TITLE: THE SCOPE AND SPECTRUM OF CHALLENGES PRESENTED TO THE GENERAL SURGEON BY PATIENTS AFFECTED WITH THE HUMAN IMMUNODEFICIENCY VIRUS (HIV): A REVIEW

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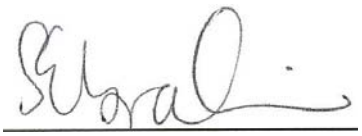

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LIST OF ABBREVIATIONS

- AAC: Acute Acalculous Cholecystitis
- AC: Acquired Immunodeficiency Syndrome Related Cholangiopathy
- ACTG: AIDS Clinical Trial Group
- ADC: Acquired Immunodeficiency Syndrome Defining Cancers
- AIDS: Acquired Immunodeficiency Syndrome
- AVF: Arterio- Venous Fistula
- BLEC: Benign Lymphoepithelial Cysts
- BLEL: Benign Lymphoepithelial Lesions
- CBD: Common Bile Duct
- CD4 count: Cluster of Differentiation 4 count
- CDE: Cyclophosphamide, Doxorubicin, Etoposide
- CHOP: Cyclophosphamide, Hydroxydoxorubicin, Vincristine (Oncovin), Prednisone
- CMV: Cytomegalovirus
- CNS: Central Nervous System
- CR: complete response
- CT scanning: Computed Tomography scanning
- DFS: disease free survival

- DILS: Diffuse Infiltrative CD8 Lymphocytosis Syndrome
- DLBCL: Diffuse Large B-Cell Lymphoma
- DVT: Deep Vein Thrombosis
- EBV: Epstein Barr Virus
- EPOCH: Etoposide, Prednisone, Vincristine (Oncovin), Cyclophosphamide, Hydroxydoxorubicin
- ERCP: Endoscopic Retrograde Cholangiopancreatography
- EUS: Endoscopic Ultrasound
- FNAC: Fine Needle Aspiration Cytology
- GI: Gastrointestinal
- GIT: Gastrointestinal Tract
- Gy: Grey (International system of units/ SI unit of absorbed radiation)
- HAART: Highly Active Antiretroviral Therapy
- HHV8: Human Herpes Virus 8
- HIDA scanning: Hepato- Iminodiacetic Acid scanning
- HIV: Human Immunodeficiency Virus
- HIV-SGD: Human Immunodeficiency Virus associated Salivary Gland Disease
- HIV-1 Tat protein: Human Immunodeficiency Virus 1- Transactivating Protein

- HL: Hodgkin’s Lymphoma
- HLA: Human Leukocyte Antigen
- INR: International Normalised Ratio
- IPI: International Prognostic Index
- KS: Kaposi’s Sarcoma
- MALT: Mucosa- Associated Lymphoid Tissue
- m-BACOD: Methotrexate, Bleomycin, Doxorubicin (Adriamycin), Cyclophosphamide, Vincristine (Oncovin), Dexamethasone
- MRCP: Magnetic Resonance Cholangiopancreatography
- MRI: Magnetic Resonance Imaging
- MTB: *Mycobacterium tuberculosis*
- NHL: Non- Hodgkin’s Lymphoma
- PE: Pulmonary Embolism
- PET scanning: Positron Emission Tomography scanning
- PI: Protease Inhibitors
- PJP: *Pneumocystis jiroveci* Pneumonia
- RCT: Randomized controlled trial
- SA: South Africa

- SSA: Sub- Saharan Africa
- SMC: Human arterial Smooth Muscle Cells
- TB: Tuberculosis
- VTE: Venous Thromboembolism

LIST OF TABLES

ABSTRACT

Title: The Scope and spectrum of challenges presented to the general surgeon by patients affected with the Human Immunodeficiency Virus (HIV): A Review

Background: Surgical disease related to HIV is scantily documented with a paucity of data detailing the manifestations of HIV in surgery especially in resource-poor, high prevalence settings such as in South Africa. This review provides an update on the topical issues surrounding HIV and surgery.

Objectives: The objective of the study was to determine the incidence, pathogenesis, clinical presentation, aspects of diagnosis and management of: HIV- associated salivary gland disease in particular parotid gland enlargement; Kaposi's sarcoma (KS) and lower limb lymphoedema; AIDS- related abdominal malignancies due to KS and lymphoma; Acalculous cholecystitis and HIV- cholangiopathy and HIV- associated vasculopathy.

Methods: A collective review of the literature was performed and data sourced from a search of relevant electronic medical databases for literature from the period 2000 to the present date. Studies under each section were selected based on inclusion and exclusion criteria. Content analysis was used to analyse data.

Results: The HIV pandemic has resulted in an increased frequency of benign lymphoepithelial cysts making it the commonest cause of parotidomegaly in most surgical practices. KS should be considered in the differential diagnosis of a patient with chronic lymphoedema. Lymphoedema may be present without cutaneous lesions, making clinical diagnosis of KS difficult. The gastrointestinal tract is the commonest site of extra- cutaneous KS. Surgical management of the lymphoma patient is restricted nowadays to determining the diagnosis and in some cases to evaluate disease stage. Highly active antiretroviral therapy

(HAART) is an important part of the management of biliary tract conditions in addition to relevant surgical procedures. HIV- vasculopathy represents a distinct clinico- pathological entity characterized by a vasculitis with probable immune- mediated or direct HIV- related injury to the vessel wall.

Conclusion: The rising incidence of HIV in South Africa and other developing countries has been associated with new and unusual disease manifestations requiring surgical management for diagnostic, palliative or curative intent. It is crucial that surgeons remain abreast of new developments related to the challenging spectrum of HIV and its protean manifestations.

CONTENTS

CHAPTER 1

1.1 Introduction

Acquired immunodeficiency syndrome (AIDS) was first described in the United States of America in 1981. The afflicted individuals included previously well, young homosexual men, who presented with rare infections such as *Pneumocystis jiroveci* pneumonia (PJP), mucosal candidiasis, disseminated cytomegalovirus (CMV), and Kaposi's sarcoma (KS) (1).

The aetiology of AIDS remained an enigma, leading to a number of theories. Shortly thereafter, amid considerable debate, the causative agent was recognized as Human Immunodeficiency Virus (HIV). HIV infects and destroys the immune effector cells or the CD4 T lymphocytes. The identification of HIV led to the development of definitive diagnostic tests and exposed to the world a disease entity of epic proportion (1).

It is estimated that 22.5 million people are currently living with HIV in sub-Saharan Africa (SSA) and in 2009, approximately 1.3 million people died from AIDS in the region. South Africa, with an estimated 5.7 million people living with HIV, has the highest burden of HIV disease globally (2). Thus HIV/AIDS has become the foremost cause of death and years of life lost (3).

As surgeons we find ourselves struggling with many of the issues surrounding HIV and our standard of care to our patients (4). Health care personnel face many unique challenges in managing the sequelae of HIV, particularly in Africa, where resources are limited (5). Surgical intervention for patients with HIV infection may be necessary for problems related and unrelated to HIV infection for example, trauma (6). As the incidence of HIV continues to rise in South Africa and other developing countries, so too will the surgeon be faced with

new and unusual diseases requiring surgical management for diagnostic, palliative or curative intent (5) (6) (7).

In a proportion of patients, surgical illness unique to HIV/AIDS may be the initial manifestation of HIV infection, for example HIV- related salivary gland disease and parotid enlargement, allowing for diagnosis of HIV and ensuring timely access to highly active antiretroviral therapy (HAART) (7) (3). Thus surgeons are uniquely positioned to assist in preventing HIV transmission through screening in patients who are not aware that they are infected (8). They also aid in preventing further HIV- related morbidity by ensuring that those patients testing HIV positive have timeous access to appropriate clinical care (8). Surgeons therefore have a key, synergistic role to play, with HIV practitioners in the management of HIV positive patients (6).

The epidemiology of HIV/AIDS has altered significantly since the introduction of HAART over a decade ago, with mortality rates having declined appreciably. While there are few studies assessing the prevalence of HIV infection in surgical patients, it is likely that since the introduction of HAART these numbers are steadily growing (8). This presents a new and diverse workload for all surgical specialties, which have also had to evolve in order to deal with the challenging spectrum of this disease entity (6).

Hitherto, the emphasis has been on the medical and paediatric aspects of HIV and in particular on opportunistic infections. Surgical diseases related to HIV are seldom documented and there is a lack of literature detailing the manifestations of HIV/AIDS in surgery particularly in resource-poor, high prevalence settings such as South Africa (3).

This study reviews HIV- related conditions of interest to the general surgeon, such as parotid gland enlargement, the protean manifestations of KS, AIDS- related abdominal malignancies,

HIV- associated biliary tract diseases and HIV- associated vasculopathy and provides a much needed update on the topical issues surrounding HIV and surgery.

1.2 Problem statement

Due to the high prevalence of HIV in SSA, surgeons are confronted by many factors associated with HIV- related surgical pathology such as aspects of clinical presentation, establishing the diagnosis, management and the role of HAART. At present there is a lack of literature relating to these aspects and there is a need for practical guidelines in order to improve the standard and quality of care we provide to our patients.

1.3 Significance of the study

The study provides a comprehensive update on the issues surrounding HIV- related surgical pathology. New developments and gaps in the existing literature were highlighted and implications for clinical practice as well as future research were discussed.

1.4 Aim of the study

The study aimed to provide a critical overview of the current literature with respect to certain HIV- related conditions of interest to the general surgeon.

1.5 Specific Objectives

The objective of the study was to determine the incidence, pathogenesis, clinical presentation, aspects of diagnosis and management of:

- HIV- associated salivary gland disease in particular, parotid gland enlargement
- Kaposi's sarcoma and lower limb lymphoedema
- AIDS- related abdominal malignancies due to KS and lymphoma

- HIV- related acalculous cholecystitis and cholangiopathy
- HIV- associated vasculopathy

CHAPTER 2: METHODS

2.1 Ethical Considerations

Ethical approval for this study was waived by the University of KwaZulu- Natal (UKZN) Biomedical Research Ethics Committee (BREC), BE 099/011. On 02/08/2011, the Postgraduate Education Committee at UKZN ratified the study (Appendix 1 and 2).

2.2 Study Design

The study consisted of a literature review of relevant published material.

2.2.1 Search strategy

A review of the literature using the relevant search engines and search terms (as listed below) was undertaken and involved a thorough search of the existing literature to collate evidence.

Search engines and electronic databases

- University of KwaZulu Natal (UKZN) Primo search
- Biomed central
- Science Direct
- Cochrane library
- CINAHL
- EBSCO host research databases
- Google scholar
- MD consult
- Medline/ Pubmed

An experienced medical librarian was consulted to ensure that appropriate methods for conducting a comprehensive search of the above databases as well as accessing full text articles were done.

Relevant search terms included the following keywords and Medical Subject Headings (MeSH) terms were used

- HIV- associated salivary gland disease, parotid enlargement
- Kaposi's sarcoma, HIV and lymphoedema
- AIDS- related abdominal malignancies, Kaposi's sarcoma and lymphoma
- Acalculous cholecystitis, cholangiopathy and HIV
- HIV- associated vasculopathy

2.2.2 Inclusion and Exclusion criteria

The inclusion criteria were:

- Human subjects
- Adults (>19 years old), infected with HIV
- English language text
- From the year 2000 to the present date
- Studies from both developed and developing countries
- Patients being treated with HAART and those not on antiretrovirals
- Quantitative research studies

The exclusion criteria were:

- Literature published before the year 2000
- Foreign language publications
- Conference proceedings

2.2.3 Data collection methods

The titles and abstracts of relevant articles and studies were collected and appropriate full text articles obtained. The studies for each disease were assessed for suitability according to the inclusion and exclusion criteria. Duplicate articles were discarded and further articles sourced from a manual search of the reference lists. The relevant results from each article were summarized and entered into a prepared Microsoft Office Excel database by the researcher.

2.3 Data analysis

Due to the variety of research designs and study variables used, heterogeneity of results was expected. This prevented the ability to perform meta- analyses of the search findings and the studies were evaluated through content analysis (9).

Content analysis as a research method may be applied to both qualitative or quantitative data (10). It allows for a systematic and objective means of describing and quantifying phenomena, and may be used in an inductive or deductive way. The inductive approach was applied as prior knowledge of this subject is limited and fragmented in the literature. Deductive content analysis was used when the data analysis was based on previous knowledge and the purpose of the study was theory testing. The three main phases in both the inductive and deductive processes are: preparation, organizing and reporting (10). The preparation phase involved identifying common themes in each study namely incidence,

pathogenesis, clinical presentation, diagnosis and management. In the organization phase, studies with similar themes were grouped together and the results analysed. In the reporting phase, the findings were documented.

Each condition was analysed with respect to:

- Study design
- Incidence: including differences between developed and developing countries
- Pathogenesis/ pathophysiology of disease processes
- Clinical presentation
- Aspects of diagnosis
- Staging and prognosis where applicable
- Management/ treatment strategies
- HAART in the management

New developments and gaps in the existing literature were highlighted and implications for clinical practice as well as future research were discussed.

Studies were categorized according to the 'methodological hierarchy of evidence' proposed by Sackett *et al* (2000), which are described as follows (11):

- 1A = Systematic Review of Randomized Controlled Trials (RCTs)
- 1B = RCTs with Narrow Confidence Interval
- 1C = All or None Case Series
- 2A = Systematic Review Cohort Studies
- 2B = Cohort Study/ Low Quality RCT
- 2C = Outcomes Research

- 3A = Systematic Review of Case- Controlled Studies
- 3B = Case- controlled Study
- 4 = Case Series, Poor Cohort Case Controlled
- 5 = Expert Opinion

The stratification is in order from the strongest to the weakest levels of evidence namely Level 1A to Level 5 respectively (12). The levels can also be understood as starting with the most reliable type of study or the study least vulnerable to bias, to the least reliable type of study or the study most vulnerable to bias (12).

One chapter was dedicated to each of the five HIV- related surgical pathologies as follows:

- HIV- associated salivary gland disease, in particular parotid enlargement
- HIV- associated KS and lower limb lymphoedema
- AIDS- related abdominal malignancies due to KS and lymphoma
- HIV- related acalculous cholecystitis and cholangiopathy
- HIV- associated vasculopathy

CHAPTER 3: HIV- ASSOCIATED SALIVARY GLAND DISEASE

3.1 Introduction

Oral lesions can be an early occurrence in HIV infection and may be used to predict its progression to AIDS (13). These lesions affect the patients' quality of life (14) and a better understanding of these orofacial complications is therefore vital for all health care professionals (13). A wide spectrum of pathological conditions including infections, neoplasms, salivary gland disease and other miscellaneous conditions have been implicated (15). This chapter reviews the epidemiology, pathogenesis, clinical presentation, aspects of diagnosis and management of HIV- salivary gland disease (SGD) in particular, parotid gland enlargement.

3.2 Methods

A collective review of the literature using the relevant search engines and search terms as described in Chapter 2 (Methods) was undertaken. Relevant search terms included: "HIV-associated salivary gland disease", "HIV and parotid enlargement". A total of 112 articles were identified for the period 2000 to the present date. Of these, 43 articles fulfilled the inclusion criteria and were considered suitable for review. Studies were evaluated using content analysis as described in Chapter 2 (Methods). (Table 1) presents the types of studies and methodological quality of studies reviewed. Systematic reviews of cohort studies and cohort studies were the commonest methodological approaches. Case series and case reports made up the remainder of the studies. Randomized controlled trials and systematic reviews of these were not represented.

Table 1: Type of studies and methodological quality

Type of study	Number	Level of evidence
Systematic reviews of cohort studies	19	2A
Cohort studies	14	2B
Case series	2	4
Case reports	8	4
Total	**43**	

3.3 Incidence of HIV- associated salivary gland disease

Head and neck lesions associated with HIV arise in more than 50% of HIV- positive patients and occur in nearly 80% of all patients with AIDS (16). The prevalence of HIV- associated salivary gland disease in Africa is 19.04% and in Thailand 1% (14). In developed countries, parotid gland enlargement occurs in about 1%- 10% of HIV- infected patients, with benign lymphoepithelial cysts (BLEC) present in 3%- 6% of these cases (17) (16). Oral lesions in HIV have been well described in literature from developed countries, however in developing countries, these reports have been scanty (14).

3.4 Pathogenesis

Parotid gland enlargement is commonly due to the development of BLEC within the parotid gland. The precise aetiology of these lesions is unknown (18) and much controversy exists as to its pathogenesis (16). BLEC is defined as single or multiple cysts within lymph nodes trapped during parotid gland embryogenesis (18). As these lymph nodes are situated mainly along the tail of the parotid gland, this part enlarges early on in the course of the disease process (18). This lymphoid proliferation may result in ductal obstruction and ductal

dilatation that mimics a true cyst (16). Parotid enlargement may also result from proliferation of the glandular epithelium that is trapped within these intraparotid lymph nodes (16). HIV has a predilection for lymphoid tissue and elevated concentrations of the virus can be found within these nodes (18).

There is considerable debate as to the terminology used to describe these lesions. The terms include: benign lymphoepithelial cysts (BLEC), benign lymphoepithelial lesions (BLEL), cystic BLEL, AIDS- related lymphadenopathy, diffuse infiltrative CD8 lymphocytosis syndrome (DILS), cystic lymphoid hyperplasia and HIV- (SGD) (16).

3.5 Clinical presentation

In HIV- infected patients, the most common salivary gland presentation is salivary gland swelling with or without xerostomia. This may be due to acute sialadenitis or to HIV-SGD (16). However, a wide spectrum of benign and malignant pathological conditions may be implicated as listed below, (Table 2). Oral lesions are often an early manifestation of HIV (16). They may lead to considerable morbidity in terms of discomfort or dysfunction (16) and are also important as indicators of disease progression and immunosuppression (14).

Table 2: Revised Classification of Oral Lesions Associated With HIV Infection (19)

Group 1: Lesions strongly associated with HIV infection
Candidiasis†
Erythematous
Pseudomembranous
Hairy Leukoplakia
Kaposi sarcoma
Non-Hodgkin lymphoma
Periodontal disease
Linear gingival erythema
Necrotizing (ulcerative) gingivitis
Necrotizing (ulcerative) periodontitis
Group 2: Lesions less commonly associated with HIV infection
Bacterial infections
Mycobacterium avium-intracellulare
Mycobacterium tuberculosis
Melanotic hyperpigmentation
Necrotizing (ulcerative) stomatitis
Salivary gland disease
Dry mouth due to decreased salivary flow rate
Unilateral or bilateral swelling of major salivary glands
Thrombocytopenic purpura
Ulceration NOS (not otherwise specified)
Viral infections
Herpes simplex virus
Human papillomavirus (warty lesions)
Condyloma acuminatum
Focal epithelial hyperplasia
Verruca vulgaris
Varicella–zoster virus
Herpes zoster
Varicella
Group 3: Lesions seen in HIV infection
Bacterial infections
Actinomyces israelii
Escherichia coli
Klebsiella pneumoniae
Cat-scratch disease
Drug reactions (ulcerative, erythema multiforme, lichenoid, toxic epidermolysis)
Epithelioid (bacillary) angiomatosis
Fungal infection other than candidiasis
Cryptococcus neoformans
Geotrichum candidum
Histoplasma capsulatum
Mucoraceae (*mucormycosis/zygomycosis*)
Aspergillus flavus
Neurologic disturbances
Facial palsy
Trigeminal neuralgia
Recurrent aphthous stomatitis
Viral infections
Cytomegalovirus
Molluscum contagiosum
*As agreed at a meeting of the EC Clearinghouse on oral problems related to HIV infection
†The terms “candidosis” and “candidiasis” are used here interchangeably

For the purposes of this study BLEC and DILS leading to parotid gland enlargement were reviewed as they are conditions of interest to the general surgeon.

Benign lymphoepithelial cysts: While these usually present as painless bilateral parotid enlargement (15), unilateral parotid swelling has also been documented (16). The cysts can enlarge, cause discomfort, or may be cosmetically unacceptable to patients (20). The other salivary glands are rarely affected, however, the submandibular gland may be involved in some cases (16). The association between BLEC and HIV is usually during the early phases of viral infection, but it can affect patients at any stage of HIV (21) (22).

The differential diagnosis of these cysts include: branchial cysts, salivary duct cysts, traumatic sialocoeles, Sjogren's syndrome, lymphangiomas, tuberculous abscesses, cystic tumours, malignancies for example cystadenocarcinoma, as well as those due to Non-Hodgkin's lymphoma (NHL) and Kaposi's sarcoma (KS) (20). These conditions are important to consider and exclude in general surgical practice using the diagnostic methods described below.

Diffuse infiltrative CD8 lymphocytosis syndrome: This disease process is seen in a subgroup of HIV- positive patients and is characterized by a CD8 lymphocytosis, bilateral parotid swelling, a diffuse visceral CD8 lymphocytic infiltration (usually involving the lung), and cervical lymphadenopathy (23). An immunogenetically distinctive group (HLA- DR5) is particularly predisposed to this pathology (24).

In summary, the clinical assessment of patients with HIV and parotid swelling, involves taking a thorough history related to the time of onset, rate of growth as well as symptoms associated with the mass for example pain and discomfort. Constitutional symptoms such as fever, loss of weight and night sweats, should alert the practitioner to the possibility of

tuberculosis (TB) or lymphoma and a sudden increase in gland size should arouse suspicion of possible lymphomatous transformation. On physical examination, one must examine both parotid glands for masses and the neck for lymphadenopathy. Features of malignant transformation such as induration, pain, fixation and facial nerve pathology should also be noted (25).

3.6 Aspects of diagnosis

The diagnosis of BLEC is very specific to HIV infection. Thus, if it is confirmed in a patient with an unknown HIV status, it is mandatory to perform an HIV test as part of the diagnostic work- up (26).

Diagnostic modalities may be non- invasive and invasive. Non- invasive diagnostic evaluation consists of an ultrasound scan of the parotid gland, computed tomography scanning (CT) and/ or magnetic resonance imaging (MRI) in cases of diagnostic ambiguity. Ultrasonography allows for evaluation of both cystic and lymphoproliferative lesions of the parotid glands. Furthermore, its advantages include that it is easy to perform, painless, inexpensive, readily available and obviates radiation exposure to patients (27). In a study by Kabenge *et al* (2010), four distinctive ultrasound patterns in the parotid glands of HIV-positive patients were described. These included: lymphocytic aggregations; lymphoepithelial cysts (prominent round hypoechoic areas with well circumscribed margins and internal septa); fatty infiltration (in patients on protease inhibitor HAART) and lymphadenopathy (28).

Invasive procedures include fine needle aspiration cytology (FNAC) of the parotid gland, which is a safe and suitable diagnostic modality and is recommended to exclude the lesions described above (26). It is also important to exclude malignancy, which may occur in a small

percentage (1%) of patients with HIV- associated cystic lesions, and in solid lesions where the incidence of malignancy can be as high as 40% (29). Aspiration of yellow mucous type fluid is indicative of HIV-SGD (30). FNAC of BLEC reveals a heterogeneous lymphoid population, scattered foamy macrophages and anucleated squamous cells in a proteinaceous background. Diagnosis of DILS is confirmed on minor salivary gland biopsy which reveals lymphocytic infiltration (25).

The aetiology of BLEC remains obscure and the role of epidermotropic viruses such as EBV and CMV has been suggested. However conflicting reports exist in the literature as to the main causative organism. Further laboratory evaluation with immunohistochemistry and insitu hybridization techniques are therefore necessary to elucidate the role of these viruses in the pathogenesis of HIV-SGD (31).

3.7 Management of HIV- related parotid gland enlargement

The management of parotid gland BLEC is not well described with different opinions regarding the best treatment approach (16). The options include: serial follow- up and observation of lesions, aspiration of lesions, sclerosing therapy, HAART, radiation therapy and surgery (16).

For asymptomatic lesions, monitoring is a viable option and should be at six- monthly intervals, with radiographic and histopathologic analysis where necessary to exclude malignancy. BLEC are slowly progressive lesions and any sudden increases in gland size requires prompt investigation due to the risk of lymphomatous transformation (16).

Aspiration is a quick procedure, but results are short- lived, as cysts tend to recur within weeks to months and continue to enlarge (16). Sclerotherapy with tetracycline and doxycycline (16) as well as intralesional bleomycin (20) and alcohol (32) have been used

resulting in cyst size reductions of between 42% to 100% being reported (16). However its role is limited in cases where multiple, loculated cysts of varying size are present (18).

Antiretroviral therapy has been shown to reduce the incidence of BLEC and DILS (16) (33) (25). However, some studies show an overall increase in the prevalence of HIV-SGD in the HAART era (30), (see results below). HAART may also be combined with a short course of tapered- dose corticosteroids in the treatment of these lesions (18). Promising results have also been reported with the use of low- dose external beam radiotherapy (24Gy in 1.5Gy daily fractions) (18). However, the reduction in size of lesions usually lasts less than ten months (25).

Superficial parotidectomy has been practised, but due to the significant morbidity (facial nerve injury and the need for repeat procedures) that is associated with what is mainly a cosmetic procedure, it is rarely recommended (16). It may be feasible in cases of poor response of parotid lesions to the treatment options listed above, or where there is concern that a lesion may have malignant potential (18).

3.8 HAART in the management of HIV- associated salivary gland disease

As oral manifestations of HIV are usually the earliest sign of infection and may also point toward progression to AIDS, they are a useful proxy measure of the success or failure of antiretroviral therapy (34). In a study of a cohort of women enrolled in the Women's Interagency HIV Study (WIHS), results showed that higher viral loads and lower CD4 and CD8 counts correlated with the possibility of developing SGD (35).

Therapy with HAART has been successful in eradicating parotid swellings due to a cessation of viral replication, a decrease in viral load and stabilization of CD4/CD8 cell counts (36). Treatment is life- long due to the fact that the immune system cannot clear residual virus

(36). Several studies however have shown conflicting results with respect to the prevalence of SGD in the era of HAART, some studies showing an increase or unchanged prevalence rates (30). The reasons postulated for this include: size of pre-existing lesions, duration of therapy, different HAART regimens (34), and discrepancies in HAART availability in developing countries (37). In contrast, significantly lower prevalence rates of DILS in the post- HAART era were reported, signifying that DILS is an antigen (viral) - driven response and the key treatment being antiretroviral therapy. (38).

The possibility of HAART induced lipodystrophy syndrome and deposition of fat in the paraparotid region has been proposed. This may clinically mimic parotidomegaly and is easily distinguished from true HIV- associated parotidomegaly on imaging modalities (23).

3.9 Discussion

Reasons for the high prevalence rates of HIV-SGD in Africa are unknown. It may be due to the presence of HLA-DR5 and untreated advanced stage AIDS in Africans (14). Malnutrition is rife in many African countries and this is an important factor in inducing oral mucosal disruptions, thus playing a role in the pathogenesis of HIV-SGD (39). The few studies on the incidence rates of HIV-SGD reviewed (review articles and cohort/ observational studies), reflect a dearth in literature from developing countries where the prevalence of HIV and its associated manifestations is high and the need for emerging research cannot be over emphasized (39).

The management options for HIV-SGD and parotid enlargement are numerous and much debate exists as to the ideal treatment algorithm (16). Studies used to gain information on diagnostic and management aspects of HIV-SGD, included review articles, cohort studies and case reports. Most studies concurred that with the advancements in imaging modalities and

cytolopathological evaluation, surgery is rarely indicated for diagnosis of possible malignant lesions (16). There is also a shift away from surgery for what is essentially described as a cosmetic procedure, for a benign pathological entity, due to its attendant morbidity and it is recommended only as a last resort when all other treatment options have been exhausted (16).

3.10 Conclusion

The HIV pandemic has resulted in an increased frequency of BLEC, making it the commonest cause of parotidomegaly in most surgical practices (18). FNAC is mandatory to exclude the possibility of other lesions such as lymphoma or KS (18). The treatment of HIV-SGD remains non-specific (40). While the frequency of HIV-SGD may increase on HAART, it may also be resolved with HAART (24). There is a shift away from surgical management of these lesions (18).

In our setting the general surgeon usually represents the first point of care practitioner for patients with parotid gland enlargement related to HIV. It is thus crucial that the general surgeon be knowledgeable about the aspects of clinical presentation, common diagnostic modalities and available treatment options for this disease entity.

There is a paucity of literature describing aspects of HIV-SGD and parotid enlargement especially from developing countries, including South Africa. In these areas, where HIV infection is rampant, and healthcare resources are limited, epidemiological studies and research on feasible diagnostic and management modalities are critical to reduce further morbidity (39).

CHAPTER 4: HIV- ASSOCIATED KAPOSI'S SARCOMA AND LOWER LIMB LYMPHOEDEMA

4.1 Introduction

Kaposi's sarcoma (KS) is a vascular tumour of lymphatic endothelial origin affecting mucocutaneous sites and visceral organs (41) and is the commonest form of cancer in HIV-positive patients (42). Lymphoedema associated with HIV-KS frequently involves the lower extremities, face and genitalia leading to significant morbidity (41) (42). This review highlights the epidemiology of KS and associated lymphoedema, its pathogenesis, clinical manifestations, diagnosis, staging, prognosis and management.

4.2 Methods

A collective review of the literature using the relevant search engines and search terms as described in Chapter 2 (Methods) was undertaken. Relevant search terms included: "HIV" and "Kaposi's sarcoma" and "lower limb lymphedema". A total of 278 articles were identified for the period 2000 to the present date. Of these, 52 articles fulfilled the inclusion criteria and considered suitable for review. Studies were evaluated using content analysis as described in Chapter 2 (Methods). (Table 3) illustrates the types of studies and methodological quality of studies reviewed. Systematic reviews of cohort studies and cohort studies were the commonest methodological approaches. Other study types included: systematic reviews of randomized controlled trials, randomized trials, a low quality RCT, case series and case reports.

Table 3: Type of studies and methodological quality

Type of study	Number	Level of evidence
Systematic review of randomized controlled trials	3	1A
Randomized controlled trials	1	1B
Systematic reviews of cohort studies	28	2A
Cohort studies	13	2B
Low quality RCT	1	2B
Case series	2	4
Case reports	4	4
Total	**52**	

4.3 Incidence of Kaposi's sarcoma and lower limb lymphoedema

KS is the most common tumour among the AIDS patient group and is recognised as an AIDS-defining illness (43). KS is endemic in Africa (44) and prior to the HIV/AIDS epidemic in Africa, its incidence varied geographically, with the highest levels in central Africa (45). This geographical association is most likely due to the prevalence of human herpesvirus 8 (HHV8), the aetiologic agent for KS development (45). This endemic form of KS was predominantly a disease of the elderly, with a male predominance (45). Following the advent of HIV/AIDS, these areas in Africa (Uganda, Malawi, Zambia and Swaziland) where KS was common, now demonstrate much higher incidence rates (20- fold increase). It has thus become the most frequently diagnosed malignancy in males in Africa, constituting 12.9% of all cancers in males, and 5.1% of all cancers in females, making it the third commonest cancer in females (45).

Incidence of Kaposi's sarcoma- associated lymphoedema: The incidence of lower limb lymphoedema has not been consistently reported in the studies reviewed. In two cohort studies, the incidence rates of lower limb lymphoedema were 30% and 15% respectively (46) (47).

HHV8 seroprevalence and mode of transmission: HHV8 is the main aetiological factor for KS (48). Although necessary, it is not sufficient on its own to cause KS (49). High rates of HHV8 in many parts of SSA, have been shown on seroepidemiological studies, with up to 40% of adult populations found to have antibodies to HHV8 (50). The modes of transmission of HHV8 are multiple and need to be better clarified (50) (51). HHV8 may be detected in a variety of body fluids and possible modes of transmission include vertical, horizontal, blood transfusion, injection drug use, as well as solid organ or bone marrow transplantation (52).

4.4 Pathogenesis

KS development can be regarded as the complex interaction of HIV- induced immunosuppression (Tat- protein), HHV8 and various cytokines. HHV8 can infect the vascular endothelial cells resulting in stimulation of various growth factors and ultimately leading to significant vascular spindle- cell proliferation, subcutaneous fibrosis and hyperkeratosis (53) (41).

HHV8 infection of different cell types in lymph nodes can lead to lymph vessel obstruction, lymph node enlargement and lymphoedema (53). Lymphoedema is categorized by an abnormal accumulation of protein- rich interstitial fluid in the presence of normal capillary function (41). The extremities are commonly affected as these regions have few collateral lymphatic channels which cannot readily drain excess fluid (41).

The lymphoedematous region is associated with local immune impairment and is prone to secondary bacterial infection (41). Thus, factors such as lymphatic and venous obstruction, protein- rich interstitial fluid, tissue haemosiderin and subcutaneous infection are believed to be important in the evolution and perpetuation of KS associated chronic lymphoedema (54).

There are ten morphologic variants of KS: patch, plaque, nodular, lymphadenopathic, exophytic, infiltrative, ecchymotic, telangiectatic, keloidal and cavernous or lymphangioma-like (55). Lymphoedematous variants for example lymphangioma- like KS (LLKS) may be associated with prominent lymphoedema and soft tissue swelling (56).

4.5 Clinical presentation

KS was first described in 1872 by Dr Moritz Kaposi, a Hungarian dermatologist, as an 'idiopathic, multiple, pigmented sarcoma' (57). Classic, endemic (African), epidemic (AIDS-related) and iatrogenic forms are the four major types described (57). AIDS- related KS can be diagnosed at any phase of HIV infection, but it is a common manifestation in the background of severe immune suppression (58). The clinical course of AIDS- associated KS varies among individuals from being minimal, aggressive or if untreated, uniformly progressive (59).

KS affects the skin primarily, particularly the lower extremities, face and genitalia (60). The lesions may be symmetric, arise in skin lines or creases (58), are pigmented with a distinctive appearance, ranging from pink to purple, or brown in colour and do not disappear with pressure (58) (61). In the early stages of the disease, lesions are flat (patch stage), and can progress to elevated lesions (plaque stage) which may coalesce to form large areas of tumour (nodular stage) (60) (58). These may ulcerate, bleed and become infected and are often associated with lymphoedema especially of the lower limbs, genitalia and face (60).

Dermal and lymphatic infiltrations may lead to cosmetically unacceptable lesions which can affect physical and sexual activity (50). Importantly, lymphoedema associated with KS may be present before the appearance of clinically overt KS lesions. This may be explained by the associated subcutaneous fibrosis and hyperkeratosis that masks the cutaneous KS lesions particularly in dark- skinned persons (41) (62).

Tumour associated oedema is a feature of advanced KS (43). Tumour associated oedema, colour and nodularity at initial and follow- up visits should be documented. Mucocutaneous manifestations presenting with more than 10 new lesions in the past month is typical of rapidly, progressive disease (43). This affects prognosis and the likelihood of response to treatment (43).

The differential diagnosis of cutaneous KS lesions include: pyogenic granuloma, tufted angioma, melanocytic naevi, melanoma, cavernous haemangioma, angiokeratoma, Stewart-Treves syndrome, carcinoma cutis, arterio- venous malformations, severe statis dermatitis and bacillary angiomatosis (55).

Visceral involvement is commonly of the oral cavity, other areas of the gastrointestinal tract, lungs, lymph nodes and eyes and may involve almost any organ (60). This necessitates performing a thorough physical examination, particularly of the skin, extremities, oral cavity and rectum (43).

4.6 Aspects of diagnosis

Diagnosis of KS is possible through a combination of clinical assessment, biopsy of lesions as well as the use of various imaging modalities. Skilled clinicians can often diagnose KS lesions on clinical appearance alone, but it is mandatory to confirm the initial diagnosis of KS by biopsy of the skin lesion, lymph node or any other tumour involved tissue, as other lesions

for example bacillary angiomatosis and other vasculitides may present similarly (58) (63). Investigations such as upper and lower gastrointestinal endoscopy, bronchoscopy and CT chest should be guided by the patients' symptomatology, clinical presentation or contributory laboratory studies (43).

Biopsy findings

Typically, KS lesions are characterized by a normal epidermis with proliferation of abnormal vascular structures in the dermis (64). They display slit- like vascular spaces with lympho-plasmacytic infiltrates, lined by malignant- looking endothelial cells and are surrounded by spindle- shaped cells, containing HHV8 (50). There is also an extravasation of erythrocytes and haemosiderin pigment (50).

Imaging techniques

In a study describing the ultrasound patterns of patients with classic and AIDS-KS, colour Doppler imaging demonstrated predominantly hypervascular lesions in AIDS-KS patients. This type of imaging may play a role in evaluation of disease activity in both of these forms of KS; however additional studies and larger patient numbers are needed for better evaluation of this modality in assessing disease progression (65).

With respect to novel imaging techniques for example ^{99m}Tc- tetrofosmin scintigraphy and ^{99m}Tc- hexakis-2-methoxy isobuyl isonitrile (MIBI) imaging, a study showed that the former may be beneficial as an additional tool to clinical and other diagnostic modalities in the detection of KS lesions and in staging of the disease (66). In a similar study, ^{99m}Tc- MIBI imaging may provide additional information on the extent of lymph node involvement and, staging of disease and, can be valuable in assessing response of cutaneous KS to treatment

(67). The radiotracers used in the above two studies are useful as oncotropic radiotracers in the detection of several solid neoplasms and their metastases (66).

4.7 Staging and prognosis of Kaposi's sarcoma

With the advent of HAART, criteria for staging AIDS-KS have been modified (52). The current prognostic indicators include tumour extension (T) and HIV- related systemic illness (S) only (Table 4) (68). The severity of immunosuppression reflected in the CD4 count is not an independent prognostic indicator as initially suggested by the AIDS Clinical Trial Group (ACTG) (52) (68). Thus, the two different risk categories include: a 'good prognosis' category; T_0S_0, T_1S_0, and T_0S_1 with a respective 3- year survival of 88%, 80% and 81%; and a 'poor prognosis' category T_1S_1 with a 3- year survival of 53% (68).

Table 4: Staging of AIDS- Kaposi's sarcoma in HAART era (69)

T0: Tumour confined to skin &/or lymph nodes &/or minimal oral disease (a)	**T1:** Tumour- associated oedema/ ulceration; extensive oral KS; gastrointestinal KS; KS in other non- nodal viscera
S0: No history of opportunistic infections/ thrush; no B symptoms (b); performance status >/= 70 (Karnofsky)	**S1:** History of opportunistic infection &/or thrush; B symptoms; performance status < 70 (Karnofsky); other HIV- related illness (i.e. neurological disease, lymphoma)
(a) Minimal oral disease defined as non- nodular KS confined to the palate	
(b) B symptoms: fever, drenching night sweats, &/or > 10% involuntary weight loss	

4.8 Management

There is no cure for KS at present (43) and the ideal therapy for newly diagnosed cases has yet to be defined, while its management, either local or systemic, should be individualized (64) (70). Factors such as the extent and rate of tumour growth, visceral involvement and tumour- related symptoms must be taken into account (70). Other factors to consider include: the overall AIDS- related prognosis, cytopaenias, concomitant opportunistic infections, neurologic complications, as well as patient goals and preferences (43) (71).

The major goals of treatment are symptom palliation, reducing morbidity by shrinking the tumour to control the associated pain and oedema, reducing the progression of the systemic disease, and improving the quality of life by treating disfiguring lesions (72) (71). Patients with few skin or oral lesions, not associated with symptoms may be managed by observation alone (63).

Local therapy is indicated for patients with localized disease; small, asymptomatic lesions limited to the skin, localized bulky KS lesions and for cosmesis (43) (72) (71).

Local Treatment options

- **Radiation therapy:** KS lesions are radiosensitive (73). Low dose fractionated radiotherapy use (15- 30 Gy), is associated with complete remission of local disease in about 20-70% of cases (58). Due to the tissue fibrosis that may occur over time with radiotherapy, this modality may be challenging in patients with extensive lymphoedema of the extremities (58). Severe mucositis is a common complication in oro- pharyngeal irradiation, thus reduced doses (1-5 Gy) are shown to decrease this risk (73).

- **Cryotherapy:** using liquid nitrogen in the management of minor, cosmetically unacceptable lesions of the face, neck, hands and other exposed areas is associated with response rates of approximately 85% (71). Recurrences are common as cryotherapy has no dermal penetration. It is not an acceptable treatment modality in those patients with extensive cutaneous lesions or visceral disease (71).

- **Intralesional chemotherapy:** has been used to treat extensive oral lesions and cutaneous lesions (71). Low dose intralesional vinblastine or vincristine may be used (71) (58). Response rates of between 70- 90% have been reported (58). However, injections may be painful and associated with post- inflammatory hyperpigmentation (58).

- **Photodynamic/ laser therapy:** useful for localized KS lesions, but recurrence rates are high (58).

- **Topical retinoic acid:** retinoids are biologic modulators that have anti-KS effects (71). Topical therapy has been shown to be efficacious resulting in response rates of 35-50% (58).

- **Surgical excision:** KS is a systemic disease, thus local surgical excision should only be used for single, difficult to manage cutaneous lesions (71). Recurrence commonly occurs at the site of excision (58).

Systemic therapy

For patients with advanced disease- extensive and rapidly progressive mucocutaneous disease causing lymphoedema, ulceration and pain, symptomatic visceral disease and those with debilitating KS-related symptoms have improved outcomes with systemic agents (43) (71).

The most active agents include: vinca alkaloids, bleomycin, liposomal anthracyclines, paclitaxel and interferon alpha (71) (58) (50). The use of HAART in management of HIV-KS will be elaborated upon below.

Experimental therapy

Other novel agents include anti- angiogenic agents for example thalidomide, cytokine inhibitors, matrix metalloproteinases as well as antiviral approaches targeting HHV8 (58). These agents interfere with the pathogenetic mechanisms of AIDS-KS but are largely experimental at present, and should be administered within the confines of clinical trials (70) (71).

Kaposi's sarcoma- associated lymphoedema management

Treatment of KS- associated lymphoedema incorporates the management options listed above including HAART and systemic chemotherapy. Lymphoedema is treated with the use of diuretics as well as lymphatic drainage manoeuvres. In cases of lower extremity involvement these include: manual lymph drainage massage, limb elevation, compressive wrapping and exercises (41) (53) (42). The maintenance of skin integrity is crucial to avoid the development of secondary bacterial and fungal infections (41). Thus it is necessary to use emollients on the affected lymphoedematous skin as well as applying antimicrobial agents if skin breakdown has occurred (41).

Therapeutic evaluation

In general, two or three lesions are selected as a reference before starting treatment (61). Following treatment, lesions are re- evaluated and according to the ACTG guidelines, the criteria for response to treatment, is categorized as being: either a complete response, partial response, stable disease or disease progression (43).

4.9 HAART in the management of HIV- associated Kaposi's sarcoma

The beneficial effects of HAART are multifactorial and include: inhibition of HIV replication, overall improvement in host immunity, reduced production of HIV-1 transactivating protein (Tat protein), and an improvement in immune responses against HHV8 and perhaps a direct antiangiogenic effect with the use of protease inhibitors (72) (74).

The advent of HAART has reduced incidence rates of KS in developed countries (75). This is in contrast to the circumstances in sub- Saharan Africa (SSA) where access to and availability of HAART is limited (72). KS prevalence therefore remains high and patients present with cases of high tumour burden and rapid disease progression (72) (76) (77).

Data from cohort studies show that AIDS-KS presents less aggressively in patients already on HAART at time of diagnosis compared to HAART naïve patients (78). Regression of KS with HAART has also been shown, particularly in those with limited disease (43). Patients were reported to have longer remission periods of more than five years in certain poor- risk patients (79). The combination of HAART and other treatment modalities described above, can enhance the period of effectiveness of these treatments (72).

Immune reconstitution inflammatory syndrome (IRIS) is a well- described clinical entity characterized by a paradoxical worsening of stable, opportunistic infections and cancers in the context of HAART induced recovery of the immune system and KS- IRIS is an important complication of HAART (72) (48).

4.10 Discussion

KS is now the commonest cancer in men and the third commonest in women in many parts of Africa (45). Most of the studies describing incidence rates of KS were cohort and observational studies, with few studies describing lymphoedema incidence rates. There is a dearth of published literature on incidence rates of KS and lymphoedema from SSA and other developing nations with high prevalence rates of both HIV and KS.

It is widely accepted that HHV8 is the main causative agent of all forms of KS, however many unanswered questions remain about its mode of transmission and its influence on HIV (51) (48). There is also little documented data on the clinical manifestations of primary HHV8 infection, and how significant this may be in determining morbidity (51). This reflects a need for ongoing research in KS pathobiology and pathogenesis.

Data on appropriate diagnostic methods was obtained from review articles as well as cohort studies. The diagnosis of KS is made by clinical examination and biopsy of the involved skin and mucosal lesions or lymph nodes (66). With respect to the novel imaging modalities (colour Doppler ultrasound imaging, ^{99m}Tc- based scintigraphy or MIBI imaging), larger studies are required to validate the efficacy of these modalities in detection, staging and monitoring of treatment responses.

Widespread HAART use has led to a significant decline in incidence rates of KS in the developed world, however, incidence rates remain high in SSA and other resource- poor countries (50). This may be partly explained by an increasing incidence of untreated HIV infection, a greater spread of HHV8 in Africa (71) as well as limited access to HAART in these areas (50).

Patients with acute and chronic lower limb swelling often present to the general surgeon. The HIV pandemic has seen an increase in the prevalence of KS in SSA (62) and its associated complication of chronic lower limb lymphoedema (54). This has posed unique clinical, diagnostic and management challenges to the general surgeon (80). KS should be considered in the differential diagnosis of a patient with chronic lymphoedema. In some cases, lymphoedema may be present without cutaneous lesions, due to associated subcutaneous fibrosis and hyperkeratosis, making clinical diagnosis of KS difficult (53) (41). This also precludes confident biopsy of lesions, thus either visibly haemorrhagic nodules and/ or more than one nodule should be biopsied to ensure timely, definitive diagnosis of KS (54). Morbidity and mortality in patients with lymphoedema is due to concomitant sepsis as a result of stasis and trauma (54). Preservation of skin integrity is therefore crucial to avoid the development of secondary bacterial and fungal infections and their attendant morbidity (53) (41).

Most patients in developing countries present with advanced disease and high mortality rates. This is mainly due to late diagnosis of HIV infection, late accessibility to HAART and chemotherapy. Thus early diagnosis and improved treatment protocols are of utmost importance in these settings (76).

4.10 Conclusion

Kaposi's sarcoma is an intriguing disorder, and represents an ideal prototype for concurrent study of viral- associated carcinogenesis, inflammation and angiogenesis (72). To date, there are many unanswered questions about the underlying aetiology and aspects of its molecular pathogenesis (72). This insight will allow for the improvement of current therapeutic strategies against KS as well as the recognition of novel targets directed against this malignancy (72). However, challenges exist in SSA and other developing countries where KS

incidence remains high and access to HAART and other KS specific therapies is not widely available leading to associated high mortality rates (48).

With respect to chronic lymphoedema of the extremities, challenges remain regarding diagnosis and effective management strategies. Further trials are needed to define the efficacy of current management strategies, appropriate rehabilitation and targets for prevention of this devastating, morbid complication.

CHAPTER 5: AIDS- RELATED ABDOMINAL MALIGNANCIES DUE TO KAPOSI'S SARCOMA AND LYMPHOMA

5.1 Introduction

HIV- positive patients are at risk of developing malignancies during the course of their illness (81). Three malignancies are regarded as being AIDS- defining: KS, non- Hodgkin's lymphoma (NHL) and invasive cervical cancer (81). KS remains the most frequently reported AIDS- associated cancer with NHL recognised as the second commonest cancer associated with HIV infection worldwide (82) (83). With the advent of HAART and improved survival of patients with HIV, there may be an increase of neoplasms that are non- diagnostic of AIDS, such as Hodgkin's lymphoma (HL) (81). Cancer remains a relatively under-emphasized subject in Africa, due to the overwhelming burden of communicable diseases (45). This chapter reviews the epidemiology, clinical presentation, aspects of diagnosis and management of abdominal malignancies due to KS and HIV- related lymphomas. Staging and prognosis of KS and HIV- related lymphomas in the HAART era are described.

5.2 Methods

A collective review of the literature using the relevant search engines and search terms as described in the Chapter 2 (Methods) was undertaken. Relevant search terms included: "AIDS- related abdominal malignancies and Kaposi's sarcoma", "AIDS- related abdominal malignancies and non- Hodgkin's lymphoma", and "Hodgkin's lymphoma". A total of 256 articles were identified for the period 2000 to the present date. Of these, 113 articles fulfilled the inclusion criteria and were considered suitable for review. Studies were evaluated using content analysis as described in the Chapter 2 (Methods). (Table 5) illustrates the types of studies and methodological quality of studies reviewed. Systematic reviews of cohort studies

and cohort studies were the commonest methodological approaches. Randomized trials, a case- control study, case series and case reports made up the remainder of the studies.

Table 5: Type of studies and methodological quality

Type of study	Number	Level of evidence
Randomized controlled trial	2	1B
Systematic review of cohort study	72	2A
Cohort study	30	2B
Case- control study	1	3B
Case series	6	4
Case reports	2	4
Total	**113**	

5.3 Incidence of AIDS- related gastrointestinal malignancies

The GI tract is a common site for the development of malignancies in patients with HIV (84). On endoscopic examination of patients with KS, the GI tract is involved in 40% to 52% of patients and in up to 80% of patients at post-mortem examination (84) (85). Primary gastrointestinal lymphoma is the second most common site of extra- nodal presentation of NHL and occurs in about 28% of patients (84). The GI tract may be involved in up to one-third of patients, with the likelihood of KS greater than that of lymphoma and other miscellaneous neoplasms (84).

5.4 Pathogenesis of AIDS- related Kaposi's sarcoma and lymphoma

In immunodeficiency states, there are three main pathophysiological reasons for the development of malignant tumours: lack of autoimmune surveillance and subsequent inability

to recognize and/ or eradicate abnormal cellular clones, an imbalance between cellular proliferation and differentiation, and repeated antigenic stimulation associated with chronic viral infection, usually an oncogenic virus, leads to the proliferation of one or several cell types leading to cancer development (61). KS is associated with HHV8 and NHL with EBV in addition to HIV (86).

The aetiology and pathogenesis of KS is multifactorial and involves HHV8, altered expression and response to cytokines, stimulation of KS proliferation by HIV-1 Tat protein as well as other unknown factors (85). This has been discussed in detail in Chapter 4.

The pathogenesis of HIV- related lymphoma reflects the interaction of various factors including: HIV- induced immunosuppression, chronic antigen stimulation, genetic abnormalities, cytokine dysregulation and the role of EBV (87). Most NHL are of B-cell origin (88). HIV-1 induces polyclonal B-cell proliferation and activation in addition to the factors mentioned (89). HL is characterized by a malignant proliferation of cells of the lymphoid type (Reed- Sternberg cells) (61). A high frequency of association between HL and EBV has been shown (80- 100%), with expression of some EBV- transforming proteins in EBV- positive HL cases (90).

5.5 Clinical presentation

The clinical presentation of KS, NHL and HL and their related GI pathology is described as follows:

5.5.1 Kaposi's sarcoma

AIDS- related KS can be diagnosed at any phase of HIV infection, but is commonly associated with severe immunosuppression (58). It usually presents in two ways: an aggressive form with multi- organ involvement (gastrointestinal tract, liver, spleen and lung); or a more moderate form, characterized by localized disease involving cutaneous tissue (61). Almost any organ may be affected, but the GIT is the commonest site of extra- cutaneous KS (61) (72).

Gastrointestinal (GI) lesions can occur in the absence of cutaneous KS and are often asymptomatic (91) (92). The stomach, colon, small bowel, liver, spleen, pancreas and omentum may be affected (58). When symptomatic, KS in the GIT may be associated with nausea, vomiting, abdominal pain, dysphagia, malabsorption, weight loss and diarrhoea which may be bloody (58) (63) (92) (93). Other complications that may arise include: gastric outlet obstruction or other forms of bowel obstruction, intussusception, perforation and peritonitis and GI bleeding (91) (64).

Differential diagnoses to consider include NHL, bacillary angiomatosis, pyogenic granuloma (oral cavity and anal lesions), angiosarcoma of the GIT, leiomyomas, rhabdomyosarcomas, gastrointestinal stromal tumours, melanoma and poorly differentiated carcinoma (91) (92).

Staging and prognosis: A recent prospective evaluation of the ACTG staging system carried out in the HAART era showed that only the combination of poor tumour stage and poor systemic disease state satisfactorily identified patients with unfavourable prognoses (68).

CD4 count was no longer of prognostic influence (68). Patients with a combination of these poor prognostic factors had a 3- year survival rate of 53% versus survival rates of more than 80% in patients without the above- mentioned combination (68). See Table 4- Chapter 4.

5.5.2 HIV- related lymphoma

Lymphoma is the second commonest neoplasm among HIV- positive patients after KS (84). HIV- associated lymphomas are divided by the World Health Organization (WHO) into three categories, namely: lymphomas also occurring in immunocompetent patients; lymphomas occurring more specifically in HIV- positive patients; and lymphomas also occurring in other immunodeficiency states (Table 6). The majority of these lymphomas are aggressive B-cell NHL (91). NHL can affect any segment of the GIT and multifocal disease is common (94).

Table 6: Categories of HIV-associated lymphomas (95)

Category	Lymphoma subtype
1 Lymphomas also occurring in immunocompetent patients	Burkitt's lymphoma Diffuse large B-cell lymphoma Centroblastic Immunoblastic Extranodal marginal zone B-cell lymphoma of mucosa associated lymphoid tissue type (MALT lymphoma) (rare) Peripheral T-cell lymphoma (rare)
2 Lymphomas occurring more specifically in HIV- positive patients	Primary effusion lymphoma Plasmablastic lymphoma of the oral cavity type
3 Lymphomas also occurring in other immunodeficiency states	Polymorphic B-cell lymphoma 'PTLD-like' (post- transplant lymphoproliferative disorder)

Non- Hodgkin's Lymphoma: AIDS- NHL may be systemic, mainly involve the CNS, or may be localized to body cavities (96). Most arise systemically (80% of all cases) and the GIT is a common extranodal site (25% of cases) (91) (96) (61). The stomach and small bowel are commonly involved however, colorectal and perianal disease, liver, splenic, renal, pancreatic and omental disease have also been documented (94) (97). AIDS- related NHL is also characterized by exuberant lymph node enlargement (97).

Unlike GI-KS, GI-NHL frequently produces symptoms such as abdominal pain, tenderness, loss of weight, and GI- bleeding (91). Systemic 'B' symptoms such as unexplained fever, drenching night sweats and/ or weight loss in excess of 10% of normal body weight is also a

frequent occurrence (98). The rate of complications such as bleeding, tumour obstruction or intestinal perforation is considerably higher than in immunocompetent patients and occurs in up to 16% to 55% of GI lymphoma cases (87). With involvement of the rectum, patients may present with a rectal mass or pain on defecation (98). Lymphoma of the liver occurs in about 10% to 25% of cases, and these patients present with jaundice, systemic 'B' symptoms, abdominal pain or anorexia (98). At the time of NHL diagnosis, the CD4 T lymphocyte count is usually lower than 50/ mm^3, implying significant immunosuppression (61).

There were few studies describing presentation of NHL in Africa and this may be due to competing comorbidities for example TB which may mask the disease presentation (44). However the limited data available support frequent presentation with rapidly- growing tumours, advanced disease stage and extra- nodal involvement (44).

Other types of AIDS- related NHL lesions include

a) Primary effusion lymphoma or body cavity- based lymphomas: these are rare, accounting for 3% or less of HIV- associated lymphomas (91) (96). The lymphoma is confined to the pleural, pericardial and peritoneal cavities, without visceral spread, but may rarely involve the small or large bowel (91). Typically, they present as lymphomatous effusions in the body cavities mentioned, without a tumour mass and they are linked to HHV8 (96).

b) Mucosa- associated lymphoid tissue (MALT) lymphomas: these are rare tumours in HIV- positive patients (87). MALT is present throughout the GIT (99). These lymphomas arise in sites normally devoid of organized lymphoid tissues such as the stomach, lung, breast, skin, salivary gland and thyroid gland, usually in the setting of associated chronic infectious conditions for example Helicobacter pylori (*H pylori*)

infection or autoimmune conditions such as Sjogren's syndrome. Gastric MALT is the prototype of these tumours and patients usually present with non- specific symptoms such as dyspepsia or epigastric pain. A definitive mass is often absent at endoscopy and gastritis or ulceration is seen commonly (99).

c) T- cell lymphoma may also occur in this population group and these have been associated with GI lymphomas in association with human T- cell lymphotropic virus type I (HTLV-I) infection (84).

Hodgkin's Lymphoma: HIV-related HL is characterized by widespread disease at presentation with 'B' symptoms commonly occurring. The extranodal sites commonly involved include the bone marrow, liver and spleen. Unlike HIV- related NHL, unusual sites of disease in HIV- related HL are uncommon (100). HL seems to occur at an earlier stage of HIV infection, with an absolute number of CD4 T lymphocytes ranging from 275 to 305/ mm^3 as compared to NHL (61).

In all cases, it is important to note the general condition of the patient (performance status), the presence of peripheral lymph nodes, organomegaly (liver and spleen) as well as the any palpable abdominal masses (101).

The main differential diagnosis to consider in our setting is TB. Other diagnoses include: opportunistic fungal and viral infections, inflammatory bowel disease (Crohn's disease), KS and other gastrointestinal malignancies including sarcomas.

Staging and prognosis: Both NHL and HL are staged according to Ann Arbor criteria, (appendix 3) (100). Features that contribute to a poor prognosis include lymphoma- specific factors (such as aggressive histology, extranodal disease) and HIV- specific factors (poor bone marrow reserve, CD4 lymphopaenia and opportunistic infection) (96). According to the

ACTG prognostic model, the following four variables are associated with a worse survival: CD4 count less than 100/mm^3, Stage III or IV disease according to Ann Arbor criteria, age older than 35 years and intravenous drug use (96). Other factors related to short survival include a history of AIDS prior to the lymphoma diagnosis, poor performance status and elevated LDH levels (89). The International Prognostic Index (IPI) for NHL may also be used (appendix 4) (89).

Despite historically poor prognosis in NHL, with the majority of studies documenting median disease- free survival of between 6 months to a year (75) (102), outcomes have improved with use of HAART and more intensive chemotherapy regimens (103). Complete response (CR) rates in patients who receive chemotherapy is in the range of 36% to 70% (102). The long- term use of HAART has been shown to increase both disease- free and overall survival rates (102) (104).

The positive impact of HAART in prognosis of HIV-HL has also been reported with studies showing median survival time in patients not on HAART to be 18.6 to 19 months whereas median survival times were not reached in patients with HAART (105) (106).

5.6 Aspects of diagnosis

Aspects of diagnosis related to KS and lymphomas is described as well as staging investigations important in the diagnostic work-up of a patient with lymphoma.

5.6.1 Kaposi's sarcoma

Imaging modalities useful in aiding diagnosis of GI-KS include: upper endoscopy, colonoscopy, Barium upper GI series or enemas and computed tomography (CT) scans of the abdomen (88).

GI-KS may be present in the absence of characteristic skin lesions and lesions may only be seen on upper endoscopy or colonoscopy. KS lesions begin in the submucosa and have a typical endoscopic appearance: scattered, red- purple or violaceous macular lesions measuring between 5mm and 15mm or as multiple smoothly contoured sessile polyps in the stomach (94) (107). According to oncological principles, the definitive diagnosis of KS should be based on typical pathological findings and endoscopic biopsy of lesions is necessary. However, the yield of endoscopic biopsies may be low due to the submucosal location of the lesions and standard biopsy forceps and biopsy techniques may not be adequate to sample these lesions (50) (107). To obtain deeper samples of stomach tissue, some authors recommend "biopsy on biopsy technique" or a gastroscope with a large working channel to allow for the passage of a jumbo forceps (107).

Histology: KS lesions typically display a proliferation of abnormal vascular structures (50). These consist of slit- like vascular spaces with lympho- plasmacytic infiltrates, lined by malignant- looking endothelial cells and are surrounded by spindle- shaped cells, containing HHV8 (50). There is also an extravasation of erythrocytes and haemosiderin pigment (50). In

time, the ‘spindle cells’ become the principal cell type, forming fascicles that compress the vascular slits and the lesions become gradually more nodular (50).

On upper GI series, multiple filling defects in the distal part of the stomach may be seen. The polyps usually have a smooth contour and occasionally there is collection of barium in the centre of the lesion “bull’s eye lesion” (107). Other features include nodular KS lesions and diffuse wall thickening especially in the stomach (88). CT scans of the abdomen may show bowel wall thickening as well as masses or lymphadenopathy (88).

5.6.2 HIV- related lymphoma

The diagnosis of lymphoma in patients who present with a spectrum of clinical features is often challenging. The approach to diagnosis is guided by the mode of presentation. Once a definitive histological diagnosis is made, patients enter a common pathway typical of all patients with malignant disease. This is characterized by staging, prognostic assessment and a management plan involving either a curative or palliative approach (108).

The surgeon’s role in the management of lymphomas is to obtain a tissue diagnosis (109). The advent of CT scanning has led to the end of staging laparotomies and surgery may only aid as a diagnostic adjunct when non- invasive diagnostic studies do not accurately define the extent of disease (110) (109).

A wide range of imaging modalities is available for diagnosis and/ or staging and these include: CT scans of the neck, chest, abdomen and pelvis, positron emission tomography CT (PET- CT) scanning and magnetic resonance imaging (MRI) (97) (111).

CT scanning

The CT appearance of NHL of the GIT is characterized by focal, multicentric or diffuse bowel wall thickening or an intraluminal mass associated with ulceration in some cases (94). This bowel wall thickening is a non- specific feature which may occur with KS, TB or cytomegalovirus (CMV) infection (94).

The main manifestations of lymphomatous abdominal nodes are those of a solitary mass type, multiple nodular type (regional distribution of lymph nodes) and a diffuse type involving the whole distribution area of abdominal lymph nodes (112). With respect to lymphomatous abdominal nodes, the most important differential diagnosis is TB. The CT features that may assist in differentiating between the two include: homogeneous enhancement of lymph nodes in lymphoma, whereas peripheral enhancement with or without a multiloculated appearance is characteristic of TB (94). Nodes due to lymphoma are usually large and bulky and 88% are of soft tissue attenuation (84). Central necrosis and hypoattenuation within nodes favours a diagnosis of TB (84). Mesenteric lymph nodes are commonly involved in TB and intra-nodular calcification may occur (112). Mesenteric lymph nodes are usually not involved in lymphoma, here the lower para- aortic nodes are predominantly involved (112) (94). However, the distinction between the two is definitively made on histology and bacteriological assessment.

PET scanning

PET scanning with Fluorine- 18 fluorodeoxyglucose (FDG) shows functional metabolic status (cells that have undergone malignant transformation show increased glucose metabolism seen on PET) (94) (111). It therefore allows for comprehensive assessment of disease extent during staging and follow- up (111).

Biopsy techniques

Accurate pathological diagnosis is mandatory to allow for appropriate therapy (111). Endoscopic findings include polypoid, bulky lesions or well- defined ulcers (87). The diagnosis of gastric lymphoma requires an adequate number of biopsies from both involved and macroscopically uninvolved mucosa to enable accurate diagnosis of the type of lymphoma as well as tests for *H pylori* in cases of suspected gastric MALT lymphomas (101).

For patients with intra- abdominal or retroperitoneal lymphadenopathy as the only sites of disease, options include: image- guided biopsies, endoscopic ultrasound (EUS), laparoscopy or laparotomy (111).

Excisional biopsy of enlarged lymph nodes is regarded as the gold standard in the diagnostic evaluation of lymphomas (113). It allows for full architectural and histological information and allows for immunohistochemical staining. However, it requires the involvement of surgical, nursing, anaesthetic and theatre staff, contributing to significant costs of the procedure as well as the attendant risks of surgery and anaesthesia (114). Other minimally invasive options as described below may be employed prior to resorting to an excisional biopsy.

Image- guided percutaneous needle biopsy techniques include FNAC and core needle biopsy (114). FNAC is a quick, safe, low-cost, well- tolerated technique, however its use in lymphoma is limited as it provides only cytological and no architectural information and does not allow for histological subtyping (114). The sensitivity of FNAC ranges from 13% to 95% (115). The technique can be improved by supplementary cytological techniques for example

insitu hybridization immunocytochemistry and flow cytometry, but these are costly and may not be widely available (114).

Image- guided core biopsy is now a well- established technique and provides a core of tissue for formal histological and immunohistochemical analysis (114). Successful lymphoma classification is possible in 84% to 100% of patients using core needle biopsy (115). The use of image- guidance minimizes the danger of vascular or nerve injury and it can be performed as a day case procedure (114). However, diagnostic yield may be low especially in HL, due to a scantiness of characteristic Reed- Sternberg cells (114).

In summary, image- guided biopsy is a safe, economical, widely available diagnostic modality in lymphoma evaluation that may supply all the necessary information thus obviating the need for a surgical excision biopsy (114).

The introduction of EUS guided- FNAC and core biopsy techniques has allowed for the evaluation of deep tissues, including deep- seated lymph nodes (116). EUS- guided FNAC combined with flow cytometry has an accuracy of 70% to 90% in diagnosis of lymphoma (117). Studies conclude that it is accurate in diagnosis and classification of Diffuse large B-cell lymphoma (DLBCL), but in low- grade lymphoma and HL, EUS accuracy is modest (117).

Laparoscopy is a useful adjunct in the diagnosis of enlarged abdominal lymph nodes and masses especially if image- guided core needle biopsy techniques have been unable to make a definitive lymphoma diagnosis (115). It also plays a role in staging of disease when extent of disease is not accurately delineated on non- invasive imaging studies (118) (109). In experienced hands, it is a safe and effective procedure with a high diagnostic yield (119). It has a low morbidity rate and can be performed as an outpatient procedure in certain instances

(119). Other advantages (common to other laparoscopic procedures) include less post-operative pain, earlier resumption of activities, better cosmesis and shorter recovery time (115).

Histologic findings: The majority of AIDS- NHL involving the GIT can be classified into Burkitt's lymphoma or DLBCL (centroblastic and immunoblastic variants) (91). In HL, there is a greater proportion of unfavourable histologic subtypes including mixed cellularity and lymphocyte- depleted (91).

Staging investigations: These include CT (neck, chest, abdomen and pelvis); PET scanning; lumbar puncture (patients with systemic lymphomas) as well as bilateral bone marrow aspirate and biopsy (98) (101). Other ancillary investigations include: Full blood count (FBC) with a differential count, urea and electrolytes (U&E), liver function tests (LFT), lactate dehydrogenase levels (LDH) and β_2- microglobulin levels (111) (98). HIV-RNA viral load and CD4 cell count is necessary to aid in prognostication and decisions on concurrent antiretroviral therapy (88).

5.7 Management

The management options including surgical management for KS and HIV- related lymphomas are as follows:

5.7.1 Kaposi's sarcoma

Currently, AIDS- related KS is not curable (58) (84). Treatment approaches should focus on symptomatic disease management and avoidance of unnecessary systemic complications (84). HAART forms the mainstay of management (84) (44). Local therapy using intralesional vinblastine for oral lesions or radiotherapy for oral and anorectal lesions may be used (84). For more extensive disease, systemic therapy is necessary (84). The most effective

chemotherapeutic agents include: vinca alkaloids, bleomycin, liposomal anthracyclines, paclitaxel and interferon alpha (71) (58) (50). Other novel agents include anti- angiogenic agents for example thalidomide, cytokine inhibitors, matrix metalloproteinases as well as antiviral approaches targeting HHV8 (58). These agents interfere with the pathogenetic mechanisms of AIDS- KS. They are mainly experimental at present, and should be administered within the confines of clinical trials (71).

Surgical procedures may be necessary for obstructing lesions (94). Endoscopic measures such as injection therapy, heat coagulation and sclerotherapy may be used to manage GI bleeds (120). In some cases, surgical excision or angiographic embolization may be needed to control GI bleeding (120).

5.7.2 HIV- related lymphoma

Surgery plays a minor role in the management of HIV- related lymphomas, and is indicated to assist in establishing a diagnosis or in the management of acute complications such as intestinal obstruction, bowel perforation or GI haemorrhage (87) (84). Chemotherapy remains the mainstay of treatment (94).

Non- Hodgkin's Lymphoma

Standard chemotherapy regimens for NHL include: CHOP (cyclophosphamide, hydroxydoxorubicin, vincristine and prednisone); EPOCH (etoposide, prednisone, vincristine, cyclophosphamide and hydroxydoxorubicin), m- BACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone) and or CDE (infusional cyclophosphamide, doxorubicin and etoposide) (87). Infusional chemotherapy regimens such as EPOCH and CDE are efficacious in patients with aggressive subtypes and should be offered to patients with CD4 cell counts <100/ mm^3 (103).

The anti- CD20 monoclonal antibody Rituximab may also be used in selected patients (75). Due to a higher risk of infectious complications as reported in some studies, it is recommended that this agent be used cautiously in patients with CD4 cell counts <50/ mm^3 (121). The regimens are generally well tolerated attaining complete response (CR) rates in aggressive lymphoma patients in 50%- 75% of cases and 2- 3 years overall survival in 40%- 60% of cases (103). Supportive care during chemotherapy involves the use of trimethoprim-sulphamethoxazole for *Pneumocystis jiroveci* pneumonia prophylaxis, fluconazole for fungal infection prophylaxis, filgrastim support to prevent a prolonged neutropaenia and antibiotic prophylaxis where necessary (95).

Gastric MALT lymphomas are treated with eradication therapy against *H pylori* and consist of a proton pump inhibitor (omeprazole); amoxicillin and metronidazole. Tumours not responsive to eradication therapy may require further management with chemo- radiotherapy and/ or surgery (111).

Literature describing infusional chemotherapy regimens is lacking in Africa (44). These infusional regimens require in- hospital admission and treatment which may not be feasible in resource constrained settings (44). CHOP is thus commonly used in SA for treatment of NHL with dose modification based on the degree of immunosuppression (44). A dose- modified oral combination chemotherapy regimen is being used in Uganda and Kenya as part of a phase II trial and preliminary results are promising (122) (44). This could provide a feasible alternative treatment, with the associated labour and cost- saving advantages of oral therapy delivery in resource constrained areas in SSA (44).

Hodgkin's Lymphoma

Optimal therapy for HIV- associated HL is poorly defined. The most common combination chemotherapy regimen is ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine). CR rates were lower than that of HIV- uninfected patients, reported as being 80% in ABVD-treated patients in some studies (100).

5.8 HAART in the management of AIDS- related abdominal malignancies

The role of HAART in the management of KS, NHL and HL is described with respect to its role in curbing the incidence of these malignancies, postulated mechanisms of action and effects on outcomes.

5.8.1 Kaposi's sarcoma

The incidence of KS among patients with HIV has decreased substantially in the HAART era (43). Regression of KS lesions, less aggressive presentation of disease, lengthened time to treatment failure and longer survival rates among patients who have received chemotherapy are some of the documented beneficial effects of HAART (43).

The favourable effects of HAART are multifactorial and may be due to less cytokine production with decreased viral load, overall improvement in host immunity, and perhaps a direct antiangiogenic effect with the use of protease inhibitors (72) (74) (84).

5.8.2 HIV- related lymphoma

HAART use has been associated with a substantial decrease in KS incidence, but the magnitude of reduction in the incidence of NHL appears to be less marked, except for CNS lymphoma. Patients on HAART have an enhanced immune function with reduced B-cell

stimulation. However with longer survival and continued B-cell stimulation and dysregulation, there may be a higher risk of lymphoma developing over time (81).

HAART has also been shown to prolong survival in patients with AIDS- NHL (123). Theories to explain this phenomenon include recovery of immune function and the resulting reduced risk of opportunistic infections which may disrupt chemotherapy (123). Viral suppression due to HAART may further reduce immune damage by HIV and may allow for the development of anti- tumour immune responses (81). This is borne out in some studies where a response to HAART in patients with AIDS- NHL was associated with a better response to chemotherapy, and an increased tolerability to higher chemotherapy dose intensity regimens (124) (125).

On the other hand, the overlapping toxicities and pharmacokinetic interactions between HAART and chemotherapy, may affect the therapeutic index of the various drugs (90). Increased toxicity may lead may lead to the delay of chemotherapy cycles or early dose reductions, which may compromise curative potential of the lymphoma (90). Toxicity may also result in poor compliance with HAART and the possibility of resistant HIV strains emerging (90). Treatment should therefore be individualized. Trials using HAART and CHOP combination regimens show that therapy can be delivered safely and effectively with no observed increase in toxicity (126) (127). Caution should be exercised in zidovudine-containing HAART regimens due to its effects on haematopoiesis and its use in this setting is best avoided (127). It is generally recommended that HAART be administered concurrently with chemotherapy, until unacceptable toxicity occurs (121) (128).

With respect to HL, significant improvement in tolerance to chemotherapy and clinical outcome has been reported in the HAART era. Improvements in CR rates from 64.5% to 74.5% and 2- year disease free survival (DFS) rates from 45% to 62% have been documented

following the use of HAART. Standard full- dose chemotherapy regimens are also better tolerated (121).

The limited and sporadic availability of HAART in Africa thus far, has contributed to an increased risk of occurrence of KS and to a lesser extent NHL among HIV- infected patients in these regions compared to their counterparts in the developed world (83).

5.9 Discussion

Following the advent of HAART in 1996 in the developed world, there have been dramatic declines in the incidences of the two major AIDS defining cancers (ADC): KS and NHL (129). However, the risk for these ADC remains higher compared to the general population (129). This may be explained by inequities in the availability of HAART even in the developed world (130).

The association between HIV and NHL in SSA is weaker than in developed countries, which may be due to under diagnosis of lymphoma due to a lack of resources to enable histological diagnosis. Patients with polyadenopathies in this setting may have been misdiagnosed as having TB and died without any histological confirmation (83). Other reasons include severe immunosuppression, poorer prognosis and shorter mean survival of African patients with HIV compared to their Western counterparts (82).

Studies describing the usefulness and efficacy of EUS- guided FNAC and biopsy in the diagnosis of HIV- related lymphomas had small patient numbers and larger, prospective studies are therefore needed to better evaluate this diagnostic modality (117). These techniques may have a small role to play in resource poor countries due to their limited availability. Furthermore, ancillary cytological techniques following FNAC such as insitu

hybridization immunocytochemistry and flow cytometry, are expensive techniques that may not be available in parts of SSA and other developing countries (114).

HAART is an essential component in the management of AIDS- related cancers in most parts of the world. However there is a lack of uniformity in HAART availability and use in many parts of Africa resulting in most patients receiving sub- optimal care (131).

Patients with HIV may present to the surgeon for evaluation and management of clinical problems such as abdominal pain, abdominal emergencies or with suspected malignancy of the GI tract (132). The underlying cause may be secondary to HIV/AIDS or may be unrelated to the immunodeficient state. Opportunistic infections, TB and malignancies characterize the abdominal complications of HIV. Ultrasonography, CT scanning, endoscopy and laparoscopy are useful investigations when the cause of abdominal pain in these patients is unclear (132).

Extrapulmonary TB is one of the great mimickers in medicine, and is the main differential diagnosis to consider in cases of lymphoma. It is vital that surgeons be familiar with the radiological features that assist in distinguishing TB from lymphoma as well as the different biopsy techniques available (133). The surgeon's role in the management of the lymphoma patient is currently restricted to determining the diagnosis and in some cases to evaluate disease stage (109). Advancements in diagnostic methods has allowed for accurate diagnosis through the use of image- guided biopsy techniques (110). However, deep- seated abdominal lesions may be better approached by minimally invasive surgical procedures such as EUS and laparoscopy and so a new role is likely to develop for the surgeon in lymphoma diagnosis (110). In addition, the surgeon plays a role in managing acute complications relating to GI obstruction, perforation and haemorrhage (84).

5.10 Conclusion

Malignancies that complicate HIV disease signify a unique interaction of virology, immunology and tumour biology. They therefore provide opportunities for enhancing our understanding of cancer and for testing novel paradigms of therapy and, new drug targets that will help in eradicating both HIV and cancer (134) (135).

Due to the increasing burden of these cancers in Africa, it is vital that clinicians become accomplished in the diagnosis and management of these malignancies (136). There is limited data on incidence rates, therapeutic strategies and outcomes of patients with AIDS- related malignancies in resource limited settings and further studies are needed evaluating practical prevention and therapeutic interventions in this setting (137).

Treatment of patients with HIV- related malignancies is complex (138). It is important that surgeons maintain a high index of suspicion for these malignancies in their daily practice and collaborate with HIV specialists and oncologists to provide complete, individualized care to patients (123).

CHAPTER 6: HIV- RELATED ACALCULOUS CHOLECYSTITIS AND CHOLANGIOPATHY

6.1 Introduction

Liver and biliary tree disorders in patients with HIV are well documented (139). While, parenchymal liver diseases are extremely common, HIV- related disease of the gallbladder and bile ducts are less common (139). However, when present, they are associated with significant morbidity (140). These biliary tract disorders often have an infectious aetiology and with the advent of HAART their incidence has been declining (139) (140). This article reviews the epidemiology, clinical presentation, diagnosis and management of acute acalculous cholecystitis (AAC) and AIDS- cholangiopathy (AC).

6.2 Methods

A collective review of the literature using the relevant search engines and search terms as described in the Chapter 2 (Methods) was undertaken. Relevant search terms included: “HIV and acalculous cholecystitis”, and “HIV and cholangiopathy”.

A total of 80 articles were identified for the period 2000 to the present date. Of these, 26 articles fulfilled the inclusion criteria and considered suitable for review. Studies were evaluated using content analysis as described in the Chapter 2 (Methods). (Table 7) illustrates the types of studies and methodological quality of studies reviewed. Systematic reviews of cohort studies and case reports were the commonest methodological approaches. Cohort studies made up the remainder of the studies.

Table 7: Type of studies and methodological quality

Type of Study	Number	Level of evidence
Systematic reviews of cohort studies	16	2A
Cohort studies	3	2B
Case reports	7	4
Total	**26**	

6.3 Incidence

The incidence of AAC and AC is described as follows:

6.3.1 Acute acalculous cholecystitis

Acute acalculous cholecystitis (AAC) is defined as an acute necro- inflammatory disease of the gallbladder in the absence of gallstones (141) (140). It accounts for between 2% to 15% of all cases of cholecystitis in the United States (141) (142). It is normally a disease that develops in the intensive care unit setting in patients with multisystem failure and sepsis (140). Patients on total parenteral nutrition (TPN), burn and trauma victims may also be affected (140). However, the actual incidence of AAC in HIV- positive patients is unknown (140). Some studies report that it is more than twice as common as cholecystitis caused by gallstones in AIDS patients (143).

6.3.2 AIDS- cholangiopathy

AIDS- cholangiopathy (AC) is a well- recognized biliary syndrome, first described by Cello in 1989 (144) (145). It consists of four overlapping bile duct abnormalities, namely: papillary stenosis; sclerosing cholangitis; both papillary stenosis and sclerosing cholangitis and, long extrahepatic bile duct strictures (139). The true incidence of this disorder is unknown and is estimated to be as high as 45% with many asymptomatic patients (144). In the Western literature, patients with AC are described as being middle- aged men who have had AIDS for a year (146). The disease is also more common in male homosexual persons than it is in intravenous drug abusers, suggesting that male homosexuality may be a likely risk factor (144). In contrast, findings from an Indian study showed that patients with AC had acquired HIV by heterosexual transmission (147).

6.4 Pathogenesis

The pathogenesis of AAC and AC in HIV- positive patients is highlighted as follows:

6.4.1 Acute acalculous cholecystitis

The pathogenesis of AAC is multifactorial with gallbladder stasis, paresis and ischaemia and bacterial overgrowth playing a role (141). Also, the gallbladder in patients with AIDS is predisposed to infection with fungi, bacteria and viruses (140). The most common organism implicated is *Cryptosporidium parvum,* followed by cytomegalovirus (CMV) (148). Other opportunistic infections that may play a role include: *Mycobacterium avium- intracellulare* complex, *Mycobacterium tuberculosis* (MTB), *Pneumocystis jiroveci*, *Isospora belli*, *Cryptococcus neoformans*, *Cylcospora cayetanesis*, *and Giardia lamblia* (148) (149) (150). However in up to 50% of cases no aetiologic agent is identified following thorough microbiological evaluation (140).

6.4.2 AIDS- cholangiopathy

The aetiology and pathogenesis of AC is theoretical at present (139). It is thought to be linked to opportunistic infections in the biliary tract (151). The most commonly identified organisms are cryptosporidium and CMV (145). Other organisms implicated include microsporidia, cyclospora, *Mycobacterium avium* complex, TB, *Isospora belli*, *Salmonella enteritidis* and *typhimurium* species, *Enterobacter cloacae Candida albicans* and *Cryptococcus neoformans* (145) (151). These infections may lead to a secondary sclerosing cholangitis due to the concomitant continual inflammation (151). It is postulated that enteric infection leads to portal bacteraemia and subsequent bile duct injury and damage (151). With respect to the role of HIV itself, it has not been identified in the biliary epithelium (151) (145). A genetic predilection has also been suggested as these organisms may elicit an auto- immune mediated reaction in patients with HLA DRw52a (151).

6.5 Clinical presentation

The clinical presentation of patients with AAC and AC is described as follows:

6.5.1 Acute acalculous cholecystitis

Appropriate diagnosis of AAC can be challenging to the general surgeon and requires a high index of suspicion (142). Patients with HIV- related AAC are usually ambulatory (139) (146). The predominant symptom is right upper quadrant pain, present in more than 90% of patients (143). Fever, nausea and vomiting may also occur and jaundice is rare (143). Patients may have had a prior history of CMV and/ or cryptosporidial diarrhoea (139). The majority of the patients reported in these studies were young men with CD4 cell counts of less than $100/mm^3$ (139).

6.5.2 AIDS- cholangiopathy

Irrespective of the inciting cause, the clinical presentation of AC is similar with right upper quadrant or midepigastric pain, reported in approximately 90% of patients (143). Fifty percent of patients have fever, nausea and vomiting and 65% have diarrhoea (143). Jaundice and associated pruritis may occur in about 10% of patients (140). Patients with AC usually have advanced HIV disease with CD4 counts less than 100/mm^3 (152) (140) (145). Differential diagnosis includes: neoplasia (KS, primary bile duct lymphoma and pancreatic adenocarcinoma with papillary involvement), choledocholithiasis and primary or secondary sclerosing cholangitis (153) (144). Perihilar lymphadenopathy due to NHL, atypical mycobacteriosis and infection with MTB must also be considered in this group (154).

6.6 Aspects of diagnosis: Acute acalculous cholecystitis

Diagnostic testing for AAC involves the use of laboratory studies as well as imaging techniques such as ultrasonography, Hepato- Iminodiacetic acid (HIDA) scanning, CT scanning and MRI (140).

6.6.1 Laboratory studies

A mild to moderate leukocytosis with a left shift may be demonstrated on haematological evaluation (142). On LFTs, serum bilirubin is usually normal, serum alkaline phosphatase is elevated (mean 293 IU/L) and the transaminases are usually either normal or mildly elevated (140) (142).

6.6.2 Ultrasonography

Ultrasound is generally the first- line investigation due to its wide availability, low cost and portability to the bedside (141) (140). The sonographic features of AAC include: gallbladder

wall thickening >/= 3.5mm, pericholecystic fluid, intraluminal gas, sloughed mucosal membrane, echogenic bile, subserosal oedema in the absence of gallstones and, hydrops (140) (155) (146). The diagnostic triad of gallbladder wall thickening, echogenic bile and hydrops has a sensitivity of 50% and a specificity of 94% in the general population (140). Other studies have shown ultrasound sensitivity to be in the region of 29% to 92% with specificity being over 90% (141).

6.6.3 Hepato- Iminodiacetic acid (HIDA) scanning

HIDA scan radiolabelled with technetium 99m may demonstrate a non- functioning gallbladder (140). The three modalities that may be used include radionucleotide cholescintigraphy, morphine cholescintigraphy and cholecystokinin augmented HIDA scan (140). If the gallbladder is not visualized one hour after the radiolabelled technetium is injected, the study is considered to be positive (140). Radionucleotide cholescintigraphy is prone to false positive results in cases of prolonged fasting, thus morphine cholescintigraphy is recommended as a confirmatory study (140) (141). In a study of cholescintigraphy as a diagnostic modality for AAC in 62 critically ill patients, HIDA scanning had a sensitivity of 100% and a specificity of 88% (156).

6.6.4 Computed Tomography/ CT scanning

CT is not commonly used for the initial evaluation of AAC and its sensitivity and specificity for detection of AAC are not known (156). The diagnostic criteria is similar to that of ultrasound with the added ability to demonstrate other intra- abdominal pathology (140).

6.6.5 Magnetic Resonance Imaging

This modality is not widely used for the diagnosis of AAC. On a contrast enhanced T1-weighted fat- saturated image, the diagnosis of AAC is determined if there is an increased enhancement and thickening of the gallbladder wall (140). In practice, multiple investigations may be necessary before the diagnosis becomes apparent (141).

6.6.6 Histology

The histologic changes of AAC are similar to those related to cholelithiasis. Early changes include oedema, congestion and ulceration. With further injury, there is transmural inflammation and necrosis. Granulation tissue and collagen replace previously ulcerated or necrotic tissue. At this point, lymphocytes, plasma cells, macrophages and eosinophils may be identified. Secondary infection with anaerobic bacteria occurs in a significant proportion of patients leading to extensive gallbladder necrosis or super infection with gas- forming bacteria (emphysematous cholecystitis) in some patients (148). The likely causative organisms listed above may also be identified when present.

6.7 Aspects of diagnosis: AIDS- cholangiopathy

Diagnosis of AC is made by using laboratory investigations and imaging studies (145).

6.7.1 Laboratory studies

Laboratory analysis is useful but not specific in the diagnosis of AC (151). The typical finding is that of a raised alkaline phosphatase level (ALP) usually five- to seven times the upper limit of normal and a moderate increase in transaminase levels (151). Elevated gamma-glutamyl transferase (GGT) levels are also seen in the majority of patients (140). Jaundice is generally mild with a total bilirubin less than twice the upper limit of normal showing

incomplete obstruction (151). However, in approximately 20% of patients with documented biliary tract abnormalities on cholangiography, liver function tests are normal (140) (151). In 10% of patients, amylase levels may be raised (151). The patient's stool may also be tested for the presence of oocytes of Cryptosporidium (145) (143).

6.7.2 Ultrasonography

Abdominal ultrasonography is the most feasible initial investigation and demonstrates abnormalities in 75% of patients with AC (140) (157). Its sensitivity ranges from 75% to 97% and specificity reaches 100% (140). Ultrasound findings include mural thickening of the gallbladder and common bile duct (CBD), dilated intrahepatic ducts and pericholecystic fluid (157) (151). An echogenic nodule at the distal end of the CBD (representing an oedematous papilla of Vater) may be seen in some cases (157) (140). Endoscopic ultrasound (EUS) allows for better identification of dilatation and thickening of the CBD, and is superior to transabdominal ultrasound in excluding stones, extrabiliary pathology and tumours (151).

6.7.3 CT scanning

In the setting of normal ultrasound features, CT scanning of the abdomen is necessary to aid in diagnosis (143). CT is better than ultrasound in detecting intrahepatic strictures (151) (140). It is also useful in demonstrating abnormalities of the pancreas and liver (151). However, it is less sensitive than ultrasound in detecting CBD wall thickness and strictures (140) (151).

6.7.4 Endoscopic Retrograde Cholangiopancreatography (ERCP)

The gold standard for diagnosing AC is by direct visualization of the biliary tree using ERCP (151). It allows for biliary brushings or aspiration of biliary fluid and for biopsy samples to be taken at the time of the procedure, which can provide microbiological diagnosis (151)

(157) (144). It is also useful in patients with severe pain, allowing for sphincterotomy (151) (144). However ERCP is not indicated in patients with asymptomatic AC (151).

Four subcategories of AC have been defined: papillary stenosis (15% of cases), intrahepatic sclerosing cholangitis- like lesions (20%), both papillary stenosis and intrahepatic sclerosing lesions (50%), and long extrahepatic bile duct strictures with or without intrahepatic lesions (15%) (151). The combination of papillary stenosis and intrahepatic ductal strictures is fairly distinctive to AC (151). In an Indian study, papillary stenosis occurred in 76.6% of patients evaluated in the cohort (147). This is in contrast to the major finding of sclerosing cholangitis in patients in most Western series (147).

The cholangiographic features of AC include distal tapering, biliary mucosal beading, and irregular dilatation of the extrahepatic bile duct. The intrahepatic ducts are often also involved, with the left ductal system more severely distorted than the right. The intrahepatic ducts display irregular dilatation with focal sacculations and intraductal debris (139).

6.7.5 MRI and Magnetic Resonance Cholangiopancreatography (MRCP)

MRCP has an advantage in that it is non- invasive, does not require sedation or intravenous contrast medium and does not include radiation exposure (157). It also allows for evaluation of parenchymal diseases of the liver and pancreas (158). It can thus be used as a screening modality for biliary diseases in AIDS patients where clinically indicated and can help select appropriate patients for ERCP (157).

6.7.6 Histology

Ampullary biopsy specimens have demonstrated submucosal infiltrates, periductal inflammation with interstitial oedema, neutrophilic infiltrates and hyperplasia of periductal glands (145). Pathogen- induced cholangiocyte apoptosis and periductal inflammatory

reaction in the biliary tree thus plays a key role in the pathogenesis of AC (145). Other findings include prominent mucosal folds indicative of inflammation and oedema (151). This mucosal thickening may be diffuse or focal (151). Around 26% of patients have AIDS-related polypoid cholangitis which consists of intraluminal polypoid defects within the CBD and larger intrahepatic ducts, these correlate with the presence of granulation tissue (151). Organisms commonly identified include: *Cryptosporidium*, CMV and microsporidia (140) (147).

6.8 Management and Prognosis of AAC and AC

The management of AAC is surgical and that of AC predominantly endoscopic sphincterotomy. Prognosis of these conditions is also described.

6.8.1 Acute acalculous cholecystitis

The treatment of choice is cholecystectomy, open or laparoscopic (in the early stages of AAC) (140) (141). If a cholecystectomy is performed, the resected specimen should be sent for microbiologic and histopathologic testing (140). Percutaneous CT or ultrasound guided cholecystostomy is a viable option for gallbladder decompression in patients who are very ill or pose a high surgical risk (140). It is less invasive, does not require general anaesthesia and can serve as definitive treatment (once confirmed on post- drainage cholangiography that there are no gallbladder stones) or as a temporizing procedure until the patient is stable enough to undergo cholecystectomy (140) (142) (141). If the causative agent is identified as being MTB, then directed pharmacotherapy is indicated post- surgical intervention (159).

Complications from AAC include gallbladder perforation, peritonitis and gangrene (140). Post- operative mortality for all cholecystectomies in HIV- positive patients is in the range of 2% to 22%. Some studies reported that patients with CD4 cell counts of less than 200/mm^3

survived for an average of 25 months post cholecystectomy whilst those with CD4 cell counts greater than 200/mm^3, survived for an average of 48 months (143). Other studies report that CD4 cell count did not influence mortality but rather was associated with a longer post-operative length of hospital stay (140).

6.8.2 AIDS- Cholangiopathy

Treatment is predominantly endoscopic sphincterotomy for papillary stenosis and stenting for dominant CBD strictures (151). Patients with biliary- type pain, dilated bile ducts and abnormal serum tests of hepatocellular function (especially raised ALP levels) should be offered a sphincterotomy as per standard management guidelines and criteria for treating non-HIV patients (139). Sphincterotomy provides symptomatic relief of pain by enabling drainage and decompression of the biliary system (151) (145). However it does not prolong survival or correct transaminase levels (151). Alkaline phosphatase (ALP) levels continue to rise as intrahepatic bile duct sclerosis progresses (151).

There are no reports of endoscopic stenting of long CBD strictures although anecdotally, metal mesh stents have been used in selected patients who are poor candidates for surgery. Plastic stents should be avoided for proposed long- term stenting as these are unlikely to remain patent for longer than four to six months (139).

Treatment directed against Cryptosporidium, CMV or microsporidium does not modify symptoms or anatomical abnormalities already present (151). Nonetheless it is imperative to treat patients for any identified infections to avoid non- hepatic complications such as GI symptoms from Cryptosporidium or retinitis from CMV (151). TB treatment is necessary post endoscopic intervention if the causative agent is identified as being MTB (154).

Ursodeoxycholic acid has also been used and shown to improve liver biochemistry (151) (140).

Studies have shown that the median survival time from the diagnosis of AC to death was nine months. Patients diagnosed at a younger age had a poorer outcome than those diagnosed at an older age. The presence or history of any opportunistic infection (especially cryptosporidiosis) at the time of AC is considered a poor prognostic marker. Patients with serum ALP levels greater than 1000 IU/l have a shorter life expectancy than those with normal or marginally elevated ALP levels. CD4 lymphocyte counts, type of cholangiopathy and previous sphincterotomy do not affect survival (160).

6.9 HAART in the management of AAC and AC

There was no data describing the impact of HAART on incidence rates, clinical presentation and prognosis of AAC. A decline in the incidence of AC in the HAART era, particularly in the developed world, has been shown (140) (147). Combination antiretroviral therapy suppresses viral load and leads to elevation in CD4 counts, restoring immune function to an extent (140). This is thought to play a role in improving outcomes in patients with AC (140). In one study median survival times had improved from five to eight months in the pre-HAART era to 14 months in the HAART era (160). Another study based in India showed a median survival time of 34 months after the diagnosis of AC in patients started on HAART (147). The development of AC whilst on HAART may portend worsening immunosuppression and indirectly antiretroviral resistance (147).

6.10 Discussion

In general, there were few articles describing the association between HIV and AAC. The actual incidence of both AAC and AC in the HIV-infected population was unknown (140) (144). This could be due to under- reporting of cases in general as well as under- reporting due to limited access to advanced diagnostic imaging modalities especially in developing countries.

Almost all the studies concurred with respect to the clinical presentation of AAC in HIV-positive patients and confirm the fact that timely diagnosis of AAC is challenging, and that clinicians should always maintain a high index of suspicion in this patient group (142). The management options are standard: surgical, in the form of a cholecystectomy or percutaneous cholecystostomy. Regarding this aspect, there is congruence among all the studies reviewed.

Ultrasonography is the most cost- effective study to diagnose AC (140). ERCP may be necessary to confirm the diagnosis or to aspirate bile for diagnosis of opportunistic infections (147). MRCP is a valuable adjunct, but its use in resource constrained settings is limited by its availability and expense (147). Treatment is mainly endoscopic sphincterotomy for papillary stenosis and stenting for dominant CBD strictures (151). Most studies concur that treatment of opportunistic infections in AC does not improve symptoms or alter cholangiographic abnormalities (140). However, TB treatment is necessary if the causative agent is identified as being MTB (154).

The influence of HAART on the incidence, clinical presentation and prognosis of AAC was not well explored in the studies reviewed. It would be intuitive to speculate that due to the improved overall immunity and decreased subsequent susceptibility to opportunistic

infections following initiation of HAART, the incidence of AAC would decrease and prognosis would improve. However directed studies are necessary to prove this association.

The impact of HAART on aspects of AC has been better described in the studies reviewed. The use HAART led to improved survival rates due to immune restoration and decreased susceptibility to opportunistic infections such as Cryptosporidium (160) (144).

6.11 Conclusion

HIV- related biliary diseases are a significant cause of morbidity and mortality (152). As the prevalence of HIV continues to escalate, surgeons will be faced with an increasing number of AIDS patients with abdominal pain (143). They must therefore maintain a high index of suspicion for AAC and AC in this population. Multiple investigations and advanced imaging techniques may be necessary to aid diagnosis (141). HAART is an important part of management of these conditions in addition to relevant surgical procedures.

There is a need for data describing the incidence of AAC and AC among HIV- infected patients in SA and other developing countries in the throes of the HIV pandemic. Studies also need to focus on the influence of HAART on aspects of incidence, clinical presentation and prognosis of HIV- related biliary tract disease in SSA.

CHAPTER 7: HIV- ASSOCIATED VASCULOPATHY

7.1 Introduction

The relationship between HIV and vascular disease is well recognized (161) with HIV-vasculopathy first being described in 1987 (162). The spectrum of disease includes large vessel arterial occlusive disease, aneurysms, spontaneous arterio- venous fistulae (AVF), other vasculitides affecting small and medium- sized vessels, as well as complications of hypercoagulability (162) (161) (163) (5). This chapter provides an overview of the epidemiology, clinical manifestations, diagnosis and management of HIV- vasculopathy.

7.2 Methods

A collective review of the literature using the relevant search engines and search terms as described in the Chapter 2 (Methods) was undertaken. Relevant search terms included: "HIV-associated vasculopathy". A total of 50 articles were identified for the period 2000 to the present date. Of these, 31 articles fulfilled the inclusion criteria and were considered suitable for review. Studies were evaluated using content analysis as described in the Chapter 2 (Methods). (Table 7) illustrates the types of studies and methodological quality of the studies reviewed. Systematic reviews of cohort studies and cohort studies were the commonest methodological approaches. Case- controlled studies a case report and an experimental study made up the remainder of the studies.

Table 8: Type of studies and methodological quality

Type of study	Number	Level of evidence
Systematic reviews of cohort studies	12	2A
Cohort studies	15	2B
Experimental study	1	2C
Case- controlled studies	2	3B
Case report	1	4
Total	**31**	

7.3 Incidence of HIV- associated vasculopathy

An overview of incidence rates of HIV- vasculopathy in SA and developed countries, associated risk factors as well as incidence of the different pathologies is presented as follows.

Incidence in SA: The disease affects males in approximately 80% and 90% of cases (164) (165). The median age of patients affected is between 30 and 40 years (162). Patients also displayed a lower incidence of the characteristic risk factors associated with vascular disease such as hypercholesterolaemia, diabetes mellitus and hypertension (165) (161).Smoking was the most common risk factor in a local study, which reported that patients had a moderate smoking history of less than 10 pack- years in 50% of patients (161).

Incidence in the developed world: In a study by Periard *et al* (2008) of a cohort of 92 patients, incidence rates of peripheral arterial disease (PAD) were 20.7% with the median age of patients being 49.5 years (166). High prevalence rates of smoking in the HIV- infected patient is reported of about 60% of patients in the respective cohorts (166) (167).

Incidence of different pathologies: In a study by Robbs *et al* (2010), conducted between January 2005 and June 2009, 49% of patients in the cohort had aneurysms and 51% presented with occlusive disease (164). The incidence of VTE was 5% in this patient cohort (164). In a similar study conducted by Botes *et al* (2007), aneurysmal disease was present in 22% and occlusive arterial disease in 61% of their patients (165). In another study, 84% of patients who presented with DVT, were HIV- positive (168).

A systematic review conducted in 2005 by a group in the Netherlands, reported incidence rates of VTE in HIV- infected patients as ranging from 0.19% to 18% (168). In several American studies, the reported incidence of VTE ranges from 0.25% to 0.96% with one large prospective study involving 43,000 HIV- infected patients estimating current incidence rates of 2.6 per 1000 person- years (169) (170) (171) (172). Patients under 50 years of age were at increased risk compared to HIV- negative patients with the mean age at diagnosis reported as being 43 years (170) (171) (169).

7.4 Pathogenesis of HIV- associated vasculopathy

The exact pathogenesis of HIV- associated vasculopathy is uncertain (164). Infection by the HIV-1 virus results in diffuse endothelial dysfunction affecting multiple organ systems. This forms part of an extensive, heterogeneous spectrum of vasculopathies affecting small, medium and large- sized vessels. It also includes the non- specific systemic and infective vasculitides as well as angioproliferative lesions such as KS. In addition, a large vessel HIV-associated vasculopathy has been implicated in the pathogenesis of HIV- related aneurysms, occlusive disease and spontaneous arterio- venous fistulae (5).

An experimental study (2008) showed that human arterial smooth muscle cells (SMC) could be infected *in vitro* and *in vivo* with HIV resulting in an increase in SMC secretion of

chemokine CCL2/MP-1 (173). This was found to be an important mediator of atherosclerosis (173). It may pose an additional mechanism resulting in endothelial cell dysfunction and the development of atherosclerosis and HIV vasculopathy (173) (174).

HIV infection itself can induce metabolic changes that may promote atherosclerosis, these including: raised triglycerides, decreased high density lipoprotein (HDL) cholesterol, raised C- reactive protein, raised fibrinogen and plasminogen- activating inhibitor activity (175). HIV infection and a low CD4 count have been shown to be independent risk factors for atherosclerotic disease (174). In the era of HAART, the metabolic side- effects of certain drugs used (discussed under section 7.8) may be associated with the premature development of atherosclerosis (174).

HIV vasculopathy may be classified as follows: (163)

- HIV- related vasculitis
- HIV/ HAART- related atherosclerotic vascular disease
- mixed (both pathologies occurring in the same patient)

HIV- related vasculitis can further be sub- classified into four types: (163)

Type I: Vasculitides described in the non- HIV population group but occur coincidentally in HIV- infected individuals (Takayasu's disease, Behçet's disease, giant cell arteritis and polyarteritis nodosa)

Type II: Drug-associated vasculitis (abacavir, nevirapine, efavirenz, trimethoprim/ sulphamethoxazole)

Type III: Vasculitis- associated with known infections (cytomegalovirus, hepatitis B, hepatitis C, *and Toxoplasma gondii*)

Type IV: Vasculitis probably associated with HIV aetiology (primary angiitis of the central nervous system, Kawasaki-like syndromes, non- hepatitis B polyarteritis nodosa, HIV-related aneurysms and occlusive disease).

The distinct histological features include a leucocytoclastic vasculitis of the vasa vasorum with proliferation of slit like vascular channels within the adventitia (5). The resultant vessel wall damage leads to either aneurysmal dilatation or occlusive disease (176). The histologic and microscopic similarity between the two disease processes suggests a common primary pathological response with a variable clinical expression (176).

7.4.1 Aneurysmal disease

It is unclear as to whether or not the direct action of HIV-1 or an immune complex mechanism leading to vessel wall destruction plays a role in aneurysm formation (164) (177). Evidence to support this mechanism has not been forthcoming (177). HIV protein is noted in the lymphocytes of the vasa vasora and is present in lymphocytes throughout the body as part of the natural behaviour of the disease (164) (177). Opportunistic bacterial and other viral infections may also be responsible for the vessel wall damage (178). The bacteria implicated include mycobacteria species, *Salmonella* and *Haemophilus* (178). Viruses such as EBV, CMV and Hepatitis B may also play a role, but further work is needed to establish their role in the vasculitic process (5).

7.4.2 Occlusive disease

The role of thrombotic and thrombophilic states in HIV/AIDS is a consideration in the pathogenesis of occlusive arterial disease (5). There have been sporadic reports in the literature of anti- phospholipid antibody syndrome, deficiencies of free protein S, protein C and antithrombin III (162). In a local study (2005), tests for hypercoagulable states revealed

no abnormalities in the patient cohort evaluated (179). Thus the contributory role of hypercoagulable states in the pathogenesis of HIV- occlusive disease is unclear (5). It is most likely multifactorial comprising an arteritis on the background of a thrombophilic state (5).

7.4.3 Venous thrombo- embolic disease

The reason for the association between HIV and thrombosis has not been clearly defined (168). It is most likely multifactorial with all three aspects of Virchow's triad being involved (168). The hypercoagulable states described above may play a role in VTE development (180) (174) (168) (181) (169) (172) (171). Other comorbidities associated with hypercoagulable states include opportunistic infections such as CMV and malignancies (180) (181) (169) (171) (172) (168).

7.5 Clinical presentation

The clinical presentation of aneurysmal, occlusive and venous thrombo- embolic disease related to HIV is described.

7.5.1 Aneurysmal disease

The commonest site of involvement is the superficial femoral artery followed by the carotid artery (164). However, any site may be involved, and the aneurysms have a tendency to be multiple (162). The majority of aneurysms are asymptomatic, and are discovered on clinical examination as a pulsatile mass, or incidentally detected on radiological examination (ultrasound and plain radiography) (164) (177). Symptomatic patients present with features dependent on the location of the aneurysm. For example, patients with carotid aneurysms may present with compressive symptoms due to airway obstruction, voice changes, dysphagia, dizziness, cranial nerve palsies and hemispheric symptoms (162) (177) (182). Others present with a painful mass progressively increasing in size (177). Haemodynamic

instability due to rupture of the aneurysm, thrombo- embolic complications and venous thrombosis have also been reported (162). The majority of patients have features of advanced HIV disease as evidenced by significant weight loss, generalized lymphadenopathy and opportunistic infections (164) (177).

7.5.2 Occlusive disease

Most patients present with advanced lower limb ischaemia, as evidenced by rest pain, ulceration or gangrene (165) (162). Others may present with no antecedent claudication and acute thrombosis (164). Infrainguinal disease followed by aorto- iliac disease is common with the upper limbs and carotid artery also being affected in some cases (174). The disease is often multilevel in nature affecting only one limb with normal pulses in the contralateral limb (165) (162) (176). Associated comorbidities include deep vein thrombosis (DVT) and TB (164).

7.5.3 Venous thrombo- embolic disease

The spectrum of pathology predominantly includes lower limb DVT and pulmonary embolism however central nervous system (CNS) and upper limb involvement may also occur (171). Patients with lower limb DVT may present with leg swelling, mild- to moderate pain and tenderness in the extremity as well as low- grade pyrexia (169). The distribution of thrombosis is in the popliteal vein, femoral vein and ileofemoral vein in a small percentage of patients (169). Patients with pulmonary embolism (PE) display signs of cough, dyspnoea and chest pain (170).

7.6 Aspects of diagnosis

The ultrasound and angiographic features as well as relevant haematological and other investigations of the different pathologies are described.

7.6.1 Aneurysmal disease

Patients presenting with aneurysms should be screened for multiplicity using ultrasound and CT scanning as necessary (162). The typical ultrasound features are those of pseudoaneurysms with a defect or "blow- out" in the vessel wall and turbulent, pulsatile flow (183). Other features include the presence of marked thickening of the vessel adjacent to the aneurysm and hyperechoic "spotting" of the vessel wall. The vessels are commonly pristine both proximal and distal to the site of the aneurysm (183). Aneurysm clot specimens sent for microbiology and culture yielded *Salmonella typhi*, TB and *Streptococcus pneumoniae* (177) (182).

In addition, a chest X-ray to screen for TB and routine blood tests are performed (162) (177). Screening for syphilis may be necessary (177). CD4 counts are usually below normal in more than 90% of patients with a median of less than 400 cells/μl and reversal of the CD4/CD8 ratio indicating advanced immunosuppression (162) (177).

7.6.2 Occlusive disease

On Duplex Doppler imaging, the pathognomonic features of hypoechoic "spotting" within the vessel wall ("string of pearls sign"), also seen in patients with HIV- related aneurysmal disease, is described (162) (179). On arteriography- vessels appear pristine proximal to the occlusion, as well as in the contralateral limb (162). The involved limb may display extensive disease extending into the small and medium- sized arteries with poor run- off (162) (5).

Assessment of coagulation profile/ thrombophilia evaluation, including an international normalised ratio (INR), protein C and S levels, antilupus antibody, serum fibrinogen and antiphospholipid antibody levels may be performed, however these revealed no abnormalities in the studies reviewed (164) (179). The CD4 count evaluation and screening for pulmonary TB is also routine (179) (176). Trans- thoracic echocardiography (TTE) may be performed to exclude a cardiac source of emboli (176).

The intra- luminal thrombus sent for microscopy and culture revealed no organisms in the studies reviewed (179) (176). Arterial wall biopsy from amputation sites were evaluated on histology (179). All specimens revealed an organizing thrombus within the vessel lumen with no evidence of atherosclerosis in the intima. The media and the adventitia had scattered chronic inflammatory cells with focal calcification of the media and destruction of the internal elastic lamina and medial muscles. There was a leucocytoclastic vasculitis of the vasa vasora (179).

7.6.3 Venous thrombo- embolic disease

Doppler ultrasound and venography (in certain patients) is used to diagnose lower limb DVT (171) (169). PE is diagnosed on CT pulmonary angiography and ventilation/ perfusion lung scanning. Additional tests include thrombophilia screening as described above (171).

7.7 Management and Prognosis

Management of aneurysmal and occlusive HIV- related vascular disease involves surgical and endovascular techniques. Treatment should be individualized for each patient. Therapy for VTE disease is as per standard treatment protocols applicable to both HIV- infected and non- infected patients (168).

7.7.1 Aneurysmal disease

Management of aneurysms was according to their particular merits and treatment was individualized for each patient (162) (177). Surgery was offered to patients with symptomatic aneurysms where the extent of the planned intervention was appropriate with respect to the operative risk and predicted life expectancy (177).

Therapy involved open surgery following standard vascular surgical principles- surgical bypass, interposition grafting (autologous vein or prosthetic grafts) and ligation (where aneurysms were suspected of being infective in origin especially those involving the common carotid artery where neurological deficits following ligation were rare) (162) (5) (182). Endovascular therapy was being increasingly employed, and presented an attractive option in patients deemed too ill to withstand an open procedure (162) (182). There was no data available comparing surgery with endovascular procedures for aneurysmal disease and at present, is reserved for patients unfit for surgery (180) (182). Patients with severe immunocompromised states and attendant severe comorbidities were best managed conservatively (162) (180) (177). All patients should be optimized as per conventional practice prior to intervention considering the use of peri- operative antibiotic prophylaxis and anticoagulation where appropriate (162) (5).

In a study by Robbs *et al* (2010) at one month follow- up, overall mortality in the total of 80 patients who underwent surgery was 9%; 5% of patients developed graft sepsis and 11% developed pulmonary infection (164). The combination of low CD4 count and low albumin levels has been used to prognosticate and predict post- operative morbidity and mortality (162) (174). However recent studies have shown that there was no association between these two variables and outcome (164) (182).

In a local study (2011) of a 22 patient cohort with carotid artery aneurysms, patients who underwent stenting had a worse outcome. Reasons postulated for this included high likelihood of endoleaks, the inability to biopsy the arterial wall thus leading to "missed" pathologies which were not addressed, which could have led to further complications (182).

7.7.2 Occlusive disease

Basic vascular surgical principles should be followed when managing patients with HIV-associated occlusive disease and management individualized (162). Patients with acute thrombosis underwent thrombectomy with or without thrombolysis, as well as bypass surgery in an attempt to salvage the limb (164). Those in whom limb salvage was deemed impossible, primary amputation was performed (164). In patients with chronic occlusive disease, management options include: primary amputation (those patients with late stage, advanced arterial disease and extensive tissue necrosis); bypass surgery and endovascular management (164) (174) (176). For patients with advanced stage of AIDS, conservative management with adequate analgesia is an option (179). Experience with endovascular techniques is limited at present (174).

Limb salvage rates have tended to be poor (27%) (162) (164). This may be accounted for by the fact that the primary pathology in acute thrombosis is that of a vasculitic process with superimposed thrombosis (179) (162). Thrombectomy or thrombolysis did not address this thus leading to high rates of re- thrombosis (179) (162). The incidence of sepsis is generally low in the short term, but in the long term, graft sepsis rates may increase (164).

7.7.3 Venous thrombo- embolic disease

Standard treatment protocols for patients with proven VTE should be adhered to in HIV-infected individuals. With respect to thromboprophylaxis in these patients, no clear guidelines exist and thus prophylaxis is warranted as for a patient suffering from cancer (168).

7.8 HAART in the management of HIV- associated vasculopathy

The use of HAART in patients with HIV vasculopathy may have effects on controlling the HIV infection, possibly reducing or managing vasculitis and thus the attendant manifestations of HIV vasculopathy. In addition treatment of and prophylaxis against opportunistic infection in this patient group is vital. It is postulated that the pathogenetic mechanisms implicated in the development of HIV- vasculopathy such as HIV replication, opportunistic infections and/ or immune mechanisms may be curbed by HAART thus reducing the incidence of HIV vasculopathy. Further research is needed with respect to this (175).

Due to the observation that HIV vasculopathy was a marker of advanced stage of HIV disease, albeit not being an AIDS- defining condition, some authors recommend that HAART be offered to these patients irrespective of their CD4 count (162). The improvement in immune status may play a role in reducing incidence rates of HIV vasculopathy, influencing clinical presentation and improving post- operative outcomes, but further research in this regard is warranted.

Protease inhibitors (PIs) may be associated with metabolic side- effects for example hyperlipidaemia, central fat accumulation and insulin resistance as part of the metabolic syndrome. This may play a role in the pathogenesis of atherosclerosis. These metabolic

derangements have led to the rationale that PI therapy be avoided for as long as possible (175).

Thus HAART is in effect a double- edged sword, as on one hand, it reduces viral load and improves immunity which may result in less arterial damage and HIV vasculopathy. Controlling the disease may improve the metabolic derangements associated with HIV itself as described earlier. On the other hand however, antiretrovirals, and specifically the older PIs with their metabolic side effects can cause vascular damage and accelerated long- term atherosclerotic cardiovascular disease (175).

Thus, management of modifiable risk factors associated with atherosclerosis, for example smoking and hypertension, maintaining optimal blood glucose levels and statin therapy to control hyperlipidaemia, is essential (175) (184). The development of drugs with favourable risk profiles for metabolic derangements is also necessary. In the future, it is thought that with widespread availability of HAART, the disease spectrum will evolve from management of HIV vasculopathy to more chronic peripheral arterial disease (175).

7.9 Discussion

Data on the actual prevalence of venous and arterial thrombo- embolic disease, as well as on HIV vasculopathy, is limited in the literature. Most of the studies were case reports or non-controlled retrospective cohort studies (167). A common finding among the South African studies reviewed was that the incidence of HIV- related vasculopathy is on the increase (164). Although females are more frequently affected by HIV infection in SA, there was a definite male preponderance with respect to incidence rates of HIV vasculopathy and the reason for this remains unclear (164). This finding was similar to studies conducted in the developed world (165) (182) (166). A relatively younger subset of patients (average age of 40 years)

was affected with respect to HIV vasculopathy in both the South African and European studies reviewed (165) (166) (167).

In most developed countries where HAART has been widely available, for more than a decade, pathology may be explained by an increased risk of atherosclerotic disease (166) (167) (163). In SA and other developing countries, where access to HAART is limited, HIV vasculopathy represents a distinct clinico- pathological entity, characterized by a vasculitis with probable immune- mediated or direct HIV- related injury to the vessel wall (162) (177). However, HIV infection itself and a low CD4 count have been shown to be independent risk factors for atherosclerotic disease independent from HAART in both local and European studies (174) (166).

The role of other opportunistic viruses and bacteria may be prominent in the developing compared to the developed world, but evidence has not been forthcoming to support this theory and requires further testing using advanced molecular microbiological testing (177) (5). With respect to the role of hypercogulable states in the pathogenesis of HIV vasculopathy, thrombotic events were commonly venous in nature (174). The role of hypercoagulable states in HIV- occlusive disease remains vague, and extensive, uniform testing of patients is necessary to draw definitive conclusions (5) (177).

In summary, the aetiopathogenesis of HIV- vasculopathy remains theoretical, with a combination of infection, immune complex- mediated, direct HIV damage to the vessel wall and other unidentified factors operating together. The leucocytoclastic vasculitis of the vasa vasora and angiogenesis in the adventitial collagen are consistent features in both HIV-related aneurysmal and occlusive disease (5).

Pathognomonic duplex ultrasonographic features common to both aneurysms and occlusive disease include hyperechoic "spotting" in the arterial wall and the "string of pearls sign" (183). Patients with aneurysms should be screened for multiplicity using ultrasound and CT scanning as needed (162). Angiographic features of occlusive disease show pristine proximal arteries, extensive disease extending into the small and medium- sized vessels with poor run-off (176) (179) (165).

Management principles were gathered from review articles and cohort studies. Vascular surgical principles should be followed in patients with HIV- vasculopathy and treatment individualized (162). No studies were found that compared endovascular to open surgery for both aneurysmal and occlusive disease (180). At present, there is limited experience with regard to endovascular management in SA, possibly due to its availability and cost constraints (5) (174). Its use at present is reserved for those patients who are unfit for open surgery (182). The fact that it is minimally invasive makes it an attractive option; particularly in this patient group and further studies are needed to better evaluate its efficacy (174) (162).

With respect to prognostication, general consensus is that the combination of low CD4 cell counts and low albumin levels were not reliable indices of poor surgical outcomes and mortality (164) (182). Thus patients should be evaluated holistically based on clinical, other laboratory and radiological criteria as to suitability of interventions. Here, research is needed describing the role of HAART in improving overall incidence rates, clinical presentation and subsequent surgical outcomes (182) (164).

At present, inequities exist as to availability of HAART in SA and with rising incidence rates of HIV, so too will the incidence of HIV- associated vasculopathy increase (177) (180). However, in time, as HAART use becomes widespread in SA and other developing countries, clinicians and surgeons alike may be confronted with more cases of HAART induced

atherosclerotic vascular disease as demonstrated in developed countries (175) (163). Thus, patients on HAART should be screened for cardiovascular diseases, encouraged to maintain optimal blood glucose levels and control hypertension (184). Smoking cessation is essential as well incorporating statin therapy in the holistic management of these patients (184) (163).

7.10 Conclusion

The incidence of HIV- vasculopathy is increasing in SA (164). Knowledge regarding the pathogenesis of HIV vasculopathy is hypothetical at present, and is based on observational studies, thus research is needed to clarify these mechanisms (5). These include a detailed analysis of coagulation function (for occlusive arterial diseases) as well as advanced molecular microbiological techniques to evaluate for possible infective aetiologies (176) (5).

Management should be individualized and vascular surgical principles followed in patients with HIV vasculopathy (162). The use of endovascular techniques in managing these conditions is not routine at present, and is confined to a subset of patients with poor surgical risk (182). There are no randomized trials or studies comparing endovascular management to surgery in the management of both occlusive and aneurysmal disease, these being needed to determine the efficacy of endovascular options (180).

Studies evaluating the influence of HAART on incidence rates, clinical presentation and surgical outcomes are limited in the literature. Most studies describing the influence of HAART on incidence rates were from Europe and other developed countries (184) (167) (166). In SA and other developing countries with high prevalence rates of HIV, further longitudinal and observational studies are required to document the effect of HAART on these factors.

CHAPTER 8: CONCLUSION

This study aimed to provide a comprehensive update on HIV- related surgical pathology such as parotid gland enlargement, KS related lower limb lymphoedema, abdominal malignancies due to KS and lymphoma, HIV- associated biliary tract disease as well as HIV- associated vasculopathy. The areas explored were the epidemiology, pathogenesis, clinical manifestations, diagnosis and management of these disease entities. A literature review of the relevant published material was conducted. Quantitative studies from the year 2000 to the present date of HIV- infected adults from both developing and developed countries were included. The role of HAART in the management of these conditions was also described.

Medical management forms the mainstay of care of the HIV- positive patient, with medical treatment for HIV having developed significantly over the last two decades (6). With the rising prevalence of HIV in SSA, new and unique diseases associated with HIV, for example salivary gland disease and HIV- associated vasculopathy, have come to the fore (185) (5). Thus, the role of the surgeon in managing these conditions has also evolved and grown, with an increasing number of diagnostic and palliative procedures being used to treat them (6) (7).

Parotid gland enlargement is typically an early manifestation in the HIV- positive patient and should alert surgeons to the likelihood of HIV infection (21) (22) (26). FNAC of the parotid gland is required to confirm the diagnosis (18) and instituting HAART forms an important part of the management (36). There is a shift away from surgery in the treatment of this essentially ‘benign’ condition (16).

Kaposi’s sarcoma is the commonest tumour among AIDS patients with lymphoedema being a feature of advanced cutaneous KS (43). KS should therefore be considered in the differential diagnosis of a patient with chronic lower limb lymphoedema. Definitive diagnosis is based on

biopsy of the involved skin and characteristic skin nodules (66). Timeous HAART, systemic chemotherapy and lymphatic drainage manoeuvres form the mainstay of management for patients with KS related lower limb lymphoedema (43) (53). Furthermore, preservation of skin integrity is vital to curb the development of secondary bacterial and fungal infections (53) (41).

The GIT is a common site for the development of malignancies among HIV- positive patients (84). KS and extranodal NHL involving the GIT frequently occur. Extrapulmonary TB is the main differential diagnosis for surgeons to consider and exclude in a patient with suspected abdominal lymphoma. A range of imaging investigations and minimally invasive biopsy techniques exist to aid in diagnosis and staging of GI-KS and lymphoma. Chemotherapy and HAART form the basis of management with surgery reserved for acute complications such as intestinal obstruction, perforation or haemorrhage (84).

Surgeons should consider AAC and AC in the differential diagnosis of an HIV- positive patient presenting with right upper quadrant pain (142). These patients often have advanced HIV disease with low CD4 counts (139) (140) (145). Ultrasonography is the routine first line investigation for both AAC and AC (140). However, multiple investigations and advanced imaging modalities may be necessary in cases of diagnostic doubt (141). Cholecystectomy (open or laparoscopic) is the treatment of choice for AAC (140) (141). AC management includes endoscopic sphincterotomy in patients with papillary stenosis, and stenting in those with dominant CBD strictures (151). HAART plays an important role in the management of HIV- related biliary tract disease by improving patients' overall immunity and decreasing their susceptibility to opportunistic infections (144).

HIV- associated vasculopathy is a disease that primarily affects young men (164) (165). It represents a distinct clinico- pathological entity characterized by a vasculitis with probable

immune- mediated or direct HIV- related injury to the vessel wall (162) (177). The resultant vessel wall damage leads to either arterial aneurysmal dilatation or occlusive disease (176). Pathognomonic duplex ultrasonographic features include hyperechoic "spotting" in the arterial wall and the "string of pearls sign" (183). Management should be individualized and vascular surgical principles adhered to (162). The role of endovascular techniques in managing this condition is evolving and at present it is confined to patients with poor surgical risk (182). The postulated benefits of HAART in the management of HIV- associated vasculopathy include: controlling HIV infection, treating vasculitis and reducing the incidence of HIV vasculopathy (175).

There are many challenges with respect to resource constraints in SSA and other developing countries. HAART has become an integral part of patient care in developed countries, transforming a lethal disease into a chronic illness (44). Patient survival has improved considerably and the incidence of KS, AIDS- related malignancies and cholangiopathy have declined significantly (44). This is unfortunately not the case in Africa and other developing countries where the majority of patients present with advanced HIV disease and high mortality rates (76). In these regions, patients have limited access to HAART, chemotherapeutic agents and drugs for treating opportunistic infections, resulting in the delivery of sub- optimal care (44) (131). Collaboration between the different stakeholders such as pharmaceutical industries, policy- makers and international funders is therefore imperative to alleviate the impact of HIV and prevent or delay the development of certain malignancies and opportunistic infections (43) (44).

Some of the limitations of this study include the reliance solely on electronic resources for the literature search and thus the possibility of studies being missed, the exclusion of foreign language publications, conference proceedings and the absence of two or more reviewers to

independently collate and appraise the data. The majority of studies reviewed were cohort studies, systematic reviews of these as well as case series, and case reports. While these studies may be reliable in describing the epidemiology and prognosis of the diseases reviewed, their reliability is limited in guiding clinical practice relating to the use of the appropriate diagnostic tests and therapy. The most reliable study to guide management and treatment decisions is a randomized controlled trial (186) and there were only three randomized controlled trials and three systematic reviews of these included in the study.

My contribution to knowledge has been to assimilate the current literature; to highlight new developments and deficiencies in the literature and their implications for current surgical practice. An emerging theme in the studies reviewed has been the paucity of data from SSA and other developing countries. HIV- related pathology and burden of disease is high in SSA (131). There are several opportunities for further research, ranging from studies to explore the epidemiology, pathogenesis, natural history and prognosis of the diseases described above (44). Furthermore, pragmatic diagnostic and treatment modalities for resource constrained settings are needed (44). This underscores the critical need to improve research infrastructure to 'build capacity' to study these diseases and to recognize approaches for their prevention (136). In this regard it is vital that African researchers lead the way (131).

It is envisaged that this study will serve as a platform and a catalyst for further epidemiologic and interventional studies in the field of HIV- related surgical pathology. Thus, new policies and management protocols can be developed that will enhance service delivery and ultimately improve the quality of care that we as surgeons can provide to our patients.

CHAPTER 9: REFERENCES

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APPENDICES

Appendix 1: Post graduate office study approval

UNIVERSITY OF
KWAZULU-NATAL

02 August 2011

Professor B Singh
Department of General Surgery
Nelson R Mandela School of Medicine

Dear Professor Singh

PROTOCOL:" A review of the scope and spectrum of challenges presented to the general surgeon by patients effected with the Human Immunodeficiency Virus (HIV)." Student: S Ebrahim, student number: 993212478. (Department of General Surgery).

The Postgraduate Education Committee ratified the approval of the abovementioned study on 02 August 2011.

Please note:

- The Postgraduate Education Committee must review any changes made to this study.
- The study may not begin without the approval of the Biomedical Research Ethics Committee.

May I take this opportunity to wish the student every success with the study.

Yours sincerely

Professor SJ Botha
Chair: Postgraduate Education and Research Committee

CC. Dr S Ebrahim
Dr SS Ramklass

Biomedical Research Ethics Committee
Westville Campus

Postgraduate Education Administration,
Medical School Campus

Postal Address: Private Bag 7, Congella, 4013, South Africa

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Founding Campuses: Edgewood Howard College Medical School Pietermaritzburg Westville

Appendix 2: Ethics approval letter

UNIVERSITY OF
KWAZULU-NATAL
INYUVESI
YAKWAZULU-NATALI

RESEARCH OFFICE
Biomedical Research Ethics Administration
Westville Campus, Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 2604609
Email: BREC@ukzn.ac.za
Website: http://research.ukzn.ac.za/ResearchEthics/BiomedicalResearchEthics.aspx

14 June 2011

Dr S Ebrahim
Department of General Surgery,
Inkosi Albert Luthuli Central Hospital,
800 Bellair Road,
Mayville

Dear Dr Ebrahim,

Ethics application for study entitled: A review of the scope and spectrum of challenges presented to the general surgeon by patients affected with the Human Immunodeficiency Virus (HIV): BE 099/011.

As your methodology consists entirely of reviewing published papers and materials already in the public domain, the proposed study is exempt from ethics review.

Postgraduate approval is however still required. This letter should be forwarded to the postgraduate office for noting.

Yours sincerely

Prof. D Wassenaar
Chair: Biomedical Research Ethics Committee

Appendix 3: Modified Ann Arbor Staging Classification for Non- Hodgkin's Lymphoma (111)

Stage	Description
I	Involvement of a single lymph node region
IE	Localized involvement of a single extralymphatic organ or site
II	Involvement of 2 or more lymph node regions on the same side of the diaphragm
IIE	Localized involvement of a single associated extralymphatic organ or site and its regional lymph nodes with or without other lymph node regions on the same side of the diaphragm
III	Involvement of lymph node regions on both sides of the diaphragm
IIIE	Involvement of lymph node regions on both sides of the diaphragm accompanied by localized involvement of an extralymphatic organ
IIIS	Involvement of lymph node regions on both sides of the diaphragm accompanied by involvement of the spleen
IIIE+S	Involvement of lymph node regions on both sides of the diaphragm accompanied by both localized involvement of an extralymphatic organ or site and the spleen
IV	Disseminated (multifocal) involvement of 1 or more extralymphatic organs with or without associated lymph node involvement
IVE	Isolated extralymphatic organ involvement with distant (nonregional) nodal involvement

Appendix 4: International Prognostic Index- IPI (101)

Risk factors

Ann Arbor stage III–IV

>1 extranodal site

High LDH (Lactate dehydrogenase)

Age> 60 years

Performance status >/= 2 ECOG (Eastern Co- operative Oncology Group Performance Status)

Low risk 0–1 risk factors	
Low intermediate risk	2 risk factors
High intermediate risk	3 risk factors
High risk	4–5 risk factors