for EC, PC and AC were 71%, 72% and 67% respectively. These relatively low values indicated that patients who did not present with oral lesions were more likely to test negative for HIV compared to patients who had these lesions. The NPVs for multiple lesions were around the 60% mark and indicated that patients who presented with single lesions were less likely to test positive for HIV than those with multiple lesions.

The NPV has not been often used as a test determining the strength of a criteria/ion in the diagnosing of HIV/AIDS. The reason for this is that the NPV is not robust and accurate enough to be used alone, and often does not provide any new information (Greenberg, et al., 2001).

4.4.5. Likelihood Ratio (LR)

According to Greenberg, et al., (2001); a LR of 10 or more is considered a “good” diagnostic test. The strength of the LR test is its relative independence to the prevalence of

the lesion when making an association between the lesions and disease. For example if oral hairy leukoplakia (OHL) is used as a case study, the following results are obtained:

There were 46 patients who were diagnosed with OHL out of the total sample of 657. Of these 46 patients, 43 were diagnosed as HIV positive. This showed that 93% of patients with OHL were HIV positive. However, the sensitivity of OHL in this study was only 19% since the prevalence amongst the total sample was only 7%. This meant that the lesion is not sensitive enough to test for HIV even though more than 90% of patients who were diagnosed with this lesion tested positive for HIV.

The specificity for OHL was 99% and this meant that patients who tested negative were almost certain not to present with OHL. Since the specificity is a reciprocal to the sensitivity, the 2 tests are read in conjunction with each other and do not provide any new information.

The PPV was 93% and the NPV was 70%, this showed the prevalence of OHL amongst the positive patients and does not add any strength to the relationship/association between the lesion and the disease.

The LR value however, was 19. This was greater than 10 and meant that patients with OHL are almost 20 times more likely to test HIV positive than patients without this lesion and the relationship between the lesion and the disease had a strong correlation (>10).

Patients who presented with a combination of oral lesions had LR values as high as 55. The LR for PC and EC was 2.24 and 5 respectively. Both of these values were below 10 and therefore indicated that these lesions, when used on their own, were not good predictors of HIV infection. The reasons for these low values could be due to the fact that these lesions can occur in a number of other immune suppressive conditions and not merely HIV. AC had a likelihood ratio of 11.4 which was one of the highest ratios for a single lesion. This showed that patients who presented with AC were 11.4 times more likely to test HIV positive than a patient without AC. Since the LR value for AC was more than 10, AC could be considered a good diagnostic tool for the predicting of a patient's HIV status.

The published data on the criteria for the clinical diagnosis of HIV/AIDS does not use the LR test. The poor utilisation of the LR test in published data could be due to the fact that this test is relatively unknown and new (Greenberg, et al., 2001). Due to its absence in

most studies, the values that were reported in this study cannot be compared with other results.

4.4.6. The Odds Ratio (OR)

The LR for PC and EC was 3.0 and 6.38 respectively. Both of these values were relatively low with moderate confidence intervals (CI). This meant that patients who presented with either of these lesions were between 3 and 6 times more likely to test positive for HIV compared to patients without these lesions. There was a significant ($p < 0.05$) possibility that these patients would have tested positive for HIV. The other group I lesions, AC and OHL both had high OR values (13.0 and 33.3 respectively) but had very wide CIs. This meant that although patients with these lesions were likely to test positive for HIV, there were few patients who presented with these lesions. The high OR for OHL indicated that patients with OHL were 33 times more likely to test positive for HIV compared to a patient without this lesion. This was also statistically significant ($p < 0.05$). Patients who presented with AC were 13.0 times more likely to test HIV positive than a patient without AC.

In summary, the LR and OR yielded similar results although the OR provided a p value and a confidence interval range. The OR however, could not be used if one of the cells in the formulae is zero (i.e. a non existent prevalence of one or more lesions). The LR, although usable in low prevalence conditions, also yielded low values and should be interpreted with caution. The sensitivity and specificity tests were almost entirely dependent on the prevalence of the lesions and therefore proved its lack of strength and ability to correlate the presence of lesions and the HIV status.

The PPV test proved to be more accurate and robust than the sensitivity and specificity tests but if patients did not present with specific lesions these values were extremely high (100%) and also needed to be interpreted with caution. Lastly, the NPV test provided no information and should be excluded from other similar studies.

This study therefore showed that either the OR or LR should be used depending on the prevalence of the lesions within a specific setting.

4.5. Predictive value of clinical diagnosis in determining the HIV status

The World Health Organization (WHO) realized the importance of a clinical diagnosis for HIV/AIDS in countries that are poorly resourced and do not have sufficient and accurate laboratory testing facilities. As a result of this, a workshop on Acquired Immune Deficiency Syndrome (AIDS) was held in 1985 in Bangui, in the Central African Republic. At this workshop, a clinical case definition of AIDS was developed for developing countries, such as sub-Saharan Africa, where sophisticated diagnostic equipment is not widely available (Keou et al., 1992). This definition contained 4 major criteria (chronic asthenia, major weight loss, chronic fever, and chronic diarrhea) and 6 minor criteria (chronic cough, persistent lymphadenopathy, herpes zoster, recurrent herpetic infection, pruritic dermatitis, and oropharyngeal candidiasis). Kaposi's sarcoma and cryptococcal meningitis were sufficient by themselves for the diagnosis of AIDS. This definition was evaluated in 174 adult patients hospitalized at the Mama Yemo Hospital of Kinshasa, Zaire (Keou et al., 1992). Overall, the sensitivity for HIV infection was 59%, the specificity was 90%, and the positive predictive value (PPV) was 74%. Although the sensitivity values for the clinical diagnosis was higher than those from the oral lesions, the specificity and PPVs were lower. This implies that oral lesions could be used with confidence as HIV predictors, provided they are adequately diagnosed.

Another study by De Cock et al., (1988) evaluated the WHO clinical case definition in rural Zaire. The clinical case definition was evaluated against HIV antibody status in 72 patients in rural Zaire. The case definition had a sensitivity of 52%, a specificity of 78% and a positive and negative predictive value of 50% and 80% respectively. Calculation of the positive predictive value at different levels of prevalence of HIV infection suggested that the case definition operates at maximum reliability in selected high-risk groups. The authors further stressed that since these epidemiological tests are prevalence dependent, they should be used in caution when the prevalence rates are low. The oral lesions had lower sensitivity and NPVs than the case definitions but much higher specificity and PPVs. These differences could be attributed to the different prevalent rates between the case definition criteria and the presence of oral lesions. If we used a more robust test, like the LR, it would provide more accurate results and allow for a more realistic comparison between clinical case definitions and oral lesions in diagnosing the HIV statuses.

4.6. Predictive value of multiple Group I oral lesions

When the lesions were combined, the PPVs increased. All patients with more than three oral lesions yielded PPVs of 100%. This meant that patients who had more than two Group I oral lesions were 100% likely to test positive for HIV. Patients who presented with AC and OHL or EC and OHL had a PPV of 100%. This meant that patients presenting with these specific oral lesions, were almost certain of testing positive for HIV compared to a person without these specific lesions.

The LR_s also increased when lesions were combined and ranged from 10 for EC and OHL to 55 for PC+OHL. This meant that patients who presented with PC and OHL were 55 times more likely to test positive for HIV than someone without these two lesions. This further stressed the diagnostic importance of oral lesions in predicting the HIV status of a patient. Since a value of 10 for a LR is considered a “good” diagnostic tool, 55 (PC+OHL) should be considered as an excellent and reliable tool detecting possible HIV positive patients. The other high LR values for multiple lesions were; 48 (EC+PC+OHL), 35 (AC+EC) and 20 (AC+PC). All of these are higher than 10 and can be confidently used as screening tools in predicting a person's HIV status.

The odds ratios for many of the multiple lesions yielded undefined values since the denominators were zero. This was due to the fact that there were no patients with a combination of lesions and who tested negative for HIV. Hence, if there are no patients with a specific lesion the OR test cannot be the test of choice and the values of the LR should be used. The OR for PC and OHL was the highest (53.1; CI=7.6-1060.0), similar to the LR test which yielded 55. This meant that patients with PC and OHL were more than 50 times more likely to test positive for HIV compared to patients without these lesions. However, the CI for the combination of PC and OHL was the largest (7.6 to 1060.6) and although this result was statistically significant ($p < 0.05$), this result must be read with caution.

The sensitivity of multiple lesions remained low due to the low prevalence of multiple lesions amongst the HIV positive cohort. Hence, in a cohort having a low prevalence of oral lesions, the sensitivity will always remain low; this could in turn “skew” the results. Therefore, the LR should be used as it is not dependent on the prevalence and is a much more robust and accurate epidemiological testing tool.

The specificity values for multiple lesions were also high ranging between 97.7% (EC+PC) to 100% (AC+EC). Since the majority of patients did not present with multiple lesions, it was expected that the specificity values would be high (in contrast to the expected low sensitivity values). This implied that patients who did not present with these specific combinations of oral lesions were almost certain of testing negative for HIV.

Since patients who presented with 2 or 3 oral lesions had high LR values, clinicians should be alert when performing oral examinations as it should arouse suspicion and prompt the recommending of VCT for the patient. This would aid in early management and possible treatment for the patient.

4.7 ORAL LESIONS IN HIV/AIDS PATIENTS

Of all those who tested positive for HIV, more than a quarter (26%) presented with two or more lesions and more than half (53%) of the patients presented with one or more lesions. The prevalence of oral lesions in this sample was considerably lower compared to other studies done in South Africa (Arendorf et al., 1997 and Arendorf et al., 1998) which have shown a much higher prevalence rate of Group I oral lesions. It must be noted though that comparisons between these studies would yield different results since the cohort of patients involved differed significantly in terms of their HIV status, the clinical setting and the age groups of the patients.

Since there was a relatively high prevalence of oral lesions in the sample, it confirmed the importance of detecting and diagnosing oral lesions during routine examinations in order to detect and refer patients appropriately for Voluntary Counselling and Testing (VCT).

CHAPTER 5

CONCLUSIONS AND RECOMMENDATIONS

The HIV prevalence in South Africa is extremely high and the PHC facilities are presently attending to a large proportion of these patients. Given the fact that the HIV prevalence rate is still rising, it can be confidently estimated that the PHC facilities will be overburdened by HIV and the associated opportunistic infections in the near future.

Given the low uptake in VCT and poor response towards HIV testing in South Africa, other cost effective and reliable methods need to be employed in order to arouse suspicion. The use of the saliva test for HIV proved to be extremely easy, effective and reliable. Patients were keen to be tested for HIV using the pain free saliva kit. However, the saliva kit is much more expensive compared to the routine blood test and is not a feasible option for routine VCT.

Another more cost effective screening tool is the utilisation of Group I oral lesions in detecting possible HIV infected patients. Using the LR and OR tests, multiple oral lesions have shown to be excellent predictors of HIV in this study. Some single oral lesions such as Oral hairy Leukoplakia (OHL) and Angular Cheilitis (AC) can be confidently used in predicting the HIV status of patients. The Positive Predictive Values (PPVs) for oral lesions (single and multiple) also proved to be high. Some multiple lesions (EC+PC+AC, AC+OHL, AC+EC and EC+OHL) yielded PPVs of 100%. This meant that patients presenting with these combinations of Group I oral lesion were 100% likely to test positive for HIV. Although this demonstrated the importance and excellent predictive values for Group I oral lesions, it remains essential for clinicians to be able to detect and diagnose these oral lesions. Therefore it is essential that both oral health and PHC staff attend calibration workshops on an ongoing basis in order to detect and diagnose these lesions accurately and correctly.

Multiple oral lesions were highly predictive of HIV status and could be used in resource limited settings to aid in diagnosing and possible treatment interventions.

The LR and OR provided the most accurate and robust correlation between the oral lesions and the patients' HIV status while the other epidemiological tests proved to be inadequate and inaccurate since they were almost entirely dependent on the prevalence of the lesions.

It is therefore recommended that depending on the setting and the expected prevalence of oral lesions amongst the cohort, researchers should use the LR and/or the OR in combination to achieve the most robust and accurate predictability of the patients HIV status.

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Information sheet for adult patients (≥ 18 years) attending
Community Health Centres, April/May 2005

Good day

We are a team of people employed to help the Gauteng Department of Health collect information in its health facilities for a new surveillance system called the “HIV Impact Surveillance System (HIVISS)”.

About the surveillance system

In order to provide health services in this province, the Gauteng Department of Health needs to collect information from clinics and hospitals on a regular basis. The reason for collecting this information is to improve health services. We call this a “surveillance system”

One of the aspects the Gauteng Department of Health would like more information on is how many people attending health services need care for HIV/AIDS compared to other diseases. In April and May 2005 we will be collecting this information on patients at a few hospitals and clinics in Gauteng Province, including at this clinic. We are asking your assistance in helping us collect information on HIV/AIDS in this health facility. This study will also include an oral examination which will help in identifying HIV positive patients.

What this means for you

We would like to be able to ask you a few questions on your health, to examine (look at) your head, neck and mouth and put a swab (a flat piece on a stick) in your mouth to collect spit to test for the HI virus. We are making the same request to every third person attending this clinic who is one year of age or older, whether they have illnesses which resemble HIV/AIDS or not.

You are not obliged to agree to this request. Whether you agree or not will not affect the treatment we give you at the clinic in any way.

The interview and examination will take less than 10 minutes. The examination and test will be done by a qualified health professional in a private room as explained by the counsellor.

Your name will not appear on any of the sheets where we write down information, so it will not be possible to trace what you said or the test results back to you.

If you would like to know your HIV status (whether you have the infection or not) both the counsellor and ourselves will explain to you how and where to go to have your blood tested in this clinic.

Contact details

If you have any questions, please speak to the sister in charge of this clinic. You can also phone or write to Professor Helen Schneider, the coordinator of the project for Gauteng Province tel: 011-489 9931/36. Centre for Health Policy, PO Box 1038, Johannesburg 2000.



Information sheet for children (<18 years) attending Community Health Centres,
April/May 2005

Good day

We are a team of people employed to help the Gauteng Department of Health collect information in its health facilities for a new surveillance system called the “HIV Impact Surveillance System (HIVISS)”

About the surveillance system

In order to provide health services in this province, the Gauteng Department of Health needs to collect information from clinics and hospitals on a regular basis. The reason for collecting this information is to improve health services. We call this a “surveillance system”.

One of the aspects the Gauteng Department of Health would like more information on is how many people attending health services need care for HIV/AIDS compared to other diseases. In April and May 2005 we will be collecting this information on patients at a few hospitals and clinics in Gauteng Province, including at this clinic. We are asking your assistance in helping us collect information on HIV/AIDS in this health facility.

What this means for you

We would like to be able to ask you a few questions on your health, to examine (look at) your head, neck and mouth and put a swab (a flat piece on a stick) to collect spit to test for the HI virus. We are making the same request to every third person attending this clinic

who is one year of age or older, whether they have illnesses which resemble HIV/AIDS or not.

The interview and examination will take less than 10 minutes. The examination and test will be done by a qualified health professional in a private room and will **not be painful or cause any harm to you in any way**. Your name will not appear on any of the sheets where we write down information, so it will not be possible to trace what you said or the test results back to you or your child.

If you would like to know your HIV status (whether you have the infection or not) we will explain to you how and where to go to have your blood tested in this clinic.

You are not obliged to agree to this request. Whether you agree or not will **not** affect the treatment we give your child at the clinic in any way. Even if your parent/guardian agrees to participate, you don't have to if you don't want to.

Contact details

If you have any questions, please speak to the sister in charge of this clinic. You can also phone or write to Professor Helen Schneider, the coordinator of the project for Gauteng Province tel: 011-489 9931/36. Centre for Health Policy, PO Box 1038, Johannesburg 2000.

(Appendix B1)

HIV Impact Surveillance System

Adult consent form

Community Health Centre

Date: _____

Initials of counsellor: _____

Do you understand the purpose of the study, and what will be required of you if you agree to take part? Yes/ No

Have all your questions been answered? Yes/No

If no, what further questions do you wish to ask?

Do you understand that you are not obliged to take part in this study? Yes / No

Do you understand that whether you take part or not, you will still receive the same treatment and care that you normally receive at this clinic? Yes /No

If answers to all the above are yes

1 Do you agree to have your mouth, head and neck examined and the findings recorded anonymously onto a sheet? Yes/No

Signature of respondent (If yes)

Verbal consent:

If the respondent is not literate, or is happy to provide verbal but not written consent, I, the fieldworker, confirm that the respondent gave verbal consent to be interviewed and examined

Signature of fieldworker (If yes).....

2 Do you agree for us to take some of your spit to test it for the HI virus? Yes / No

Signature of respondent (If yes).....

Verbal consent:

As the respondent is not literate, or is happy to provide verbal but not written consent, I, the fieldworker, confirm that the respondent gave verbal consent for HIV test

Signature of fieldworker (If yes).....

3 Would you like us to arrange for you to be properly tested (using blood) for HIV?
Yes/No

(Appendix B2)

HIV Impact Surveillance System

Paediatric consent/assent form

Community Health Centre

Date: _____

Initials of counsellor: _____

Do you understand the purpose of the study, and what will be required of you/your child if you agree to take part? Yes/ No

Have all your questions been answered? Yes/No

If no, what further questions do you wish to ask?

Do you understand that you are not forced to take part in this study? Yes / No

Do you understand that whether your child takes part or not, he/she will still receive the same treatment and care that you normally receive at this clinic? Yes /No

If answers to all the above are yes

1 Do you agree to have your child's' mouth, head and neck examined and to record these findings anonymously onto a sheet? Yes/No

Signature of respondent (If yes)

2 Do you agree for us to take some of your child's spit to test it for the HI virus?
Yes/No

Signature of respondent (If yes)

Verbal consent:

If the respondent is not literate, or is happy to provide verbal but not written consent, I, the fieldworker, confirm that the respondent gave verbal consent for the HIV test.

Signature of fieldworker (If yes).....

3 Does the child agree to the procedure?

Signature of child (if yes and able to sign).....

If child is unable to provide written consent does he/her provide verbal assent?

Signature of field worker.....

Verbal consent:

As the respondent is not literate, or is happy to provide verbal but not written consent, I, the fieldworker, confirm that the respondent gave verbal consent to be interviewed and have the child examined

Signature of fieldworker (If yes).....

4 Would you like us to arrange for your child to be properly tested (using blood) for HIV/ Yes/No

(Appendix C) HIVISS - ORAL, HEAD AND NECK EXAMINATION

Normal Extra-Oral Appearance		Lymphadenopathy		M/FIXED	T/NON-T
Ulceration (head, neck, limbs)		Submental			
Ulceration (nose, cheeks, chin)		Submandibular			
Ulceration (commissures)		Parotid			
Ulceration (vermilion border)		Auricular			
Generalised lymphadenopathy (head, neck)		Occipital			
Molluscum contagiosum		Cervical			
Other (specify)		Other swellings, specify			

Salivary Glands

Normal salivary gland appearance	
Parotid gland enlargement (unilateral)	
Parotid gland enlargement (bilateral)	
Xerostomia	
Pain	
Other salivary gland swelling/symptoms (specify)	

STUDY BAR CODE

Condition	Location
1 No abnormal condition	11 upper lip
2 Pseudomembranous Candidiasis	12 lower lip
3 Erythematous Candidiasis	13 mucosa of the upper lip
4 Hyperplastic Candidiasis	14 mucosa of the lower lip
5 Angular Cheilitis	15 mucosa around the corner on R side
6 Herpetic Ulceration	16 mucosa around the corner on L side
7 Aphthous Ulceration	17 cheek mucosa on R side of patient
8 Infective (TB, STDs) Ulceration	18 cheek mucosa on L side of patient
9 Atypical Ulceration	19 mucosa of upper jaw, bet lip/cheek & gums
10 Erythema Multiformae	20 mucosa of lower jaw, bet lip/cheek & gums
11 Oral Hairy Leukoplakia	21 mucosa of gums of upper teeth
12 Kaposi's Sarcoma	22 mucosa of gums of lower teeth
13 Non-Hodgkin's lymphoma	23 top surface of tongue
14 HPV - related lesions	24 sides of tongue
15 Leukoplakia	25 under surface of tongue
16 Melanotic hyperpigmentation	26 mucosa bet under surface of tongue & gums of L teeth
	27 mucosa of hard palate
	28 mucosa of soft palate
	29 mucosa behind last molar of U & L jaws

General Periodontal Status

0 = normal

1 = Linear gingival erythema

2 = HIV-Gingivitis

3 = HIV-Necrotising gingivitis

4 = HIV-Necrotising periodontitis

5 = Cancrum Oris

6 = Gingivitis

7 = Periodontitis

8 = Other

9 = Not recorded

HIV Status:

+

-

Age:**Gender:**

M

F

Condition	Location

(Appendix D)- Directions for using the OraQuick saliva test

(Appendix E) Ethics Clearance Certificate