ORAL LESIONS IN HIV/AIDS PATIENTS BEFORE AND AFTER HAART TREATMENT

by

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DECLARATION

I, the undersigned, Antonette Masiiwa, hereby declare that the work contained in this dissertation is my original work and has not been previously in its entirety or in part been submitted at any university for a degree.

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Dr Antonette Masiiwa Date

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DEDICATION

This dissertation is dedicated to my beloved Sister Alice and my three daughters,

Zvikomborero, Ruvimbo and Fadzai.

ABSTRACT

The initiation of highly active antiretroviral therapy has shown to result in successful suppression of viral replications followed by an increase in CD4 lymphocytes, a partial recovery of T-cell specific immune responses and decrease susceptibility to opportunistic pathogens. *Aim:* The aim of the present study was to determine the prevalence of oral lesions in patients before and after undergoing HAART. *Methods:* The study design was longitudinal and descriptive, investigating the prevalence of oral lesions presenting in HIV/AIDS patients at baseline, 3 and 6 months after taking HAART. A convenience sample size of 200 participants was targeted. *Results:* 210 HIV positive patients participated at baseline. At 3 months, 96 (46%) and at 6 months, 52 (25%) were available for review respectively. At baseline 210 HIV positive patients were recruited into the study from three hospitals. Two infectious disease hospitals belonged to the City of Harare and the other is a government hospital. Just over two thirds were female (64.3%) and the age ranged as follows: 21-30 (17%); 31-40 (44%); 41-50 (26% and 51-60 (9%). *Discussion*: HAART appears to be effective in reducing the prevalence of oral lesions in persons with AIDS likely due to the immunological reconstitution. Oral candidiasis remains the most prevalent oral opportunistic infection in immuno-suppressed individuals and hence its important predictive value for immuno-suppression defined as CD4-cell count level <200/mL of blood. All oral lesions strongly associated with HIV infection with the exception of non-Hodgkin's lymphoma were diagnosed at baseline. CD4 cell count level increased after initiation of HAART. T-lymphocytes that are formed after the introduction of HAART may not provide sufficient protection against some lesions like parotid gland disease and HPV conditions (planar warts). HAART failure was detected in some patients who had negative CD4-cell count at 6 months compared to the baseline parameters. *Conclusions:* HIV-positive patients experience oral pain during the course of their disease, eating, drinking and swallowing. Further longitudinal studies are required in order to ascertain the prevalence of these lesions at three and six months and the effect of HAART.

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CHAPTER ONE: INTRODUCTION

Oral manifestations of HIV infection include fungal, viral and bacterial infections. Neoplasms, periodontal disease, salivary gland disease and lesions of uncertain origin are also seen. Oral lesions such as candidiasis, herpetic ulcers and Kaposi's sarcoma are among the first symptoms of HIV infection. These conditions cause pain, discomfort, eating restrictions, and provide a source of constant opportunistic infections. Early detection of HIV-related oral lesions can be used to diagnose HIV infection, elucidate progression of the disease, predict immune status, efficacy of HAART and can result in timely therapeutic intervention.

The treatment and management of oral HIV lesions can considerably improve well-being (Naidoo and Chikte, 2004). Recent publications report that HAART reduces the prevalence of oral lesions in infected adults and children (Schmidt-Westhausen et al, 2000; Ceballos-Salobrena et al, 2005; Miziara et al, 2005). These studies emanate mainly from North America and Europe; there are only 2 documented studies from the African continent, Nigeria and Tanzania (Olaniyi and Sunday, 2003; Hamza et al, 2006).

Studies from Zimbabwe have documented the prevalence of oral manifestations in people with HIV/AIDS before the advent of HAART (Jonnson et al, 1998; Chidzonga, 2003). The programmeme of rolling out HAART, together with laboratory testing (*CD4* cell count) began in April 2004 in Zimbabwe and 2006 in the City of Harare hospitals (MOHCW, April 2006). This provides an ideal opportunity to investigate the effect of HAART on oral lesions in an African population at baseline, 3 and 6 months.

CHAPTER TWO: LITERATURE REVIEW

This chapter provides a review of the literature that is directly or indirectly related to this topic of study.

2.1 Introduction

The HIV/AIDS epidemic has caused untold suffering to millions of individuals and families in the world. 33.2 million people are estimated to be infected with the virus that causes AIDS globally. 22.5 million of the affected reside in sub-Saharan Africa, the epicentre. Naturally, it has become the leading cause of death in the region. Women (61%) are more affected than men (UNAIDS, 2007). The life expectancy at birth in 9 African countries has dropped below 40 years of age, including Zimbabwe (UNAIDS, 2004). Zimbabwe with a population of about 12 million, is experiencing a mortality rate of 3 000 deaths per week from HIV-related illnesses (Looman and Barnabas, 2006). Estimates of 1.6 million people are living with HIV/AIDS are on record. A drop in prevalence from 24.6% to 20.1% and to18.1% in 2003, 2005 and 2006 respectively was reported (MOHCW, April 2006). In 2007, the prevalence dropped further to 15.6%. A total of 1 320 739 people are infected in Zimbabwe with 75 420 receiving ART and 404 376 needing ART (MOHCW, 2007).

Oral manifestations in HIV-infected patients have a prevalence of about 70-90% (Vaseliu et al, 2006). At least 40 types of oral lesions (OLs) have been identified (Miziara et al, 2006). Oral lesions earn recognition as clinical indicators and earliest signs of HIV-infection. They are predictors of disease progression and also used as clinical markers for the classification and staging of the disease (Vaseliu et al, 2006). Besides, they are indicators of treatment failure (Miziara and Weber, 2006). OLs are associated with oral discomfort and pain, which may interfere with speech, nutritional intake leading to malnutrition especially in children. The quality of life is affected (Naidoo, 2001).

The introduction of highly active anti retroviral therapy (HAART) in 1996 has significantly reduced the incidence rate of opportunistic infections (OIs) associated with HIV/AIDS including oral lesions (Nicolatou-Galitis et al, 2004; Hamza et al, 2006). Zimbabwe in April 2004 introduced HAART; in line with the WHO 3*5 Strategy (MOHCW, April 2006). The advent of HAART and improvement in laboratory tests necessitates the need to re- examine orofacial lesions in Zimbabwe. Studies before the era of HAART exist (Jonnson et al, 1998; Chidzonga, 2003). To date there are no published studies with relevance to the use of HAART and effects on oral lesions. This has become the basis of this research.

2.2 HAART

The initiation of highly active antiretroviral therapy has shown to result in successful suppression of viral replications followed by an increase in CD4 lymphocytes, a partial recovery of T-cell specific immune responses and decrease susceptibility to opportunistic pathogens.

To date there are 4 classes of HAART drugs in use, administered in combinations to curb resistance development: 1. Nucleoside Reverse Transcriptase Inhibitors (NRTIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), Protease Inhibitors (PIs) and Experimental Drugs (EDs). EDs include: - a) Entry (Co-receptors) Inhibitors b) Fusion Inhibitors c) Integrase Inhibitors d) Maturation inhibitors (Frezzini et al, 2005). HAART is a combination of 2 or more NRTIs with at least 1PI and/ or 1NNRTIs.

In Zimbabwe, the regimens are available in fixed dose combinations and referred to as triple therapy, in this document also referred to as generic HAART. First line regimen include zidovudine, stavudine, lamivudine, nevirapine, effavirenz). Second line regimen, with PIs are distinguished and are as follows abacavir, kaletra (lopinavir/ritonavir), saquinavir/ritonavir, didanosine (MOHCW/WHO, 2006). HAART is mainly used in public institutions for post exposure prophylaxis (PEP).

2.3 Advantages of using HAART

HAART reduces the replication of virus thereby allowing the body's immune system to recover from the progressive destruction of CD4- cells. This in turn reduces HIV- related morbidity and eventually mortality (Umadevi et al, 2007). The quality of life is improved (Naidoo and Chikte, 2004; Hodgson, 2006). HAART transforms HIV/AIDS into a chronic manageable disease. The reduction of oral lesions minimizes the use of available resources in treating them. More people are accepting HIV testing and counselling. The stigma associated with the infection is also minimized since people know that treatment is available. The number of potential orphans is also reduced. HIV transmission is minimized and this forms the basis for PMTCT programmes. HIV/AIDS destroys and kills expensive and highly trained human resources at the very prime of their productive lives; HAART boosts economies and revitalizes communities (MOHCW, November 2006).

2.4 Oral side effects of HAART

Adverse effects include oral warts, salivary gland disease (SGD) with or without xerostomia, taste alterations and mucosal hyperpigmentation. Furthermore drug specific effects have been noted in association with such lesions as recurrent oral ulcerations, erythema multiforme, toxic epidermal necrosis, lichenoid reactions, dysgeusia, cheilitis, and circumoral paresthesia. There is increased risk of developing squamous cell carcinoma (Hamza et al, 2006; Hodgson et al, 2006). Some syndromes emerging are lipodystrophy and Stevens-Johnson's syndromes. Hyperglycaemia has been associated with the use of Protease Inhibitors (Aquino-Garcia et al, 2008). Apart from interfering with food intake, swallowing and speech, there is disfigurement as in the case after a herpes zoster attack (Greenspan, 2001; Frezzini et al, 2005, Hamza et al, 2006; Hodgson et al, 2006).

2.5 **HAART and immunological parameters** (CD4 count / Viral load)

2.5.1 CD4 cell count

CD4 cells are T-lymphocytes responsible for cell-mediated response combating infections in the body and activating humoral reactions by B-lymphocytes to produce immunoglobulins. Normal range is between 500 to 1500cells/ml of blood (Scully, 2004). The CD4 cells are targeted by the HIV and used to generate new viruses, thereby causing the depletion of the CD4 cells. The body becomes prone to opportunistic infections as in the orofacial region where some specific infections indicate diminishing immunity (Ceballos-Salobrena at al 2000; Vaseliu et al, 2006). A CD4 cell count of <200cells/mL defines AIDS (CDC-Classification, 1993), and used as the basis to commence HIV-infected individuals on HAART in poor resource countries. The CD4 cells increase with the use of HAART. Umadevi et al (2007) noted an increase from 241cells/mL at first visit to 416cells/mL after 9months. The newly formed cells have compromised immunocompetency as proven by the existence of some oral lesions in individuals on HAART as the increase in oral warts SGD as well as hyperpigmentation (Frezzini et al, 2005; Miziara and Weber, 2006; Hodgson et al, 2006).

2.5.2 Viral load count

The amount of viruses in the blood is also used to determine the severity of the infection by clinicians. HAART reduces the viruses in circulation; in turn more CD4-cells mature and fight infections better (Tappuni et al, 2001; Greenspan et al, 2004; Nicolatou-Galitis et al, 2004; Hodgson et al, 2006). However in Zimbabwe viral load counts are omitted due to prohibitive costs.

2.6 HAART, Oral lesions and IRIS

Immune reconstitution inflammatory syndrome (IRIS) occurs when the CD4 cells raises to >500cells/ml of blood and a viral load below the detectable levels through the use of HAART. Severe opportunistic infections resurface in contrast to the generally reported decrease in such conditions when HAART is employed.

Oral candidiasis is one such condition, which has been reported in individuals with IRIS (Gaitan Cepeda et al, 2008). Corti and co-researchers in 2007 defined the diagnosis of non-Hodgkin's lymphoma of the oral cavity as an IRIS condition in a patient with CD4 cell count of 198/ml and undetectable viral load. These studies highlighted the existence of oral lesions (OLs) in IRIS condition and suggest for the inclusion of OLs in the conditions associated with IRIS.

2.7 HAART and most common Oral Lesions

2.7.1 General response of oral manifestations to HAART

HAART significantly reduces the prevalence and severity of opportunistic infections including orofacial lesions in HIV infected individuals (Tappuni et al, 2001; Miziara et al, 2006; Hodgson et al, 2006; Umadevi et al, 2007). Ceballos-Salobrena et al (2000) reported a decline of 30%. Parveen et al (2007) and Hamza et al (2006) found no changes among adults and children respectively.

Oral warts increased in patients on HAART (Greenspan et al, 2001). Hamza et al (2006) and Umadevi et al (2007) noted an increase in hyperpigmentation. After at least 6months on HAART, a more favourable response was reported in patients who received HAART including effavirenz than HAART and protease inhibitors, 32% and 63% respectively (Aquino-Garcia et al, 2008).

2.7.2 Fungal infections

Oral candidiasis (OC) represents the most prevalent opportunistic infection in HIV-infected individuals. The prevalence is estimated to be 70% to 90%. It appears relatively early and the recurrence rate and severity are used as markers of progression into AIDS (Scully, 2004; Vasiliu et al, 2006). The three commonest types are Psuedomembranous candidiasis (PC), Erythematous Candidiasis (EC) and Angular Cheilitis (AC). PC the most prevalent, indicate very low CD4-cell count and very high viral load. The second most common is EC. AC is dominant in children. A significant reduction in the occurrence of these lesions through HAART has been reported by Greenspan et al (2004). PC and EC dropped from 6.70 to 2.85% and 5.48 to 2.99% respectively. Similarly Umadevi et al (2007) reported OC at first visit and after 3months and none at 6 and 9 months in patients on HAART.

EC is more prevalent in patients on HAART and those with IRIS than PC (Gaitan Cepeda et al, 2008; Aquino-Garcia et al, 2008). Oral candidiasis is also used in WHO classification and staging of HIV infection. Recent studies are pointing at the presence of OC in patients on HAART after 3 months as a sign of treatment failure (Flint et al, 2006; Ramirez-Amador et al, 2007). This could be used by clinicians especially in poor resource settings to monitor response in patients on HAART, instead of relying on costly immunological parameters.

2.7.3 Bacterial infections

This category has 3 forms of lesions, necrotising ulcerative gingivitis (NUG), necrotising ulcerative periodontitis (NUP) and linear gingival erythema (LGE). Periodontal diseases are earliest signs of HIV- infection (Winkler et al, 1998). The prevalence of periodontal diseases ranges from 0-47% in adults and 0-20% in children (Frezzini et al, 2005). Eyeson et al (2002) registered NUG decline from 8% to 2%. The oral hygiene conditions and smoking adversely affect these bacterial infections (Kroidol et al, 2005; Frezzini et al, 2005).

2.7.4 Viral infections

2.7.4.1 Herpes Simplex Virus (HSV 1) infection

Vaseliu et al (2006) noted a prevalence of 10-35% in both adults and children. A decline from 2.9% to 0% in prevalence of HSV-1 infection with HAART was reported by Schmidt -Westhausen et al (2000).

2.7.4.2 Herpes Varricella Zoster (HVZ) infection

The infection is caused by reactivation of the latent chicken pox virus and seldom seen in adults and children. The trigeminal nerve is affected to 15-20% of patients (Laskaris, 1996). In Zimbabwe, Jonsson et al (1998) reported prevalence of 12%. Nicolatou-Galitis et al (2004) reported 1 patient on ART. Any association with low CD4 cell count has not been concluded.

2.7.4.3 Oral hairy leukoplakia (OHL)

OHL is believed to be caused by EBV. It dominates in adults than in children, with prevalence of 20-25% and 2-3% respectively (Vaseliu et al, 2006). Arendorf and Holmes (2000) noted a prevalence of about 6% in Africans and 26% in Americans and Europeans. Schmidt-Westhausen et al (2000) reported 65% MSM and reported no OHL at second evaluation. Sroussi et al (2007) reported after 6months a four fold increase in prevalence of OHL in smokers compared to non-smokers, 12.1% and 3.4% respectively.

2.7.4.4 Human Papilloma Virus (HPV) infection (Oral warts, OWs)

The infection was a rarity before the advent of PIs. In HIV negative and positive individuals, the prevalence reported by Frezzini et al (2005) were 7.6% and 25.3% respectively. Greenspan et al (2001) had noted 5% OWs in persons on and not on ART, 23% were on HAART (P=0.01).

There is dominance among men having sex with men (MSM) who practise oral sex. HPV has been implicated as the cause of oral squamous cell carcinoma (Frezzini et al, 2005; Hodgson et al, 2006).

2.8 Malignancy

2.8.1 Kaposi's sarcoma (KS) [HHV-8: Human Herpesvirus 8 infection

The lesion is recognised as the commonest neoplasm in individuals with HIV-infection and is caused by HHV 8. In Zimbabwe, Jonsson et al (1998) reported 72% of the patients with oral KS with male predilection. Low CD4-l count and high viral load are risk factors. KS is an AIDS condition according to WHO clinical staging. HAART has direct anti-tumour activity from PIs.

2.8.2 Non-Hodgkin Lymphoma (NHL)

It is the second most prevalent tumour in HIV- infected persons, and is an AIDS defining condition (EC Clearinghouse Classification, 1993; CDC, 1993). The condition is of dual infection with EBV and HHV-8. It appears more in children. Chidzonga (2003) reported 7.1%. HAART reduces the prevalence of NHL as noted by Naidoo (2001).

2.9 Salivary Gland Disease (SGD) and Xerostomia

SGD presents as benign hypertrophy of the parotid glands, with a prevalence in children of between 10-30% (Naidoo and Chikte, 2004). Frezzini et al (2005) reported a prevalence of 3-10% in adults. Most HAART studies show an increase in prevalence. Ceballos-Salobrena et al (2000) found a rise in SGD from 0.9 to 4.5% associated with high viral load. Associated xerostomia can be an adverse effect of NRTIs (ddI, ddC) and PIs. Differential diagnosis should exclude use of antidepressants, tumours and Sjogren Syndrome especially in women. Reduced saliva flow increases the risk of developing caries and periodontal diseases.

2.10 Oral ulcerations

There are recurrent aphthous ulcerations (RAU) and non-recurrent ulcerations (NRU). RAU responds to steroid therapy unlike the NRU. Major ulcers cause discomfort in mastication, speech and dysphagia. Eyeson et al (2002) reported almost similar prevalence for RAU in patients on ART (24%) and non- HAART (22%). Visalia et al, 2006 mentioned severe RAU as a marker of CD4- count of <100. Recurrent oral ulcerations can have a prevalence of up to 30% in patients on zalcitabine as side effects as mentioned by Hodgson et al (2006). Oral ulcerations have been reported in individuals with Behnet's disease in HIV/AIDS (Mahajan et al, 2005).

2.11 Mucosal Hyperpigmentation

Melanosis is found in HIV/AIDS patients increasing with the use of HAART. Zidovudine use is also implicated (Hodgson et al, 2006). In 2006, Hamza et al found the condition to be the second most prevalent as did Umadevi et al (2007), who reported 14.8% and 43.8% in non-HAART and HAART patients respectively.

2.12 Molluscum contagiosum

The condition is found in patients with AIDS and CD4 count <200. A CD4- count of <50 causes numerous facial lesions, thus interfering with aesthetics. The recurrence rate is high. HAART and a raised CD4- count eventually eradicate the lesions. (Naidoo, 2001; Kekitinwa and Schwarzwald, 2006).

CHAPTER THREE: RESEARCH METHODOLOGY

3.1 Introduction

This chapter discusses the aims and objectives of the study as well as its research design and methodology. It discusses the study population and sampling and gives consideration to the methodology used by other researchers that had done similar studies. It also describes the development of the research instrument as well as the research method. Oral manifestations of HIV-infection are a common presentation in HIV/AIDS patients. Their frequency and severity increases with the deterioration of the immune system. The advent of Highly Active Antiretroviral Therapy (HAART) has led to the decrease in prevalence of most opportunistic infections including oral lesions. The effect of HAART on the prevalence of oral lesions has been investigated elsewhere and in the African region in Nigeria (Olaniyi et Sunday, 2003) and Tanzania (Hamza et al, 2006). In Zimbabwe some studies were done prior to the era of HAART by Jonnson (1998) and Chidzonga (2003). The availability of HAART in Zimbabwe forms the foundation of this study, which shall be comparable with other global studies.

3.2 Aims and Objectives

The aim of the present study was to determine the prevalence of oral lesions in patients before and after undergoing HAART

The broad objective was to describe the effect of HAART on oro-facial lesions in Zimbabwean HIV/AIDS patients at baseline, 3 and 6 months.

The specific objectives were to determine the: (i) demography of the sample (ii) prevalence of oral lesions at baseline, 3 and 6 months and (iii) the relationship between CD4 counts and oral lesions

3.3 Study site

Zimbabwe is in both the eastern and southern hemispheres. It is a landlocked country covering 390,624 sq km and is positioned in southern Africa, and bordered by the countries of Botswana, Namibia, Zambia, Mozambique and South Africa. It has a population of 12 360 000. Harare is the capital. It is the most populous city in the country, though physically the smallest. It has a population of over 1 533 190 million people. Eighty per cent of the population reside in rural areas of the state.

Figure 1: Map of Zimbabwe (Courtesy: www. nationalgeographic.org)

Table 1: Population distribution of Harare (2008 estimates)

CATEGORY	NUMBER	PERCENTAGE
Male	769 043	50.1
Female	764 147	49.9
Total	**1 533 190**	**100**
Children<5yrs	203 528	13.3
Children 5-14yrs	285 631	18.6
15-64yrs	1 011 661	66.0
>65yrs	32 370	2.1
Total	**1 533 190**	**100**

Harare is the nation's commercial centre due to the numerous banks and financial institutions situated there. There are 10 clinics, 17 primary health care centres, 12 polyclinics, 2 infectious disease hospitals and 2 tertiary health facilities in Harare.

These 33 institutions constitute the public health sector in Harare. The private sector comprises of 5 hospitals, 350 surgeries, 10 maternity homes, 8 nursing homes, 83 dental surgeries, 39 physiotherapy clinics, 60 medical laboratories of which 11 are public institutions, 36 ophthalmic/optic centres, 18 radio diagnostic centres and 10 ambulance services, 91 pharmacies, 4 natural therapy clinics. To manage these private and all public institutions in the country are 905 medical practitioners, 82 dental practitioners, 53 dental therapists, 1 dental hygienist, 4 maxillo-facial surgeons, 1 periodontist, 1 oral pathologist, 1 orthodontist and 10 dental technicians. It is obvious that the dental and medical practitioners are too few to efficiently and effectively administer the health services in Zimbabwe and greater Harare.

3.4 Study design

The study design was longitudinal and descriptive, investigating the prevalence of oral lesions presenting in HIV/AIDS patients at baseline, 3 and 6 months after taking HAART.

3.5 Research strategy

The research consisted of both quantitative and qualitative elements. The latter involved the diagnosis of the lesions and the quality of life information. The medical history identified opportunistic infections that are associated with HIV/AIDS. Quantitative data included the age of the participants and the CD4 counts. Furthermore, the main aim of research requires the quantitative analysis of the data.

3.6 Instrument used

A data capture sheet was used as the tool for entering the data during the study. The basic format was adopted from the UWC, the Department of Community Dentistry and modified by the researcher, the Principal Investigator (PI). The data capture sheet was designed for recording information necessary for the study design adopted (Appendix III).

The data captured was grouped into the following categories:

Demographic information

The demographic information included the identity of the participants, which was subdivided into groups that included the age, gender, the project code number, the hospital code number and the patient hospital number.

Medical history

Medical history from records and the patients including smoking: Conditions noted included TB, STIs, Herpes zoster, Oral thrush, Meningitis- cryptococcal, severe persistent rash, 10% loss of weight, prolonged diarrhoea, persistent fever and others.

Physical examination

- Physical examination for the diagnosis of lymphadenopathy and salivary gland function.

- The appearance of the marginal gingivae according to Loe and Silness, 1963.
- Oral mucosa included the orofacial lesions associated with HIV infection and their location as on the lesion report form: fungal, bacterial and viral infections, oral ulcerations and neoplasm. The conditions were reported at baseline, 3 months and 6 months.

HIV status

- The HIV status from records: parameters reported included: the type of HIV test done, date of HIV test, the mode of transmission, the WHO clinical stage, the CD4-cell count and date taken. The CD4 count was also noted at 6 months.

Therapy

- Cotrimoxazole prophylaxis: date commenced and stopped.
- HAART treatment combinations: first line and second line regimen available in Zimbabwe.
- Treatment of oral lesions: current antimycotic, antibacterial prophylaxis and others and lastly

The Quality of life information:

- Past and current history of oral problems ranging from the type of lesion from the perception of the participant, when it happened, duration of pain or discomfort and difficulties encountered.

  The description of the oral function, capturing dysphasia, xerostomia, taste alterations, dental caries and periodontal disease experiences and sleep disturbances.

3.7 Selection of study population

The study population consisted of patients with HIV recruited from the Opportunistic Infection Clinics (OICs) at Wilkins Infectious Disease Hospital (WIDH), Beatrice Road Infectious Disease Hospital (BRIDH) and Parirenyatwa Pediatric Opportunistic Infection Clinic (PPOIC). These City of Harare and Government hospitals have been mandated to

initiate HAART. Patients are started on HAART and reviewed monthly for re-supply of drugs by OIC Clinicians. The participants were selected in November 2007 through to January 2008 and reviewed from February to July 2008 from Opportunistic Infection Clinics (OICs) at BRIDH, WIDH and PPOIC. BRIDH and WIDH belong to the City of Harare while PPOIC is government owned.

HAART is defined as a combination of 2 Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and 1 Protease Inhibitors (PIs) with or without 1Non Nucleoside Reverse Transcriptase Inhibitors (NNRTIs). ART comprises of 2 NRTIs and 1 NNRTI.In this study HAART is synonymous with Antiretroviral Therapy (ART). The participants booked for initiation of HAART were first examined by the OIC doctor and put on HAART then referred to the principal investigator (PI) AM, a dentist in a separate consultation room for extra- and intra-oral assessment. The examination followed after the signing of the consent form (Appendix 1). A junior dentist assisted in recording the findings on a data capture sheet (Appendix II). Examinations were conducted on individual basis under strict confidentiality. A pilot study (October, 2007) was done at BRIDH and PPOIC.

Referrals to specialists were facilitated through the OI clinicians. A statistician together with the PI analyzed the results of the study. Permission was sought and obtained from relevant authorities namely the Medical Research Council of Zimbabwe, City of Harare and Parerenyatwa Group of Hospitals.

Inclusion criteria were:

- Confirmed HIV positive patients willing to participate and providing informed consent
- HIV patients not on HAART before
- HIV positive with a CD4 cell count <200 cells/mL of blood
- HIV positive children (<18 years) with CD4 percent of <25%

Exclusion criteria were:

- Very ill patients, unable to give consent and
- In- patients

3.8 Sample size

A convenience sample of 210 patients with HIV were enrolled at baseline.

3.9 Measurement

This study employed the use of a structured data capture sheet. It collected demographic information. It tried to ensure that it suited the aim and objectives of the study and was simple, clearly understood and unambiguous. Planning of the questionnaire began in February 2007. It was designed following discussions with academics and other dental professionals working in the field and was based on the following:

- It suited the aim of the study
- It suited the nature of the participants
- It was clear, simple, unambiguous
- The design minimized potential errors from principal investigator and coder
- The subject of the questionnaire was of interest to the participants, and hopefully encouraged their co-operation and elicited truthful answers
- Well worded questions were essential, and pitfalls were avoided, for example, ‘double-barrelled questions’ that is, when two questions are included in one- the questions were separated so that the respondent and the researcher can distinguish between the two.
- The wording of the questions did not lead the respondent to feel obliged to answer in a particular way, which may not be truthful
- Questions did not alienate either the respondent nor the researcher
- Efficient and meaningful analysis of the acquired data should have been possible.

3.10 Pilot study

A pilot study was done on 6 patients in October 2007 at BRIDH and PPOIC. The process tested the suitability and adequacy of the data capture sheet for the study. The information collected was supposed to allow the aim and objectives of study to be met. Any unnecessary items were omitted. It also provided an estimate on the time taken to carry out one interview.

3.11 Final draft preparation

After the piloting, irrelevant and unclear questions were identified and either deleted or appropriately modified. Question 4 was added to enable follow up of patients who were referred to their local clinics for reviews. Included also were the quality of life information. This improved the efficiency of the data capture sheet and reduced the time planned per interview. At the end, a total of 16 questions were printed for the main study.

3.12 Data collection

The participants were conveniently selected consecutively for 3 months from BRIDH, WIDH and PPOIC. The principal investigator (AM) informed the participants in their language of choice (English, Shona) about the study and invited them to participate on voluntary basis. The patients were assured of strict confidentiality and the provision for opting out at any time without penalties, before signing the consent form. Medical history information was taken from the medical records.

The participants were examined while seated on an ordinary chair at WIDH and PPOIC. At BRIDH they were sitting on dental chairs in the dental department. A physical examination was then undertaken, extra orally first, with palpation of the head and neck region followed by the oral examination.

Extra-oral assessment involved palpating cervical lymph nodes and the parotid glands and other visible swellings including skin lesions. Mouth mirrors were used and extra light from a torch for intraoral examination. A systematic examination was used as provided in the oral mucosa assessment manual (Appendix III).

3.13 Oral examination

3.13.1 Oral mucosa - Examination procedure

An examination of the oral mucosa and soft tissues in and around the mouth was made on every subject. Any abnormalities of the mucosa or of the gingiva were reported on the chart on the data capture sheet (Roed-Petersen and Renstrup, 1969). In addition, a full description of the lesion's size, shape, type and anatomical site was documented. If the cause of the lesion was obvious it was noted.

The examination was thorough and systematic and was performed in the following sequence:

(i) Labial mucosa and labial sulci (upper and lower)
(ii) Labial part of the commisures and buccal mucosa (right and left)
(iii) Tongue (dorsal and ventral surfaces, margins)
(iv) Alveolar ridges/gingiva (upper and lower)
(v) Floor of the mouth
(vi) Hard and soft palate

Two mouth mirrors were used to retract the tissues. The following procedure was used and the following codes were used to record the absence, presence or suspected presence of the condition: The lips were examined with the mouth closed and open. The colour, texture and any surface abnormalities of the vermillion border were noted. The mandible vestibule was examined visually with the mouth partially opened. The colour and any swelling of the vestibular mucosa was reported. The maxillary vestibule and fraenulum with the mouth partially opened was examined. Using the plane mouth mirrors as retractors and the mouth wide open, the entire buccal mucosa extending from the commisures and back to the anterior tonsillar pillar was examined.

With the tongue at rest and the mouth partially opened the dorsum of the tongue was inspected for any swelling, ulceration, coating or variation in colour or texture. The patient was then asked to protrude the tongue and the examiner noted any abnormality of mobility. The margins of the tongue were inspected with the aid of the mouth mirrors and then the ventral surface was reported. While the tongue was still elevated, the floor of the mouth was inspected for swellings or any other abnormalities. With the mouth wide open and the subject's head tilted backwards, the base of the tongue was gently depressed. The hard palate was inspected first followed by the soft palate. Any mucosal or facial tissues that seemed to be abnormal, as well as the submandibular and cervical lymph nodes, were palpated. The criteria used for diagnosis of oral mucosal lesions can be found in Appendix III.

3.14 Standardization and calibration

The objectives of the standardization and calibration exercises are to:

(i) ensure uniform interpretation, understanding and application of the criteria for the various diseases and conditions that were reported and reported.

(ii) ensure that each examiner could examine consistently to a standard.

(iii) minimize variations between different examiners.

3.14.1 Intra-examiner calibration

The principal investigator (AM) carried out the extra-oral and intra oral examinations. This promoted the maintenance of consistency through out the study. She also conducted the interview on the quality of life.

3.14.2 Inter-examiner calibration

At the start of the study, the PI (AM) carried out extra-oral and intra-oral examinations on 10% of the participants. An experienced oral pathologist was engaged in the triangulation process. The principal investigator would examine the participant first, then the

pathologist independent of each other. The results of the examinations would be compared and if the there was disagreement, the patient was re-examined by both examiners. The pathologist was disengaged when agreement of diagnosis reached 85-90%. By comparing the results of the two examinations on the same participant, the PI was able to obtain an estimate of the extent and nature of the diagnostic errors.

3.15 Follow-up strategy

- Participants had to attend for HAART follow up at 3 and 6 months and the oral examination and follow up will take place at the same visit.
- 2 months after the first assessment, a remainder was written in their hospital files about the re-examination on their next visit to the OIC and the OIC-clinicians advised also to emphasise this when the examined them.
- The principal investigator phoned the participants to remind them of the re-examination dates.
- Furthermore, reminders were hand delivered to the participants through the Department of Health Education and Promotion, City Health at 5 months.
- The postal services were excluded due to its current unreliability.
- The original sample size of 200 was increased by 5% to cater for drop-outs.
- The examiner took unpaid leave in April, June and July 2008 to consolidate follow-ups.

3.16 Data analysis

The data was entered on the data capture sheet (Appendix II). Descriptive statistics were used to summarize socio-demographic factors and other variables. Prevalence of oral lesions was determined by calculating the percentage ratio of patients presenting with OLs. Frequency tables were used to summarize and identify the most common oral lesions. Multiple linear regressions were carried out to identify factors (socio-demographic, presence of OLs, period on HAART) that were significant in predicting CD4-cell count.

Multiple logistic regressions were performed to identify socio-demographic factors that are significant in predicting presence of oral lesions. Chi-square test was done on qualitative socio-demographic factors to determine factors that are statistically associated with presents of OLs. Odds ratio and 95% Confidence intervals were also be calculated. Questionnaire data were categorized, coded and entered into the computer. Epi-info version 3.2 was employed in the statistical analysis of the data.

3.17 Ethical considerations

3.17.1 Establishing contacts

Access to participants was sort initially by letter to the participating hospitals through the A/Director of City Health Department and Clinical Director Parerenyatwa Group of Hospitals. An introduction of the researcher, basic aims, objectives of the study and the time frame was explained. Emphasis was made on strict confidentiality and assurance of anonymity in the presentation of study results. Once a signed consent form was received from each participant, the clinical examination was carried out during hospital schedules. The participants signed the consent form translated into Shona for easy understanding.

3.17.2. Ethical considerations

The protocol was submitted and approved by the Research Ethics Committee of the University of the Western Cape for ethical approval (see attached copy). Permission from the A/ Director of Health Services for Harare City and Clinical Director of Parerenyetwa Group of Hospitals was obtained to access participants at the various hospitals. The research commenced after authorization by the Medical Research Council of Zimbabwe. Informed consent in his or her language of choice (Shona or English) was obtained from each participant.

Participants were referred (if specific treatment and other interventions were required) to the Gershon Dental Clinic, BRIDH. Referrals to specialists were provided accordingly through the OIC clinicians. Furthermore, each participant received an individual oral health report within 3 months of completing the survey with appropriate advice. The participants were advised to take their individual reports to their private dental practitioners or to seek alternative treatment at the dental school or nearest dental clinic.

3.19 Conclusions

The study was a descriptive longitudinal study on HIV/AIDS patients in Harare. It aimed at a population sample of 210 and utilized a data capture sheet which was analyzed using Epi-info version 3.01.

CHAPTER FOUR: RESULTS

4.1 Introduction

One of the problems associated with longitudinal study designs is the inability to follow up participants to the end of the study. The present study was carried out at one of the worst periods in the political stage in Zimbabwe – during the highly contested and violent national elections. The response to follow up in this present study was very much affected by sociopolitical factors at play during this period. Furthermore, health care workers prolonged the recruitment period and minimized the initiation of patients on HAART during this challenging period. Consequently, the follow-up rate was tremendously reduced during the election period in March and subsequently June 2008 due to the violence and fact that many people had fled the country and it was impossible to contact all the participants in time for their 6 month follow-up. In Zimbabwe, the standard protocol for CD4 counts dictates that they can only be taken at 6months intervals.

4.2 Final Response rate

A convenience sample size of 200 participants was targeted. 210 HIV positive patients participated at baseline. At 3 months, 96 (46%) and at 6 months, 52 (25%) were available for review respectively.

4.3 Demographic data

At baseline 210 HIV positive patients were recruited into the study from three hospitals (Table 2). Two infectious disease hospitals belonged to the City of Harare and the other is a government hospital. Just over two thirds were female (64.3%) and the age ranged as follows: 31-40 (44%) years of age followed by 41-50 (26%) then 21-30 (17%) and 51-60 (9%). The minimum age at baseline was 3.0 years and maximum 83.0 years, with a mean age of 38.3years (S.D 10.3).

Table 2: Study sites and Gender Characteristics

Variable	Frequency	Percent
Hospital		
Beatrice Road Infectious Disease Hospital	184	87.6
Wilkins Infectious Disease Hospital	24	11.4
Parirenyatwa Opportunistic Infection Clinic	2	1.0
Gender		
Female	135	64.3
Male	75	35.7

4.4 HIV Tests, Route of transmission, Cotrimoxazole prophylaxis, Year CD4 count taken

The participants were diagnosed HIV positive from the year 2004 through to 2008, with the majority 87.62% (184) diagnosed in 2007 and 9.05% (19) in 2006 (Table 3). Rapid HIV testing was mostly used for the confirmation of the HIV. The predominant means of transmission was sexual in heterosexual relationships followed by vertical transmission. The majority of the patients (84.76%) were in the WHO clinical stage 3 and 11.43% in stage 4. CD4-cell counts were taken in 2007 (98%). 186 participants were started on either Cotrimoxazole or fluconazole prophylaxis in 2007 and 12 in 2006. The rest (12) were commenced on the prophylaxis in 2000 (1), 2004 (1), 2005 (6) and 2008 (4).

Table 3: HIV Tests, Route of transmission, Cotrimoxazole prophylaxis, Year CD4 count taken

Variable	Freq	%
Year of HIV Diagnosis		
2004	1	0. 48
2005	2	0.95
2006	19	9.05
2007	184	87.62
2008	4	1.90
HIV Test Method		
Elisa	6	3
Rapid	204	97
Route Of Transmission		
Sexual	202	96.19
Unknown	3	1.43
Vertical	5	2.38
WHO Clinical Stage		
1	1	0.48
2	7	3.33
3	178	84.76
4	24	11.43
Year of CD4 Count was taken		
2007	205	98
2008	5	2
Year started on Cotrimoxazole / fluconazole		
2004	1	0. 5
2005	6	3
2006	12	6
2007	186	88
2008	4	4

4.5 Medical history conditions

The most prevalent medical condition was loss of weight which affected more than two thirds of them. Sexually transmitted infections contributed 66% followed by oral thrush at 58%. Other common conditions experienced were herpes zoster (35%), severe persistent rash (33%) as well as cryptococcal–meningitis (10%). There were no active smokers at the time of the study, but 24% used to smoke (Table 4). The most frequent condition was cervical lymphadenopathy which affected 40% of the patients followed by 8% with parotid swelling and the least 2% had xerostomia.

4.6 Appearance of marginal gingivae

More than two thirds (68%) had varying degrees of gingival inflammation ranging from 4% to 24%. A third at baseline presented with a normal gingival. Mild gingivitis followed by a distinct red band from papilla to papilla affected 24% and 22% of the participants respectively. Only 4% presented with severe gingival inflammation (Table 4).

Table 4: Medical history and oral examination

Variable	N=210	
	Yes	**%**
Medical History Condition		
1. Tuberculosis	101	48
2. STI	138	66
3. Herpes Zoster	74	35
4. Oral Thrush	121	58
5. Meningitis-cryptococcal	10	5
6. Severe persistent rush	69	33
7. >10% loss of weight	147	70
8. Smoking	51	24
Physical exam lymphadenopathy & Salivary Glands		
Lymphadenopathy	83	40
Parotid gland swelling	9	4
Xerostomia (Dry mouth)	2	1
Appearance of marginal gingivae (Loe & Silness, 1963)		
Normal gingiva	68	32
Mild marginal gingivitis, slight colour change and oedema	51	24
Moderate gingival inflammation, redness and glazing	36	17
A distinct red band along the marginal gingiva	46	22
Severe inflammation, marked redness and oedema, with ulceration	9	4

4.7 Oro-facial lesions at base line, 3 months and 6 months

Table 5 shows the prevalence of oro-facial manifestations at baseline, 3 months and six months.

Table 5: Oro-Facial Lesions: Overall baseline, 3 months and 6 months

Lesion	Baseline n=210		3 months n=96		6 months n=52	
	Yes	%	Yes	%	Yes	%
Any Lesion	**176**	***84***	**61**	***64***	**31**	***60***
Oral candidiasis						
Pseudomembraneous candidiasis	59	*28*	6	*6*	2	*4*
Erythematous candidiasis	54	*26*	6	*6*	1	*2*
Rhomboid glossitis	18	*9*	1	*1*	0	*0*
Hyperplastic candidiasis	1	*0.5*	1	*1*	0	*0*
Angular cheilitis	24	*11*	8	*8*	0	*0*
Hairy leukoplakia	43	*20*	10	*10*	3	*6*
Oral ulcerations						
Herpetic ulceration	12	*6*	6	*6*	3	*6*
Aphthous ulceration	10	*5*	3	*3*	0	*0*
Atypical ulceration	6	*3*	0	*0*	0	*0*
Periodontal diseases						
Necrotizing ulcerative gingivitis	9	*4*	0	*0*	0	*0*
Necrotizing ulcerative Periodontitis	3	*1*	3	*3*	0	*0*
Linear gingival erythema	3	*1*	1	*1*	0	*0*
Salivary gland disease						
Parotid gland enlargement	9	*4*	2	*2*	5	*10*
Xerostomia	2	*1*	0	*0*	0	*0*
Ranula	1	*0.5*	0	*0*	0	*0*
Kaposi's sarcoma	5	*2*	1	*1*	0	*0*
Non-Hodgkin Lymphoma	0	*0*	0	*0*	0	*0*
Oral warts	2	*1*	0	*0*	0	*0*
Mucosal Hyperpigmentation	13	*6*	16	*17*	6	*12*
Molluscum contagiosum	19	*9*	7	*7*	3	*6*
Herpes zoster	10	*5*	0	*0*	0	*0*
Others						
Fissured depapilated tongue	8	*4*	0	*0*	0	*0*
Hairy black tongue	4	*2*	0	*0*	0	*0*
Tonsillitis/pharyngitis	4	*2*	0	*0*	0	*0*
Herpetic ulceration healed	34	*16*	0	*0*	0	*0*
Ringworms/facial rash	15	*7*	9	*9*	5	*10*
Facial palsy	3	*1*	0	*0*	0	*0*
Planar warts	6	*3*	21	*22*	10	*19*

Oral candidiasis

At baseline, 176(84%) participants had 375 orofacial lesions. Oral candidiasis was the most predominant condition clinically diagnosed contributing 74% (156) (Table 5). Intraorally, erythematous candidiasis including median rhomboid glossitis 34% (72) was the most frequent condition followed by pseudomembranous candidiasis at 28% (59) then angular cheilitis 24 (11%) and hyperplastic candidiasis 1 (0.5%). Hairy leukoplakia affected 20% (43).

Oral ulcerations

Herpetic ulcerations were reported in 6% (12) of the patients while 16% (34) had healed lesions. Aphthous ulcers and atypical ulcers affected 5% (10) and 3% (6) respectively.

Periodontal diseases

Periodontal lesions presented in 15 participants in the following order: necrotizing ulcerative gingivitis 4% (9), necrotizing ulcerative periodontitis and linear gingival erythema 1% (3) each.

Salivary gland disease

The most prevalent condition was parotid gland enlargement found in 4% (9). Xerostomia was diagnosed in 1% (2) and ranula in 0.5% (1).

Other common intra-oral and extra-oral lesions

Kaposi's sarcoma was reported in 5 (2%) of the patients and melanosis affected 13 (6%). Among extraoral lesions, molluscum contagiosum 19 (9%) was the commonest lesion followed by and herpes zoster reported in 10 (5%).

Uncommon extraoral lesions

Ringworms/facial rashes were found among 15 (7%) of the patients, 6 (3%) presented with planar warts and the least were 3 (1%) patients with facial palsy.

4.8 Immunological status at baseline

The CD4-cell count was 200cells/mL of blood or less, indicating that all the participants had AIDS. A mean value of 104.61cells/ml was determined for 208 patients. The standard deviation was 54.82. The minimum and maximum CD4-cell counts were 1 cell/ml and 200 cells/ml of blood. Some 2 children had CD4 percent of 2% and 12% (Table 6).

Table 6: Age and CD4 Counts (baseline and at 6 months)

Variable	N	Mean	Std Dev	Minimum	Maximum
Age (Years)	210	38.31	10.25	3	83.03
CD4 Count (Baseline)	208*	104.61	54.82	1	200
CD4 Count (6 mths)	52	211.98	132.67	7	742

2 children had CD4-percent: 2% and 12% (these were excluded when the mean CD4 count was calculated)

4.9 Oro-facial lesions after 3 months on HAART (n=96)

Prevalence of Oral Lesions

At 3 months on HAART, 96 participants were followed up (Table 7). 186 (65%) and 101 (35%) lesions were identified at baseline and at 3 months respectively among the 96 participants representing a 30% decrease (Table 7). Just over two thirds (61%) presented with 16 different oro-facial lesions.

Oral candidiasis affected 23% (22). Angular cheilitis was the most prevalent found in 8 participants (8%) followed by erythematous candidiasis 7 (7%) including 1 case of rhomboid glossitis and pseudomembranous candidiasis 6 (6%). Only 1 (1%) person was diagnosed with hyperplasic candidiasis (1%).

The second most common oral lesion was mucosal hyperpigmentation 16 (17%) followed by hairy leukoplakia 9 (9%). Other oral lesions were distributed as follows: herpetic ulcerations 6 (6%), aphthous ulcers 3 (3%), necrotizing ulcerative periodontitis 3 (3%), Kaposi's sarcoma 1 (1%), linear gingival erythema 1 (1%). The most predominant extraoral lesions were facial planar warts (20%), ringworms/facial rash (9%) and molluscum contagiosum (7%). Parotid gland enlargement was reported in 2 patients (2%).

Table 7: Oro-facial lesions at baseline and 3 months (n=96)

Lesion	Baseline n=96		3 months n=96	
	Yes	%	Yes	%
Any Lesion	**83**	***86***	**61**	***64***
Oral candidiasis	75	*78*	22	*23*
Pseudomembraneous candidiasis	23	*24*	6	*6*
Erythematous candidiasis	32	*33*	6	*6*
Rhomboid glossitis	8	*8*	1	*1*
Hyperplastic candidiasis	0	*0*	1	*1*
Angular cheilitis	12	*13*	8	*8*
Hairy leukoplakia	26	*27*	10	*10*
Oral ulcerations	9	*9*	9	*9*
Herpetic ulceration	3	*3*	6	*6*
Aphthous ulceration	5	*5*	3	*3*
Atypical ulceration	1	*1*	0	*0*
Periodontal diseases	7	*7*	4	*4*
Necrotizing ulcerative gingivitis	3	*3*	0	*0*
Necrotizing ulcerative Periodontitis	1	*1*	3	*3*
Linear gingival erythema	3	*3*	1	*1*
Salivary gland diseases	6	*6*	2	*2*
Parotid gland enlargement	6	*6*	2	*2*
Xerostomia	0	*0*	0	*0*
Ranula	0	*0*	0	*0*
Kaposi's sarcoma	1	*1*	1	*1*
Non-Hodgkin Lymphoma	0	*0*	0	*0*
Oral warts	0	*0*	0	*0*
Mucosal Hyperpigmentation	9	*9*	16	*17*
Molluscum contagiosum	9	*9*	7	*7*
Herpes zoster	8	*8*	0	*0*
Others	36	*38*	30	*31*
Fissured depapilated tongue	4	*4*	0	*0*
Hairy black tongue	1	*1*	0	*0*
Tonsillitis/pharyngitis	2	*2*	0	*0*
Herpetic ulceration healed	18	*19*	0	*0*
Facial palsy	2	*2*	0	*0*
Ringworms/facial rash	6	*6*	9	*9*
Planar warts	3	*3*	21	*22*

4.11 Oro-facial lesions at 6 months prevalence of oro-facial lesions (n=52)

At 6 months there were only 52 participants available for follow-up. 9 types of lesions were identified compared to 16 at 3 months and 26 oro-facial lesions at baseline (Table 8). Oral candidiasis had decreased to a prevalence of 6%. An outstanding finding was the increased prevalence of planar warts contributing 19% (10) followed by parotid gland enlargement and ringworms/facial rash with10% (5) each then the least was 6% (3) molluscum contagiosum. Considering only the 52 patients, at baseline there were 94 (52.81%) lesions, at 3 months 46 (25.84%) lesions and at 6 months 38 (21.35%) lesions (Table 8).

Table 8: Oro-facial lesions at baseline, 3 months and 6 months (n=52)

Lesion	Baseline N=52		3 months n=52		6 months n=52	
	Yes	***%***	**Yes**	***%***	**Yes**	***%***
Any Lesion	**43**	***83***	**29**	***56***	**31**	***60***
Oral candidiasis	37	*71*	8	*15*	3	*6*
Pseudomembraneous candidiasis	10	*19*	2	*4*	2	*4*
Erythematous candidiasis	17	*33*	1	*2*	1	*2*
Rhomboid glossitis	5	*10*	1	*2*	0	*0*
Hyperplastic candidiasis	0	*0*	1	*2*	0	*0*
Angular cheilitis	5	*10*	3	*6*	0	*0*
Hairy leukoplakia	8	*15*	3	*6*	3	*6*
Oral ulcerations	5	*10*	3	*6*	3	*6*
Herpetic ulceration	2	*4*	2	*4*	3	*6*
Aphthous ulceration	3	*6*	1	*2*	0	*0*
Atypical ulceration	0	*0*	0	*0*	0	*0*
Periodontal diseases	2	*4*	0	*0*	0	*0*
Necrotizing ulcerative gingivitis	2	*4*	0	*0*	0	*0*
Necrotizing ulcerative Periodontitis	0	*0*	0	*0*	0	*0*
Linear gingival erythema	0	*0*	0	*0*	0	*0*
Salivary gland diseases	5	*10*	2	*4*	5	*10*
Parotid gland enlargement	5	*10*	2	*4*	5	*10*
Xerostomia	0	*0*	0	*0*	0	*0*
Ranula	0	*0*	0	*0*	0	*0*
Kaposi's sarcoma	1	*2*	1	*2*	0	*0*
Non-Hodgkin Lymphoma	0	*0*	0	*0*	0	*0*
Oral warts	0	*0*	0	*0*	0	*0*
Mucosal Hyperpigmentation	7	*13*	9	*17*	6	*12*
Molluscum contagiosum	5	*10*	5	*10*	3	*6*
Herpes zoster	5	*10*	0	*0*	0	*0*
Other	19	*37*	15	*29*	15	*29*
Fissured depapilated tongue	2	*4*	0	*0*	0	*0*
Hairy black tongue	1	*2*	0	*0*	0	*0*
Tonsillitis/pharyngitis	1	*2*	0	*0*	0	*0*
Herpetic ulceration healed	9	*17*	0	*0*	0	*0*
Facial palsy	1	*2*	0	*0*	0	*0*
Ringworms/facial rash	3	*6*	6	*12*	5	*10*
Planar warts	2	*4*	9	*17*	10	*19*

4.12 HAART combinations and treatment for oral lesions

At the time of commencement on HAART at baseline, 11% (24) were taking antifungal and 1% (2) antibacterial medication. The HAART combinations used included 2 NRTIs (stavudine and lamivudine) and 1 NNRTI (nevirapine or efavirenz). The majority of participants 98% (205) were started on stavudine, lamivudine and nevirapine and only 2% who were on anti-TB treatment received stavudine, lamivudine and efavirenz (Table 9). Three months later, the most predominant combination of drugs was stavudine, lamivudine and nevirapine (95%; n=91). Four patients were on stavudine, lamivudine and efavirenz. Only 1 individual was taking zidovudine, lamivudine and nevirapine at the time of examination after 3 months on HAART. At 6 months the combination of drugs consisted of stavudine, lamivudine and nevirapine (83%); stavudine, lamivudine and efavirenz (2%) and zidovudine, lamivudine and nevirapine (15%). The third combination was not prescribed at baseline and only 1 participant had it at 3 months. None of the individuals was taking medication for the treatment of oral lesions at 3 and 6 months (Table 9).

Table 9: Treatment combinations for first line regimen

	Baseline (n=210)		**3 months (n=96)**		**6 months (n=52)**	
Combinations:	Yes	%	Yes	%	Yes	%
Stavudine + lamivudine + nevirapine	205	98	91	95	43	83
Stavudine + lamivudine + efavirenz	5	2	4	4	1	2
Zidovudine + lamivudine + nevirapine	0	0	1	1	8	15
Zidovudine + lamivudine + efavirenz	0	0	0	0	0	0
Treatment for oral lesions: Medication						
Antibiotic	2	1	0	0	0	0
Mouthwash	0	0	0	0	0	0
Antifungal	24	11	0	0	0	0

4.13 Quality of life information

Quality of life information was only obtained at baseline and is reported below in Table 10.

Table 10: History of Oral Problems

Question	n=210 Yes	%
Have you ever had any sores/ ulcers in your mouth?	102	49

	n=102 Freq	%
a. If yes, what problem did you have?		
Discomfort	17	17
None	0	0
Pain	85	83
b. When did you have them?		
1 to 3 months ago	36	35
Currently having the problem	8	8
Less than a month ago	23	23
More than 3 months to 6 months ago	14	14
More than 6 months ago	21	21
c. Did they cause you pain or discomfort? (yes, n=102)	102	84
• **If Yes (n=102), please explain for how long**		
1 to 2 weeks	63	62
Less than a week	18	18
More than 1 month	9	9
More than 2 weeks to 1 month	12	12
d. Are you having any pain or discomfort with your mouth now?	74	35
***If Yes (n=74), is this pain /discomfort causing difficulty with:**		
Eating	63	85
Drinking	24	32
Swallowing	17	23
Speaking	9	12
Working	1	1
Sleeping	5	7
*** More than one response was allowed**		

History of oral problems

Nearly half of the participants reported having oral ulcers or sores and 83% reported experiencing pain. The duration of the pain or discomfort per episode was less than 7 days for 17.64% to more than a month for 8.82%. The majority (61.78%; n=63) suffered pain for between 1 to 2 weeks. More than a third admitted having some pain or discomfort at baseline. The commonest difficulty was eating (85%; n=63) followed by drinking (32%; n=24). Swallowing was affected in just less than a quarter (23%) of patients.

Table 10 presents the findings on the oral function at baseline (n=210). Nearly half (45%; n=94) experienced a painful throat either often (8%; n=16) or sometimes (37%; n=78).A third reported having difficulties in swallowing liquids (30%; n=63).

More than half of the patients (55%; n=116) had suffered from xerostomia during the course of their illness and three quarters (76%, n=140) reported having problems with their sense of taste, with 27% (n=57) reported suffering from an altered taste often (Table 10).

Nearly three quarters (73%; n=154) of the participants experienced problems with their teeth. 120 (73%) patients had pain (106) and discomfort (14) during eating. Just under two thirds reported that their sleep was disturbed due to mouth problems. Just under twenty per cent reported having a dry mouth.

Table 11: Oral Function at baseline (n=210)

Question	Responses	n=210	
		Yes	%
Have you had a painful throat?	Often	16	8
	Sometimes	78	37
	Never	116	55
Have you had problems swallowing liquids?	Often	14	7
	Sometimes	49	23
	Never	147	70
Have you had problems swallowing solid food?	Often	17	8
	Sometimes	54	26
	Never	139	66
If Yes (n=94), when did you have them?	1 to 3 months ago	30	32
	Currently having the problem	11	12
	Less than a month ago	18	19
	More than 3 months to 6 months ago	19	20
	More than 6 months ago	16	17
Have you had a problem with a dry mouth	Often	58	28
	Sometimes	58	28
	Never	94	45
Have you had problems with your sense of taste?	Often	57	27
	Sometimes	83	40
	Never	70	33
Have you had problems with your teeth?		154	73
If yes, explain (n=154)	Food impaction	3	2
	Hypersensitivity	4	3
	Toothache	147	95
Have you had trouble eating?		120	73
If yes, explain (n=120)	Discomfort	14	12
	Pain	106	88
Have you had problems with your gums?		85	40
If yes, please explain (n=85)	Bleeding	43	51
	Halitosis	2	2
	Pain	40	47

Question	Responses	n=210	
		Yes	%
Have any of your mouth problems stopped you from sleeping?		122	58
If yes, please explain(n=122)	Dry mouth	22	18
	Painful gums	7	5
	Sores/ulcers	1	1
	Toothache	92	75

4.4 Immunological results at 6 months

There were only 52 patients available for follow-up at 6 months, compared to 96 at 3 months and 210 at baseline. The mean CD4 cell count was 211.98 at 6 months while at baseline it was 104.61 cells/ml of blood (Figure 2). At six months, 31 (59.62%) had CD4- cell counts of less than 200, with 19 (36.54%) between 200-500 and only 2 (3.85%) had more than 500 cels/ml of blood (Table 12).

In Table 13 the mean differences in CD4- cell counts at 6 months and baseline were calculated, only for the 52 participants, using a bi-varient analysis. The mean CD4- cell count difference was 99 cells/ml of blood with the minimum being -88 and maximum 552 cells/ml. The standard deviation found was 124 cells/ml. Using the paired T-test, the T- Value (DF) was 5.78 (51) and the difference was significant ($p < 0.0001$).

Figure 2: Mean CD4 at Baseline and 6-Months for the 52 patients (follow-up at 6 months)

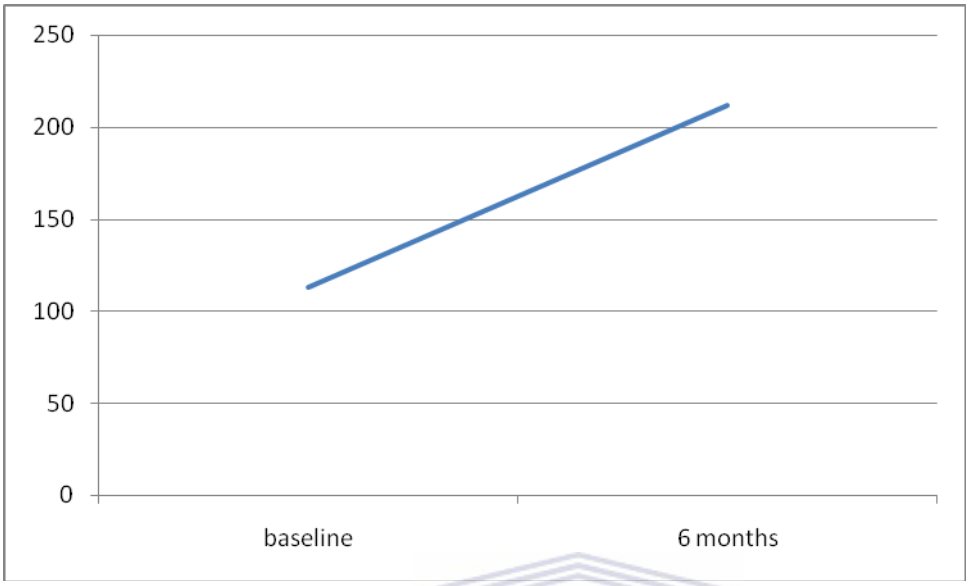

Table 12: CD4-cell count at six months (n=52)

CD4 cell counts	n=52	%
<200	31	59.62
200-500	19	36.54
>500	2	3.85

Table 13: Mean Differences in CD4 Counts (6 months- baseline)

	Summary Statistics of CD4 Differences (6-months- baseline)					Paired T-test	
Variable	**N**	**Mean**	**Std Dev**	**Min**	**Max**	**t-value (DF)**	**p-value**
CD4 Change (6 months – baseline)	52	99	124	-88	552	5.78 (51)	<0.0001

Conclusion

In conclusion, the prevalence of oral lesions decreased with HAART as the immunological function improved. HAART without protease inhibitors is effective in reducing orofacial lesions although HPV infections increased as well as mucosal hyperpigmentation. Remission of molluscum contagiosum is slower than other lesions like oral candidiasis. There was an increase in the absolute values of CD4-cell counts for most patients and one showed no change while 8 had a negative increase.

CHAPTER FIVE: Discussion

In this chapter, the findings of this study are highlighted. It begins by discussing the limitations of the study, demographic information of the participants, the effect of HAART on the prevalence of oro-facial lesions.

There was a very high loss of participants to follow-up and this was mainly due to the political and economic turmoil that prevailed in the country during the run up to the elections. The worsening socio-economic conditions resulted in many patients relocating and moving out of the cities and into the rural areas and villages. The violent political front caused much displacement as people fled, especially after the March 2008 elections towards the June election re-run.

Poor communication systems also affected the study: most of the patients did not have telephones at home. The postal services were functioning intermittently. Written reminders were delivered to the participants' addresses through the Department of Health Education and Promotion within the City of Harare, but follow-up remained low.

The study could not include assessments of viral loads at all stages and CD4-cell counts at 3 months due to financial constraints.

The recruitment of children was minimal as most of the children were undernourished, very sick and required hospitalization before commencement on HAART. Furthermore, the shortage of paediatricians in the department limited HAART initiation in children.
In summary, lack of funding, the violent political environment, economic and communication constraints made it difficult to consolidate the project and to follow it through as was originally planned. Extension of the period of follow up was not practical due the rising costs and inability to make contact with participants after the six month period had passed. This has affected the power of the study and weakened the results somewhat, but the findings are still comparable with studies from different continents.

Demography

The study was conducted at hospitals that were mandated by the central government of Zimbabwe to provide HAART. The selection of patients for HAART is uniform throughout the country. As such the findings of the present study especially at baseline, are likely to be represent the national picture, where the participants were consecutively selected into the study and none of the patients approached refused to participate.

The national prevalence of HIV infection in Zimbabwe is 15.6% with the ratio between men and women being 1:1.5 (MOHCW, 2007). In the present study the ratio is 1:1.8 respectively. These proportions differ from the previous studies conducted in the country by Chidzonga, 2003 (1:1) and Jonsson et al, 1998 (4:1). The most likely reason being the selection criteria used. It does reflect the shift from higher prevalence in men to women over time.

In the present study the most affected age range was in the 31-40 year age group. These results concurred with the studies by Chidzonga (2003) and Jonsson et al. (1998). The most common mode of HIV transmission was heterosexual. Vertical transmission affected tow per cent of children.

Oro-facial lesions

The literature has attested to the fact that HAART is associated with a reduction in oral lesions associated with HIV infection (Gaitan Cepeda, 2008; Ramirez-Amador et al, 2003; Tappuni and Flaming, 2001; Patton et al. 2000; Schmidt-Westhausen et al.2000). In developed countries the decline in the prevalence ranged from 10-50% (Hodgson et al. 2006). In the present study a decrease in prevalence orofacial lesions was reported from baseline, through to 3 months and 6 months, despite the fact that patients were lost to follow up at all stages.

This finding is consistent with other studies: Schmidt-Westhausen et al (2000) reported a reduction from 85.4% before HAART to 8.2% after HAART initiation. The prevalence of oral lesions declined from 47.6% to 37.5% after introduction of HAART (Patton et al. 2000). A study by Ramirez-Amador et al (2003) over a 12 year period reported a statistically significant decrease in the prevalence of oral lesions. Tappuni and Fleming (2001) reported a prevalence of 30% in patients on any ART and 46% in patients not on ART. A reduced prevalence of 30% was found by Ceballos-Salobrena and co-researchers in 2000. Tappuni and Flaming (2001) reported a reduction 24%, while Gaitan Cepeda (2008) a decline from 66.3% to 46.5% before and after HAART respectively.

Fungal infection has been reported as the most prevalent oral opportunistic infection in HIV-seropositive individuals. 70-90% of HIV-infected develop oral candidiasis and hence it being considered as a marker for the progression into AIDS (Scully, 2004; Vasiliu et al, 2006). Oral candidiasis including median rhomboid glossitis declined from 73% at baseline to 23% at 3 months to 6% at six months. Similar results were obtained by Schmidt-Westhausen et al (2000) and Nicholatau-Galitis et al (2004).

Hamza et al (2006) found a significantly lower risk of oral candidiasis (OR = 0.28; 95% CI = 0.18 – 0.44; p = 0.003) in adult patients in Tanzania who were on HAART. These researchers reported even better results for patients who had been on HAART for more than 6 months. Umadevi et al (2007) in Southern India reported a reduction in oral candidiasis in nearly all participants taking HAART. Tappuni and Fleming (2001) reported a reduction in the prevalence of oral candidiasis as follows: monotherapy (25%), dual therapy (22%) and HAART (17%). HAART including Protease Inhibitors (PIs) has a superior effect on oral candidiasis compared to generic HAART due to the direct inhibition of asparitic proteinase produced by candida by PIs (Umadevi et al, 2007; Nicolatau-Galitis et al, 2004; Arribas et al, 2000). The improvement in immunity as a result of an increase in CD4-cell counts due to the effect of any HAART is responsible for the reduction in opportunistic infections including oral candidiasis (Umadevi et al, Aquino-Garcia et al, Hamza et al, Tappuni and Fleming, 2001). Hodgson et al (2006) noted a significant decrease in oral candidiasis from prospective studies analyzed.

Hairy leukoplakia has been documented as the second commonest oral opportunistic infection after oral candidiasis before HAART therapy is initiated (Ceballos-Salobrena et al, 2000; Schmidt-Westhausen et al, 2000; Eyeson et al, 2002; Ramirez-Amador et al, 2003; Gaitan Cepeda et al, 2008), ranging from 0.42 to 38% (Frezzini et al. 2005). Arendorf and Holmes (2000) reported an average prevalence of 6% in Africa. The present study reflects the same finding unlike the previous Zimbabwean studies (Chidzonga, 2003; Jonsson et al.1998). The prevalence of hairy leukoplakia in the present study at baseline was 20%, at 3 months 10% and 6% at 6 months. The difference could be due to the immunological status of the patients. The present study had patients with severe immunosuppression with CD4- cell counts of =/< 200.

HAART has been reported to decrease the prevalence of oral hairy leukoplakia (Reznik and O'Daniels, 2006; Patton et al. 2000; Ramirez-Amador et al. 2003). Greenspan and colleagues (2001) registered a reduction of hairy leukoplakia for patients on ART and HAART compared to those who were receiving no treatment ($p < 0.001$). Hamza et al (2006) found that patients on HAART had a low risk of hairy leukoplakia. There are however, other studies that report no significant changes in prevalence (Miziara and Weber (2006); Gaitan Cepeda (2008); Greenspan et al. 2004). The reduction in the prevalence of oral hairy leukoplakia is associated with the increase in CD4- cell count (Eyeson et al, 2002).

Hairy leukoplakia is associated with smoking - Sroussi et al (2007) reported the prevalence for non-smokers as four times less than smokers. Similar findings were noted by Schmidt-Westhausen et al (2000) and Greenspan et al (2004) among women heroin/ methadone, cigarettes and/or marijuana users. Frezzini et al (2005) and Flint et al (2006) reported a male dominance especially in with men who have sex with men. Hairy leukoplakia is a persistent condition that has been reported by most studies including after initiation of HAART (Eyeson et al, 2002; Hamza et al, 2006; Gaitan Cepeda, 2008). The presence or absence of the lesion therefore reduces its potential to be considered both as a sign of HAART failure and a component of IRIS (Flint et al, 2006; Gaitan Cepeda, 2008).

The malignancies strongly associated with HIV infection include Kaposi's sarcoma. In the present study the prevalence dropped from 2% (5/210) to 1% (1/96) and 0% at 6 months among 52 patients. A steady decline in prevalence has been reported by Jonsson et al (1998) and Chidzonga (2003). Frezzini et al (2005) reported the prevalence of oral Kaposi's sarcoma ranging from 0-12% in Africa and 0-38% in North America and Europe. The prevalence reported in the present study is in line with those reported in other African countries. Another southern African study by Hamza et al (2006) reported a prevalence of 3.2% among patients who had received HAART for a period ranging between 1-14 months. The risk of Kaposi's sarcoma was significantly lower for individuals who were on HAART in comparison with non-HAART patients after controlling CD4-cell count.

Gaitan Cepeda (2008); Greenspan et al (2001); Schmidt-Westhausen et al (2000); Ceballos-Salobrena et al (2000) and Corti et al (2007) all reported a significant reduction in the prevalence of Kaposi's sarcoma. While Ramirez-Amador (2003) and Patton and colleagues (2000) reported a non-significant decline. The improvement in the immune status recognized by the increase in CD4-cell counts and decreased viral load are responsible for the decline in Kaposi's sarcoma among individuals on HAART. The PIs have been found to have a direct anti-tumour activity (Frezzini et al, 2005). Apart from these findings, Arendorf and Holmes (2000) highlighted the prevalence of Kaposi's sarcoma in relation to the sexual preferences in developed countries, with men who have sex with men affected the most. In summary, HAART reduces the prevalence of Kaposi's sarcoma as seem in the present study and reported on other continents.

In the present study, there was no case of Non-Hodgkin's lymphoma and this could be due to the small sample size. It is the second common cancer after Kaposi's sarcoma and the most frequent in children (EC Clearinghouse Classification, 1993). Chidzonga (2003) reported a prevalence of 7.1%. Corti et al (2007) noted that the lesion resolved after chemotherapy and HAART. They suggested that non-Hodgkin's lymphoma be considered for inclusion in conditions in immune reconstitution syndrome (IRIS).

HIV- associated periodontal diseases are among conditions strongly associated with HIV infection. In the present study, the prevalence decreased from 7% to 4% and 0% after 6 months. The prevalence reported from several studies range from 0%-50% (Vaseliu et al, 2006; Frezzini et al, 2005). Jonsson et al (1998) and Chidzonga (2003) reported a 2% prevalence of NUG and 8.3% of NUG/NUP in Zimbabwe before HAART respectively. Arendorf and Holmes (2000) noted a higher incidence rate of periodontal diseases in the developing world than in the industrialized world.

The recipients of HAART have shown a reduction in the frequency of periodontal diseases (Kroidl et al. 2005; Ceballos-Salobrena et al.2000; Patton et al. 2000; Schmidt-Westhausen et al. 2000; Tappuni and Fleming, 2001; Eyeson et al. 2002). Ramirez-Amador et al (2003) in their 12-year study noted a significant decline in periodontal diseases from baseline. Aquino-Garcia et al (2008) noted reduced frequencies for patients on HAART with efavirenz (10.5%) compared to those on HAART with protease inhibitors (14.2%). Hamza et al (2006) reported a lower prevalence of NUG among HAART and non- HAART patients. An insignificant association between conventional gingivitis and low CD4 percent was found by Okunseri et al (2003) among children.

Oral ulcerations had a prevalence of 13% at baseline, at 3 months 9% and six months 6%. They included herpes ulcerations, recurrent aphthous ulcers and atypical ulcers. Frezzini and colleagues (2005) reported prevalence of ulcerations ranging from 1.7%-24% while Vasiliu et al in 2006 noted 10-30% in both adults and children. Patton et al (2000) reported no significant change in oral ulcerations before and after HAART. Nicolatau-Galitis et al (2004) reported 2.7%, 2.27% and 0% prevalence on patient on no ART, PI-HAART and double ART respectively. A decline was also reported by Schmidt-Westhausen et al (2000); Ceballos-Salobrena et al (2000) and Hamza et al (2006).

In the current study the prevalence of herpes simplex virus 1 (HSV-1) remained constant at 6% at baseline to 6 months. This could reflect a non-response of the HSV-1 to HAART and is mot a good indicator of immune status in HIV patients relative to HIV seronegative individuals (Frezzini et al, 2005).

The present study reported healed lesions in 16% at baseline and if active lesions were included, the prevalence rose to 22%. Miller and colleagues (2006) reported that the prevalence of HSV-1 in saliva of HIV positive individuals on HAART was 8 times more than in HIV negative people. The HSV-1 prevalence was reportedly higher in patients with CD4-cell count of < 200/ml but was not associated with the presence of oral lesions.

Recurrent aphthous ulcerations were reported 3% after 3 months and 0% at six months. Eyeson et al (2002) reported a slight increase in prevalence of the condition among patients on HAART. Patton et al (2000) reported lower prevalence differences from baseline to after HAART use. Chidzonga (2003) reported 10.9% oral ulcers, 5.1 recurrent and 5.8% non recurrent ulcerations. Vaseliu et al (2006) reported a prevalence range of 1-7% for recurrent ulcers. These lesions are very painful and effect oral function, speech, mastication and swallowing.

Naidoo and Chikte (2001) reported the prevalence of parotid gland swelling in children ranging between 10-30%, and Frezzini et al (2005) reported a prevalence of 3-10% among adults. A six per cent prevalence of salivary gland diseases was found in the present study with the highest frequency being parotid gland enlargement 4%, 2% and 10% at baseline, 3 months and 6 months respectively. This is a similar finding to that of Patton et al (2000) and Greenspan et al (2001) who also reported an increase following HAART. Nicolatou-Galitis et al (2004) reported a rising frequency from 5.4% to 14.3% before the era of ART and a drop again to 6.8% after HAART.

Parotid gland swellings were reported by Okunseri et al (2003) among HIV infected children and by Ceballos-Salobrena et al (2000). Parotid gland enlargement is considered as a disorder of the CD8-cell (DILS) diffuse infiltrative lymphocytosis syndrome (Greenspan et al, 2001, Frezzini et al, 2005). Hamza et al (2006) reported the highest prevalence of parotid gland enlargement of 19.6% in children with no differences among HAART patient and non-HAART patients. Flint et al (2006) has suggested that salivary gland disease should be included as one of the conditions seen in IRIS as opposed to HAART failure.

Xerostomia was clinically diagnosed by the dryness of the buccal mucosa and only two patients were affected at baseline and none thereafter. The prevalence of xerostomia of 2-30% was reported by Frezzini at al (2005) and Ceballos-Salobrena et al in (2000). Even though the clinical presentation was very low, more than half of the present sample reported having experienced dryness of the mouth often or sometimes during the course of their HIV disease.

Eyeson et al (2002) reported a statistically higher prevalence of xerostomia in patients on HAART compared to those on no HAART. Aquino-Garcia et al (2008) reported 18.4% and 17.1% prevalence of xerostomia in efavirenz-HAART and PI-HAART respectively. Other studies suggest that Xerostomia is associated with some HAART drugs, however, a differential diagnosis regarding the cause of the oral dryness should be made - as nucleoside reverse transcriptase inhibitors or protease inhibitors; antidepressants; salivary gland tumours and Sjogren syndrome in women have been previously implicated (Frezzini et al, 2005; Flint et al, 2006; Hodgson et al,2006). Hodgson et al (2006) found an association with women for xerostomia and reduced function of the salivary glands.

Mucosal hyperpigmentation has been reported in a number of studies with prevalence of 1.8%-10.3% (Ceballos-Salobrena et al, 2000). Hamza et al (2006) documented the condition as the second commonest lesion in their study with 20% of their sample taking a combination with zidovudine. A high prevalence was reported by Umadevi et al (2007). They noted a significant difference in the prevalence associated with CD4 cell counts. In participants with >200 CD4-cell counts, high mucosal pigmentation was reported. In the present study pigmentation was 6%, 17% and 12% at baseline, 3 months and 6 months respectively.

The causes of mucosal hyperpigmentation are mainly associated with the administration of zidovudine (Ceballos-Salobrena et al, 2000; Frezzini et al, 2005; Flint et al, 2006, Hodgson et al, 2006; Hamza et al, 2006; Umadevi et al, 2007). The mechanism has been associated with deregulation of cytokines in HIV infected persons promoting an increased release of alpha melanocyte-stimulating hormone; antiretrovirals- zidovudine,

antifungals – ketoconazole and Addison disease (Hamza et al, 2006; Umadevi et al (2007). In the present study however, no participant was on a combination with zidovudine at baseline and only 1 patient at 3 months. At 6 months, 15% got their first prescriptions that included zidovudine. The condition should be further investigated.

Other intraoral conditions reported in this study include oral warts (1%) at baseline, fissured depapilated tongue (4%), hairy black tongue (2%), and tonsillitis –pharyngitis (2%). These conditions were not reported in the later reviews. Oral warts caused by human papilloma virus were reported previously as showing a steady increase with the use of HAART with protease inhibitors. Schmidt-Westhausen et al (2000) and Patton et al (2000) reported a rise in oral warts though this finding was non-significant. In patients on PI-HAART the association of increased warts was found to be highly significant (Greenspan et al, 2001). Eyeson et al (2002) reported only 1% with papillomas in patients on HAART. Frezzini et al (2005) reported a prevalence of 9.2-18.6% and noted the presence of HPV in saliva of 25.3% HIV- positive individuals with 7.6% in HIV-negative. Prominence in male gender and a very high presence in individuals who practice oro-genital contact were noted (Frezzini et al, 2005; Hodgson et al, 2006 Umadevi et al, 2007). An association with CD4-cell count has also been reported (Frezzini and colleagues, 2005).

The increase in oral warts in patients on PI-HAART has been associated with the decrease in viral load although the mechanism is unclear (Frezzini et al, 2005; Hodgson et al, 2006). It is also associated with the immune reconstitution syndrome which is believed to be linked to the production of immature CD4-cells with compromised immunocompetence (Schmidt-Westhausen et al, 2000; Frezzini et al, 2005; Hodgson et al, 2006). Regional researchers did not mention any oral warts presence (Jonsson et al, 1998; Chidzonga, 2003; Hamza at al, 2006). The low prevalence of papillomas in the present study is in agreement with other studies which reported no difference in patients on non PI-HAART and on HAART (Frezzini et al, 2005). The short period on HAART, the type of HAART and the high loss of patients to follow up as well as the heterosexual sample could be responsible for the low prevalence in this study.

The presence of oral warts has been noted as a risk factor for the development of oral malignancies including squamous cell carcinoma (Frezzini et al, 2005; Hodgson et al, 2006; Flint et al, 2006).

Extraoral lesions reported in the present study include herpes zoster, Molluscum contagiosum, planar warts, facial palsy, lymphadenopathy and ringworms/facial rash. Hamza et al (2006) reported a prevalence of 0.4% herpes varricella zoster infection and 25.9% history of herpes zoster infection. In present study, the history of infection was higher at 35%. Jonsson et al (1998) and Chidzonga (2003) reported a prevalence of 12% and 10.3% respectively. The trigeminal branch is affected in about 17% of herpes zoster individuals (Frezzini et al, 2005).

In Zimbabwe the history of the infection is considered important in the selection of candidates for HAART. The condition seems to be more prevalent in Africa and appear in the same frequencies in HIV- infected and HIV- seronegative individuals (Frezzini et al, 2005). There is some controversy as to the association of the condition and low CD4 – cell count (Frezzini et al, 2005).

The prevalence of cervical lymphadenopathy is rarely reported. In the present study a high prevalence of 40% was found while Jonsson et al (1998) and Chidzonga (2003) reported 21% and 7.1% respectively.
Okunseri et al (2003) and Miziara et al (2005) reported a 1.0% and 15.3% in children on any HAART. These differences could be in the diagnostic methods used. In Zimbabwe, lymphadenopathy prevalence is relatively high and could be used as an indication for HIV-infection. The effect of HAART could not be ascertained since 3 and 6 months as the condition was not reviewed.

Molluscum contagiosum prevalence in the present study was 9%, 7% and 6% at six months. The viral infection is transmitted through skin contact and can be found in both HIV–positive and negative individuals. The lesions are more severe in individuals with AIDS and CD4-count of <200.

A CD4-cell count of less than 50 is accompanied by extensive lesions and large firm fleshy doom-shaped swellings usually on the face and neck. In the present study multiple non-giant lesions were found

The use of HAART accompanied by an increase in CD4-cell count, leads to the decrease in the lesions (Naidoo, 2001; Kekitinwa and Schwarzwald, 2006). Schmidt-Westhausen et al (2000) reported a decline in the prevalence of the lesions after initiation of HAART. In the present study a reduction in the prevalence was reported consistent with previous studies.

Planar warts showed a noticeably high, increasing higher prevalence from 3% at baseline; 22% at 3 months and 19% at 6 months. This is a lesion that is associated with HPV infection which has also been reported to increase in patients on HAART treatment. There was also a steady increase in ringworm/facial rash (7% to 10%). This could be linked to the use of nevirapine after HAART initiation and use of cotrimoxazole prophylaxis prior to HAART. However, in line with other studies reported worldwide, the present study also showed a significant decline in the most common oral lesions (oral candidiasis, hairy leukoplakia, periodontal lesions, Kaposi's sarcoma and oral ulcerations) after the initiation of HAART. A high prevalence of mucosal hyperpigmentation was found, but no association with HAART could be established. There was an increase in salivary gland enlargement facial planar warts.

CHAPTER SIX: Conclusions and recommendations

The present study detremined the prevalence of orofacial lesions with special reference to oral manifestations of HIV in individuals on HAART.

- HAART appears to be effective in reducing the prevalence of oral lesions in persons with AIDS likely due to the immunological reconstitution syndrome.
- Oral candidiasis remains the most prevalent oral opportunistic infection in immunosuppresed individuals and hence its important predictive value for immunosuppresion defined as CD4-cell count level <200/mL of blood.
- All oral lesions strongly associated with HIV infection with the exception of non-Hodgkin's lymphoma were diagnosed at baseline.
- CD4 cell count level increased after initiation of HAART.
- T-lymphocytes that are formed after the introduction of HAART may not provide sufficient protection against some lesions like parotid gland disease, HPV conditions (planar warts) and the persistence of oral candidiasis at 3 and 6 months.
- HAART failure was detected in some patients who had negative CD4-cell count at 6 months compared to the baseline parameters with poor compliance ruled out.
- At baseline, patients reported experiencing oral pain during the course of their disease, eating, drinking and swallowing.
- Toothache was the most common symptom among HIV patients leading to disturbed sleep.

Further longitudinal studies are required in order to ascertain the prevalence of these lesions at three and six months and the effect of HAART.

Recommendations

The following recommendations should be applied to countries with poor resource settings like Zimbabwe. Oral lesions provide an uncomplicated way of identifying potentially HIV- infected individuals.

Improvement in identification of oral lesions

- Inclusion of oral health workers in the management team of Opportunistic Infection Clinics. The prevalence of oral lesions is high in HIV-infected individuals and the effects of the lesions disturb the quality of life of PLWHA. A holistic approach to management of HIV–seropositive individuals requires dental surgeons to be incorporated in treating the affected.
- Primary health care workers need to be trained in the diagnosis of oral lesions due to their potential in detecting early HIV infection and progression of the disease and lately identification of HAART failure and as signs of immune reconstitution syndrome (IRIS).

Scaling - up of HAART

- HAART prolongs life: HAART does not only improve the oral health of infected individuals but it prolongs life. Zimbabwe is in the epicentre of the AIDS pandemic and has a large burden of orphans. Early provision of HAART will save lives and reduce the problem of orphans.
- Improvement in production and social life: AIDS affects the working class and experienced workers as the most infected are between 21-60 years of age. Debilitating effect of AIDS leads to reduced production capacity of companies and eventual loss to death of workers.
- Reduction in health costs: The cost of treating recurrent opportunistic infections in infected individuals is reduced when patients are put on HAART as their immunity improves.

Increase in oral health research

- HIV and AIDS is a public health problem in sub-Saharan Africa. Improvement in the financing of oral health research will assist in the improvement of general health of the populations.
- This study had very few children and the loss of patients to follow-up requires that similar studies be conducted so as to improve the inference of the results at 3 and 6 months to the ordinary populace.

Gender considerations

- The ratio of men to women was almost 1:2. There is need to promote the use of preventive methods in women like use of female condoms and economic empowerment as poverty make women more vulnerable to HIV infection.

Promotion of oral health associated with HIV and AIDS awareness campaigns

- Oral examination is simple and non-invasive. Self inspection of the mouth should be made aware to the general population in the identification of oral lesions associated with HIV infection for example angular cheilitis, thrush, hairy leukoplakia, recurrent ulcers, Kaposi's sarcoma and oral warts.

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APPENDIX I: INFORMED CONSENT FORM

UNIVERSITY OF THE WESTERN CAPE

FACULTY OF DENTISTRY

SUBJECT INFORMED CONSENT FOR ORAL EXAMINATION

Protocol Title: Oral Lesions in HIV/AIDS Patients Before and After HAART Treatment

Name of Researcher: Antonette Masiiwa (Dr)

Phone: 0912 390 012

Project description
Examination of patients for mouth and facial problems (orofacial lesions) before they are started on Antiretroviral Therapy (ARVs), after 3months and 6months of taking ARVs. The same patients will be followed up for 6months.

YOUR RIGHTS
Before you decide whether or not to volunteer for this study, you must understand its purpose, how it can help you, and what is expected of you. This process is called informed consent.

Purpose of study:
To find out if Antiretroviral drugs can prevent or help with mouth problems like thrush, oral sores, oral cancers, gum infections and others. The oral problems will be compared with the CD4-cell counts (the amount of cells [soldiers] that protect the body from getting infections and are destroyed by HIV leading to AIDS).

Procedures involved in the study:
1.Examination of mouth, neck and face area
2.Taking of small amount of blood for CD4-cell counts
3.Taking pictures of mouth from a few individuals when necessary.

Discomforts and Risks:
Little discomfort during the oral examination without pain
Some minimal pain during bleeding for CD4-cell count blood

Potential benefits:
1.Free consultation including examination of the whole mouth and advice on treatment options available
2.CD4-cell counts will be paid for by the Principal investigator at 3months and those who cannot afford at 6months
3.Review fees will be paid for by the dentist at baseline, 3months and 6months as a token of appreciation

Study withdrawal:
You may choose not to enter the study or withdraw from the study at any time without loss of benefits entitled to you.

Confidentiality of records:
The principal investigator the dentist will keep the information in a lockable cupboard at home. The computer version will be accessed by using a password.

Problems/Questions:
Please ask any questions about this research or consent now. If you have any questions in the future please ask Dr Antonette Masiiwa at Gershon Dental Clinic, Beatrice Road infectious Disease Hospital.
Phone:0912 390 012

AUTHORIZATION:
I have read this paper about the study or it was read to me. I understood the possible risks and benefits of this study. I know being in this study is voluntary. I choose to be in this study. I know I can stop being in the study and I will not lose my benefits entitled to me. I will get a copy of this consent form. (Including all the pages of the consent form)

Client Signature	Date
Client Name (Printed)	
Researcher signature	Date
Witness Signature	Date

APPENDIX II: DATA CAPTURE SHEET

HAART Oral Health Data Capture Sheet

Date of examination:

Q1	**Project code No.**	
Q2	**Hospital code No.**	
Q3	**Patient hospital code No.**	
Q4	**Referral centre code No.**	
Q5.1	**Date of birth**	y y mth d
Q5.2	**Age**	y y mth
Q6	**Gender code**	M F

Q7 Medical History (from records)

	Condition		Key
7.1	Tuberculosis	**Y**	**N**
7.2	STI……..	**Y**	**N**
7.3	Herpes Zooster	**Y**	**N**
7.4	Oral Thrush	**Y**	**N**
7.5	Meningitis-cryptococcal	**Y**	**N**
7.6	Severe persistent rush	**Y**	**N**
7.7	10% loss of weight	**Y**	**N**
7.8	Smoking	**Y**	**N**
7.9	Other Illness (specify)		

Q8 **Physical exam lymphadenopathy & Salivary Glands**

8.1	Lymphadenopathy	**Y**	**N**
8.2	Parotid gland swelling	**Y**	**N**
8.3	Xerostomia (Dry mouth)	**Y**	**N**
8.4	Other swellings, specify	**Y**	**N**

Q9 **Appearance of marginal gingivae (Loe & Silness, 1963)**

0=normal gingival
1=mild marginal gingivitis, slight colour change & oedema
2=moderate gingival inflammmation, redness & glazing
3=A distinct red band along the marginal gingiva from papilla to papilla
4=Severe inflammation, marked redness & oedema, *with* ulceration or spontaneous bleeding

Q10 **Oral Mucosa**

	Lesion	**Baseline**	**10A**	**3 months**	**10B**	**6 mths**	**10C**
		Y	**N**	**Y**	**N**	**Y**	**N**
10.1	No lesion						
10.2	Pseudomembraneous candidiasis						
10.3	Erythematous candidiasis						
10.4	Hyperplastic candidiasis						
10.5	Angular cheilitis						
10.6	Hairy leukoplakia						
10.7	Herpetic ulceration						
10.8	Aphthous ulceration						
10.9	Atypical ulceration						
10.1	Kaposi's sarcoma						
10.11	Non-Hodgkin Lymphoma						
10.12	Oral warts						
10.13	Other (specify)						

HIV STATUS

11.2 **HIV Test**

	Item						
11.3	**Date of HIV diagnosis**						
11.4	**Route of transmission**	Sexual	IV Drugs	Transfusion	Version		
		Baseline		3 months			
11.5	**WHO Clinical Stage**						

11.6	**CD4 count**					
11.7	**CD4 count date taken**					

Q12.1	**Date started on cotrimoxazole / fluconazole Prophylaxis**	yy	mth	date

12.2	**Date stopped on cotrimoxazole/ fluconazole Prophylaxis**	yy	mth	date

Q13 HAART Treatment combinations:

13.1	**Date started with HAART:**					
		Baseline		3 months		
	Combinations:	**Y**	**N**	**Y**	**N**	**N**
	first line regimen					
13.2	stavudine + lamivudine + nevirapine					
13.3	stavudine + lamivudine + effavirenz					
13.4	zidovudine + lamivudine + nevirapine					
13.5	zidovudine + lamivudine + effavirenz					
	second line regimen					
13.6	abacavir + kaletra (lopinavir/ritonavir) + didanosine					
13.7	abacavir + saquinavir/ritonavir + didanosine					
13.8	other (specify)					

Q14 Treatment for oral lesions:

	Baseline		3 months		
Medication	**Y**	**N**	**Y**	**N**	**N**

15. History of Oral Problems

15	Have you ever had any sores/ ulcers in your mouth?	**Y**	**N**
15.1	If Y, what problem, sores, ulcers did you have?		
15.2	If Y, when did you have them?		
15.3	If Y, did they cause you pain or discomfort?	**Y**	**N**
	If Y, please explain for how long		
15.3	Are you having any pain or discomfort with your mouth now?	**Y**	**N**
15.4	If Y, is this pain /discomfort causing difficulty with:		
	Eating		
	Drinking		
	Swallowing		
	Speaking		
	Working		
	Sleeping		
	Other (specify)		

16. Oral Function

16	Have you had a painful throat?	**Often**	**Sometimes**	**Never**
16.1	Have you had problems swallowing liquids?	**Often**	**Sometimes**	**Never**
16.2	Have you had problems swallowing solid food?	**Often**	**Sometimes**	**Never**
	If Y, when did you have them?			
16.3	Have you had a problem with a dry mouth	**Often**	**Sometimes**	**Never**
16.4	Have you had problems with your sense of taste?	**Often**	**Sometimes**	**Never**
16.5	Have you had problems with your teeth?		**Y**	**N**
	If yes, explain			
16.6	Have you had trouble eating?		**Y**	**N**
	If yes, explain			
16.7	Have you had problems with your gums?		**Y**	**N**
	If yes, please explain			
16.8	Have any of your mouth problems stopped you from sleeping?		**Y**	**N**
	If yes, please explain			

APPENDIX III: ORAL MUCOSAL EXAMINATION

Topographical classification of oral mucosa

CODE	CONDITION	CODE	LOCATION
1	No abnormal condition	**11**	Upper lip
2	Angular cheilitis	**12**	Lower lip
3	Commisural pits	**13**	Mucosa of upper lip
4	Traumatic lesions	**14**	Mucosa of lower lip
5	Geographic tongue	**15**	Mucosa around corner of mouth on r side
6	Dentoalveolar abscess	**16**	Mucosa around corner of mouth on l side
7	Herpes labialis	**17**	Cheek mucosa on r side of patient
8	Fissured tongue	**18**	Cheek mucosa on l side of patient
9	Ulcerations	**19**	Mucosa of upper jaw, bet lip/cheek & gum
10	Herpetic gingivostomatitis	**20**	Mucosa of upper jaw, bet lip/cheek & gum
11	ANUG	**21**	Mucosa of gums of upper teeth
12	Verruca vulgaris	**22**	Mucosa of gums of lower teeth
13	Papilloma	**23**	Top surface of tongue
14	Focal epithelial hyperplasia	**24**	Sides of tongue
15	Melanotic hyperpigmentation	**25**	Undersurface of tongue
16	Candidiasis	**26**	Mucosa bet under surface of tongue & gums of lower teeth
17	Other	**27**	Mucosa of hard palate
		28	Mucosa of soft palate

Criteria used for diagnosis of oral mucosal lesions

Lesion	Criteria
1. White non-adherent lesions	
(a) Candidiasis: acute pseudomembraneous	Creamy white patches, wipeable leaving red patches
(b) Aspirin Burn	White necrotic epithelium; Will slough off/rub off to reveal ulcer underneath
2. White or white/red adherent lesions	
Local aetiology suspected	
(a) Frictional white lesion	Whitish or greyish patch on the mucosa which cannot be rubbed off
(b) Cheek & lip biting	Oral mucosa shows a rough, grey-white, macerated surface with irregular, flaky desquamation. Lesion is located self-infliction by chewing is possible.
Local aetiology not present/known	
(a) Leukoplakia	- A white patch, or plaque, that cannot be wiped off and cannot be characterized clinically or pathologically as any other disease - Varies from small circumscribed areas to extensive lesions involving a large area of the mucosa - Surface appearance is variable; - May be smooth or wrinkled - Smooth-surfaced but traversed by small cracks - Nodular or speckled - Colour can be white, whitish-yellow or grey **Recommended subdivisions:** - *homogeneous*: lesions that are uniformly white with smooth or corrugated surface - *non-homogeneous*: lesions in which part is white and part appears reddened. Three types have been described: - Erythroleukoplakia (erosive leukoplakia) – white lesion that includes red areas - Nodular leukoplakia – lesion with slightly raised white areas (granules or nodules) - Verrucous leukoplakia – exophytic lesion with irregular sharps or blunt projections.
(b) **Candidiasis, chronic hyperplastic**	- Adherent white plaque, may be flat or elevated - May incorporate erythematous areas
(c) **Red lesions**	
Candidiasis, acute atrophic Erythroplakia	- Bright red atrophic patches on mucosa - burning or itching sensation is common, palate is a common location; bright red patches or plaques of mucosa that cannot be characterized clinically or pathologically as any other condition

Lesion	Criteria
3. Perioral conditions (a) Actinic keratosis (actinic elastosis or actinic cheilitis)	- Vermillion border poorly defined (loss of distinction between vermillion border, labial mucosa and skin - Border may have localized crust formation and/or a whitish colour, common in patients with outdoor occupations
(b) Angular cheilitis	- Bilateral folds in the skin of the labial commissures, surface tissue appears wrinkled, fissured or cracked - No tendency to bleeding, although a crusted exudate may be present - Mucosal surface of commissures are usually not involved
4. Tongue lesions **(a) Fissured tongue**	- Shallow or deep fissures on the dorsum of the tongue; most common pattern is a marked central fissure, from which smaller fissures radiate laterally - Food debris may accumulate in fissures and result in inflammation - Often association with geographic tongue
(b) **Geographic tongue**	- Localized absence of filiform papillae - Affected areas are irregularly shaped - Areas change location over time
(c) **Hairy tongue**	- Overgrowth of filiform papillae in which they become elongated or thickened - Colour of tongue varies from white to yellow or greenish, but is most commonly brown or black
(d) **Median rhomboid glossitis**	- Deep red or white ovoid area devoid of tongue papillae - Located in the central dorsum of the tongue near the foramen caecum - Sometimes demarcated from surrounding mucosa by a furrow
(e) **Hairy leukoplakia**	- Flat white lesion which cannot be rubbed off - Corrugated surface appearance - Usually found on the lateral borders of the tongue
5**. Ulcers** (a) ANUG	"Punched-out" papillae - Pseudomembranous exudate - Bleeding upon slight palpation - Pain, distinctive oral odour
(b) Herpetic gingivostomatitis (primary herpes)	- Severe gingival inflammation - Whitish, serofibrinous exudate - Vesicles and/or shallow ulcers; pain, malaise, fever
(c) Herpes labialis (secondary herpes)	- Clusters of vesicles or crusts - Found on vermillion border - Duration: less than three weeks - History of recurrence
(d) Recurrent aphthous ulceration	- Well-defined, greyish-white ulcer(s) - Ulcers surrounded by red halo

	- Pain; duration: 10-21 days; history of recurrence
Lesion	**Criteria**
(e) Ulcer (non-specific)	- Traumatic ulcers - Idiopathic ulcers - Toothbrushing-induced ulcers
6. Elevated lesions (a) Gingival hyperplasia	- Enlarged gingiva and interdental papillae - Papillae may be stippled or glazed in appearance - Usually presents as a generalized condition
(b) Mucocele	- Well-defined, fluid-filled swelling - Normal pink or bluish colour - Commonly found on labial mucosa and floor of the mouth (ranula)
(c) Focal epithelial hyperplasia (Hick's disease)	- Multiple circumscribed soft elevations - Whitish to normal coloration - Primary seen in American Indians and Eskimos
(d) Papilloma	- Exophytic growth, usually pedunculated - Verrucous, "cauliflower-like' surface - White or greyish colour is characteristic
(e) Verruca vulgaris	- Sessile or pedunculated lesion(s) - Papillomatous surface; common locations are the labial commissure & gingiva
(f) Tumour (non-specific)	Kaposi's sarcoma - Oral tumour(s) presenting with bluish or reddish macules in early stages - Lesions later become darker, elevated and sometimes lobular - The palate and gingiva are the common intraoral locations
Pigmented lesions (a) Amalgam tattoo	- Asymptomatic pigmented area, non-elevated - Bluish, blackish or slate-grey colour - Borders are usually poorly defined - Mucosal surface appears normal
(b) Naevus	- Well-circumscribed flat or elevated area - Pigmented with melanin - Colour range from blue to brown or black - Cannot be classified as due to exogenous pigmentation