

**A STUDY COMPARING OUTCOMES OF APPENDECTOMY BETWEEN
HIV-INFECTED AND HIV-NEGATIVE PATIENTS**

by

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DECLARATION

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LIST OF ABBREVIATIONS

HIV	Human Immune Deficiency Virus
AIDS	Acquired Immune Deficiency Syndrome
HIV+	Human Immune Deficiency Virus-infected
HIV-	Human Immune Deficiency Virus negative
GIT	Gastrointestinal Tract
HIV-1	Human Immune Deficiency Virus Type 1
HIV-2	Human Immune Deficiency Virus Type 2
gp	glycoprotein
RNA	Ribonucleic Acid
DNA	Deoxyribonucleic Acid
DC-SIGN	Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin
GALT	Gut Associated Lymphoid Tissue
HAART	Highly Active Antiretroviral Therapy
CDC	Centers for Disease Control and Prevention
TB	Tuberculosis
KS	Kaposi's Sarcoma
TAC	Temporary Abdominal Closure
MALT	Mucosal Associated Lymphoid Tissue
ICU	Intensive Care Unit
IRIS	Immune Reconstitution Inflammatory Syndrome
NIS	Nationwide Inpatient Sample
VL	Viral Load
ICD	International Statistical Classification of Diseases and Related Health Problems

ABSTRACT

A STUDY COMPARING OUTCOMES OF APPENDECTOMY BETWEEN HIV-INFECTED AND HIV-NEGATIVE PATIENTS

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Background: The high prevalence of Human Immunodeficiency Virus (HIV) has added a new dimension to the management and outcomes of many general surgical conditions in South Africa. However, there is a paucity of data describing the impact of HIV status on surgical outcomes in our setting. Appendicitis is the most common gastrointestinal emergency, and its surgical outcomes in areas of high HIV prevalence are poorly described in the literature. Thus, the aim of this study is to describe and compare the outcomes of appendectomy between HIV-infected (HIV+) and HIV-negative (HIV-) patients.

Methods: This is a retrospective study of patients undergoing appendectomy at a large regional hospital over a 12-month period. Demographic data, duration of pre-hospital symptoms, HIV status, surgical approach, operative findings, histopathology reports, hospital stay and complications were recorded. Data for the HIV+ and HIV- patient cohorts were then described, analysed and compared. Statistical analysis was performed using the Chi-Squared or Fisher's exact test for non-continuous variables, and non-parametric ANOVA and Wilcoxon ranked sum test for continuous variables. A P-value less than 0.05 was considered statistically significant.

Results: The study group comprised 134 patients; 18 (13.4 %) tested positive for HIV. HIV+ patients were significantly older (mean age of 29.3 vs. 20.3 years, P= 0.002) and had longer duration of pre-hospital symptoms (mean of 3.94 vs. 2.57 days, P= 0.03). Postoperative complications (44.4 % vs. 17.2 %, P= 0.03) and lengthier hospital stays (7.28 days vs. 5.95 days, P= 0.004) were also more frequently seen in the HIV+ patients. There were no differences in appendiceal rupture rates, histopathological findings and mortality.

Conclusion: HIV infection is common in patients admitted with clinical features of acute appendicitis in South Africa. Presentation in HIV+ patients was delayed, and surgery was associated with significant postoperative morbidity and longer hospital stay.

CHAPTER ONE:

LITERATURE REVIEW

1.1 Introduction

The Human Immune Deficiency Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS) pandemic has added a new dimension to the epidemiology, clinical presentation and outcomes of a wide array of surgical conditions in South Africa. ^[1-7] The surgical abdomen in the HIV-infected (HIV+) patient requires more than the standard armamentarium of the general surgeon because of its increased morbidity and mortality, particularly in the latter stages of the disease. ^[3,6,8-13] South Africa has the highest HIV prevalence worldwide; 6.4 million people are infected with the virus. ^[14] This has further translated into local surgical cohorts; HIV is now the most prevalent comorbid disease and is present in 13.2% of patients undergoing surgery in South Africa. ^[15]

Despite this ravaging pandemic, there is a paucity of published South African data describing and investigating the relationship between HIV and common general surgical conditions. ^[3,6,16-18] Acute appendicitis is one of the most common Gastrointestinal (GIT) surgical emergencies in South Africa. ^[19-22] Its surgical management thus presents an interesting platform to study the effect of HIV on the surgical outcomes of a common general surgical intervention.

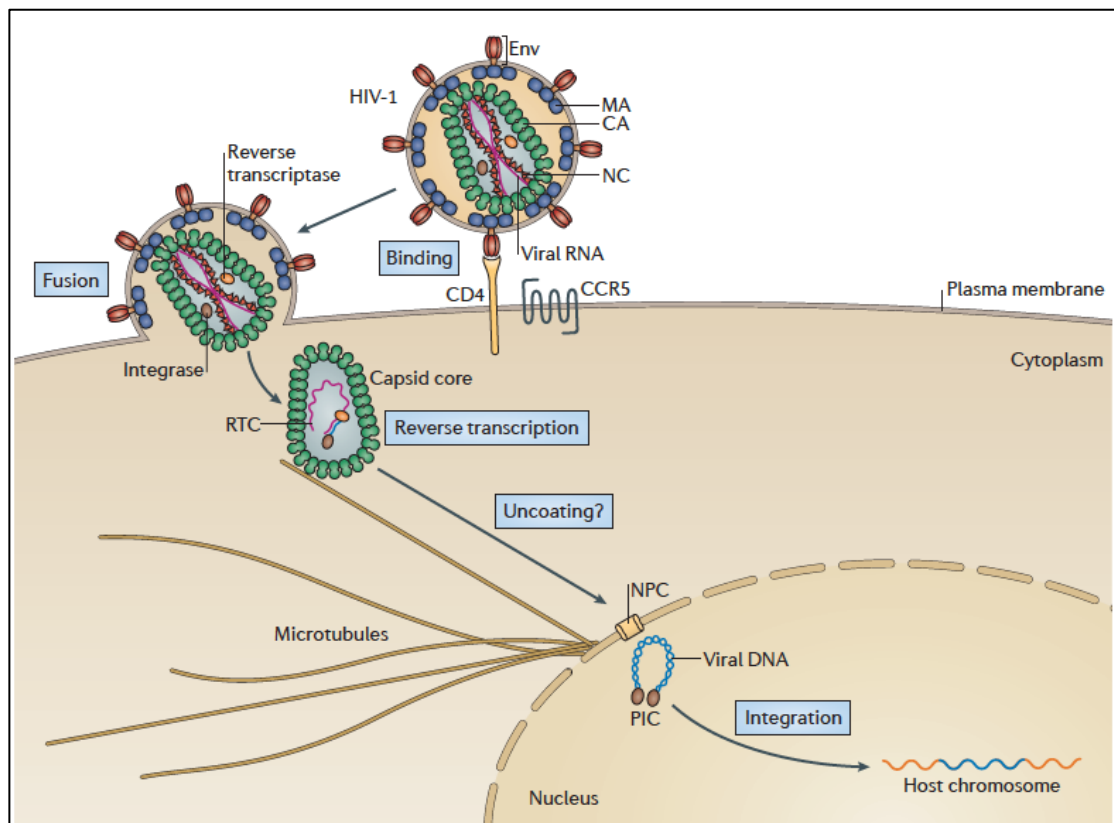
1.2 The Human Immune Deficiency Virus

HIV is a member of the retrovirus family; seven distinct genera of retroviruses exist. HIV type 1 (HIV-1) and HIV type 2 (HIV-2) belong to the genus of lentiviruses. Both types are transmitted mainly through unprotected sexual intercourse, but HIV-2 is less pathogenic and confined to West Africa. Whilst the origins of HIV remain controversial, it is well established that HIV-1 is predominantly responsible for the global epidemic. ^[23-25]

The HIV has a complex structure. It has an outer viral envelope and a central viral core. The viral envelope is derived from the host cell plasma membrane and contains a docking glycoprotein 120 (gp120) and a transmembrane glycoprotein 41(gp41). The principal components of the viral core include two copies of the HIV genome in the form of Ribonucleic Acid (RNA), protein p7 and three enzyme proteins (Reverse

Transcriptase, Protease and Integrase), which are required for replication. CD4⁺ helper T lymphocytes, monocyte/macrophage lineages and cells expressing CCR5 or CXCR4 receptors are primarily affected by HIV. Other target cells include microglial cells in the central nervous system, dendritic cells in the mucosa and the renal epithelium. The virus enters the target cell by binding its viral envelope gp120 to the CD4 receptor (*Figure 1*). [26] Within the cell cytoplasm, viral RNA is then reverse transcribed into a double stranded complementary Deoxyribonucleic Acid (DNA) by the enzyme reverse transcriptase. This complementary pro-viral DNA is inserted into the host chromosome through a series of DNA cutting and joining reactions. [26-35]

Figure 1. Early phase of HIV-1 replication [26]



Typically, HIV enters the host through the genital tract mucosa after unprotected sexual intercourse. [24] It crosses the mucosal and submucosal spaces, and is picked up by the antigen-presenting dendritic cells via Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin (DC-SIGN). The dendritic cells migrate to the regional lymph nodes and present the virus to an abundant population of CD4⁺ helper T lymphocytes. Four to 11 days after the initial infection, the virus

disseminates to the lymphoid tissues of the body through the bloodstream. This phase is characterised by a high viremia, which clinically manifests as an episodic flu-like illness. Early mucosal replication occurs mainly in the GIT, where the bulk of CD4⁺ helper T lymphocytes are housed in Gut Associated Lymphoid Tissue (GALT). HIV replication is accompanied by a profound consumption of CD4⁺ helper T lymphocytes in GALT. Low levels of T lymphocytes persist despite Highly Active Antiretroviral Therapy (HAART), in contrast to peripheral blood CD4⁺ counts which normalise with treatment. [36-40]

Untreated infection progresses to AIDS. [26-28] Early diagnosis, uninterrupted medical care and HAART remain the three most important pillars in the management of the HIV+. [29-34] The Centers for Disease Control and Prevention (CDC) has generated HIV/AIDS case definitions and classification systems for surveillance, and clinicians often refer to them when describing patients' clinical and immune statuses. The updated 2014 CDC case definitions for HIV infection stage patients based on their CD4 counts and clinical evidence of AIDS-defining conditions (*Table 1*). [41]

Table 1: 2014 CDC Case definitions for HIV infection in adolescents and adults [41]

2014 CDC Case Definition for HIV Infection Among Adolescents and Adults			
Stage	CD4 Count	CD4 %*	Clinical Evidence
Stage 0	Early HIV Infection		
Stage 1	≥500 cells/mm ³	≥26	No AIDS-defining condition
Stage 2	200-499 cells/mm ³	14-25	No AIDS-defining condition
Stage 3	<200 cells/mm ³	<14	or Documentation of AIDS-defining condition
Stage unknown	No data	No data	and No information on presence of AIDS-defining conditions
*Use CD4 percentage only if no data available for CD4 count			

It is also more flexible and allows for a patient's stage to be up-staged or down-staged after the initial diagnosis. This is in stark contrast to the previous CDC classification

which permanently classified patients according to the most advanced stage of disease experienced, irrespective of their clinical progress following treatment. [42]

Although the future of HIV research looks promising, prospects of a vaccine remain elusive. [29] This is partly due to the persistence of the virus in a latent form in resting memory CD4⁺ T cells, which are very stable and persist for years despite HAART.

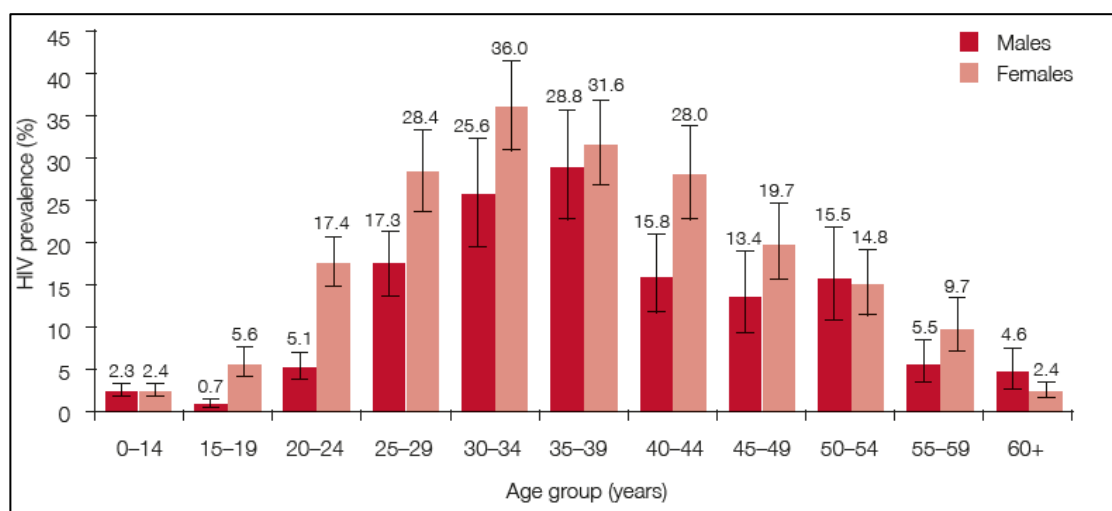
Fortunately, the roll out of HAART programs has markedly improved life expectancy in patients. [30-33]

HAART is currently recommended in those with an AIDS-defining condition regardless of CD4⁺ count or when it drops below 200 cells/μl. Recently, there has been a paradigm shift regarding the criteria to initiate HAART; a treat all policy irrespective of CD4⁺ count and clinical stage is the new therapeutic strategy. [34]

1.3 Epidemiology of Human Immune Deficiency Virus infection in South Africa

Thirty-seven million people are infected with HIV worldwide, the majority of whom (25.8 million) are from Sub-Saharan Africa. South Africa has the highest number of people living with HIV globally; the national prevalence is 12% and 6.4 million people live with the disease. There is a significantly higher number of women infected with the virus and young individuals belonging to the 30 to 34-year age group are the most affected (*Figure 2*). [14]

Figure 2. HIV prevalence by sex and age in South Africa [14]



Residents of rural informal areas are at higher risk of getting infected, with KwaZulu-Natal being the top high prevalence province in South Africa at 16.9%. Our study was conducted in the Northern Cape province, where the HIV prevalence is 7.4%. [14,30,32] South Africa currently boasts the largest HAART program in the world. Three million patients are on treatment and the annual intake includes a further 600 000. Improved life expectancy with HAART and the increasing HIV prevalence in South Africa over the past decade are both significant contributors to an epidemiological transition witnessed by surgeons. [14,30,43,44] The latter now frequently manage long term sequelae of HIV infection such as GIT lymphoma, abdominal Tuberculosis (TB), Kaposi's Sarcoma (KS) and HIV vasculopathy, as well as the complications of HAART-induced pancreatitis and lipodystrophy. [9,45-49] This epidemiological transition has also translated in medical and surgical cohorts across the country. HIV is the second most common chronic disease in South Africa after hypertension (*Table 2*). [14,50-52]

Table 2: Prevalence of chronic medical conditions in South Africa [14,50-52]

Chronic Medical Condition	Prevalence in South Africa (%)
Hypertension	30.4
HIV	12.2
Asthma	8.1
Diabetes	7.0

In the large multi-centre prospective South African Surgical Outcomes Study, Biccard et al showed that HIV/AIDS was present in 13.2% of patients undergoing surgery in South Africa (*Table 3*). [15]

Table 3: Comorbid conditions in patients recruited for South African Surgical Outcomes Study [15]

Comorbid disease	N (%)
HIV/AIDS	509 (13.2)
Chronic Obstructive Pulmonary Disease/Asthma	240 (6.2)
Diabetes	225 (5.8)
Coronary Artery Disease	160 (4.1)
Congestive Cardiac Failure	55 (1.4)

1.4 Appendicitis in South Africa

The vermiform appendix is embryologically derived from the midgut. It is a worm-shaped tubular structure originating from the posteromedial caecal wall at the junction of the taeniae, and averages 9 cm in length. Arterial supply is via the appendicular artery, a branch of the ileocolic artery. Venous drainage is through the ileocolic veins and the right colic vein into the portal vein via the superior mesenteric vein. ^[53] The appendix contains lymph follicles and an epithelial lining coated with immunoglobulins, which assist with lymphatic surveillance. ^[54]

Appendicitis is a very common GIT surgical emergency. ^[55] Inflammation and swelling of the appendix result from proliferation of intestinal bacteria within the lumen. White blood cells are recruited and pus formation causes further pressure build-up. This is followed by wall ischaemia, necrosis and subsequent rupture of the appendix. Diffuse peritonitis will ensue followed by septic shock and death. ^[56-58] Although the aetiology of appendicitis is still debatable, luminal obstruction by a faecolith remains a widely accepted theory. ^[54]

The definitive surgical management of appendicitis in South Africa is appendectomy. Antibiotics as first-line therapy for uncomplicated acute appendicitis is feasible but should be considered with a great degree of caution in our setting. The recurrence rate of appendicitis is 26% within the first year ^[59-61] Many South African patients still live in rural areas, where difficult access to hospitals and delay to definitive surgical care lead to more frequent post-operative morbidity and mortality. ^[19,21,22,62] An early appendectomy at the initial presentation therefore remains the approach of choice and must be regarded as lifesaving in South Africa.

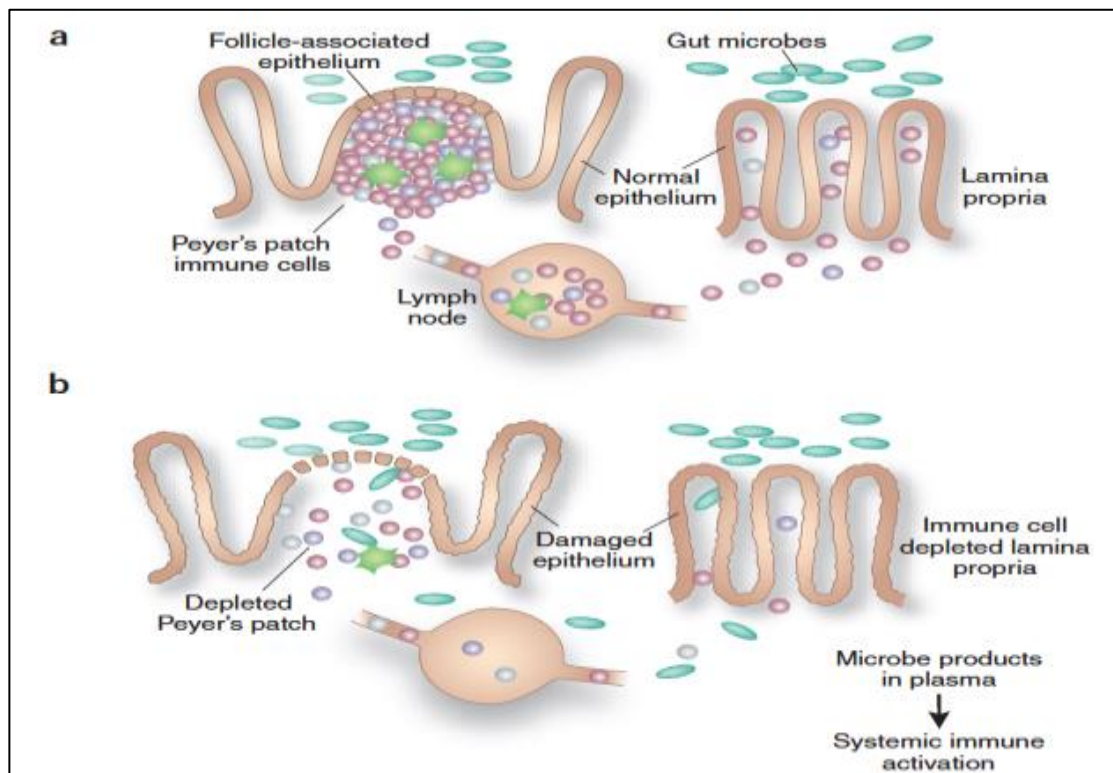
A rising incidence of appendicitis is being reported in developing nations. ^[55] This has been attributed to societal and environmental factors that are associated with industrialisation, and include low dietary fibre intake, smoking and air pollution. ^[63-66] South African data suggest that 10% of the Caucasian population have undergone surgery for acute appendicitis, but less than 1% of Africans had undergone the same procedure. This racial disparity is explained by the consumption of a low fat and high fibre diet amongst certain racial groups. ^[67] Male patients were more likely to have surgery for acute appendicitis and had higher rates of perforation than women. A recent systematic review conducted by Yang et al confirmed that appendicitis trends in South Africa are consistent with those seen in other newly industrialised countries. ^[19] However, appendicitis in South Africa has a far more serious clinical course when

compared to developed countries, mainly because of the longer delays required to receive definitive surgical care. A high perforation rate of 36% and the need for laparotomy in 18% to 60% of patients are factors that drive the high post-operative morbidity seen in these patients.^[19,21] Up to 30% of patients will require Temporary Abdominal Closure (TAC) at their initial surgery because of four quadrant peritonitis, diffuse soiling of the abdomen and the need for relook laparotomies. Furthermore, 11% of patients will require admission to the Intensive Care Unit (ICU) and 29% will require a second surgical intervention.^[22]

1.5 The Surgical abdomen in the Human Immune Deficiency Virus-infected patient

GIT complaints of diarrhoea, weight loss and malnutrition are well described in patients infected with HIV-1. In healthy adults, GIT immunity is maintained by Mucosal Associated Lymphoid Tissue (MALT). It is the largest mammalian lymphoid organ system and harbours 80% of all immune cells. Immune T cells and B cells migrate from MALT foci located in the intestine and appendix to effector sites, where pathogens and pathogen-laden cells are eliminated.

Figure 3: Chronic HIV infection causes microbial translocation and immune activation. (a) Normal bowel epithelium, (b) Chronic HIV infection^[36]



The virus disrupts the intestinal immune system, with resultant bacterial translocation and systemic immune activation. It has also been recently established that alterations in the gut microbiota contribute to further mucosal damage and endotoxemia (*Figure 3*).^[36]

The HIV pandemic has altered the practice of surgery; 20% to 25% of all HIV+ patients will need some form of surgery during their lifetime.^[68] Earlier initiation of HAART and improved long term survival of HIV+ patients mean that surgeons may manage pathologies related to chronic HIV infection, complications of HAART, as well as surgical problems common to the general population (*Table 4*).^[30-34,68,69]

Table 4. Causes of abdominal pain in HIV+ patients^[30-34,68,69]

Surgical	Infections	Immunological	Drug induced
Appendicitis	Mycobacterium avium complex	Lymphoma	Pancreatitis
Peptic ulcer disease	Cytomegalovirus	Kaposi's sarcoma	Indinavir-induced renal calculi
Diverticulitis	Microsporidia	Malignant obstruction	Gastritis
Cholecystitis	Tuberculosis		
Hepatitis			
Mesenteric ischaemia			
Abdominal aortic aneurysm			

Abdominal pain is a common ailment; 10% to 15% of HIV+ patients will experience a severe episode at least once during the course of their illness. Establishing whether patients need conservative therapy coupled with further investigations versus urgent surgical intervention is often a challenge for the general surgeon in South Africa.^[70-75] The complexities lie primarily with the interpretation of conflicting findings and investigations, and a high incidence of opportunistic infections. Moreover, emergency surgery in the AIDS patient is associated with significant morbidity and mortality.^[3,4,6,16] The most common indications for surgery in the HIV+ patient are detailed in *Table 5*.^[72]

Table 5. Indications for abdominal surgery in HIV+ patients [72]

Indications for surgery	Aetiology
Acute appendicitis	Faecolith, Lymphoid hyperplasia, Kaposi's sarcoma, Cytomegalovirus, Tuberculosis
Bowel Perforation	Lymphoma, Disseminated Tuberculosis, Cytomegalovirus
GIT obstruction	Lymphoma, Disseminated Tuberculosis, Kaposi's sarcoma
Toxic megacolon	Cytomegalovirus, Clostridium difficile infection
Cholecystitis	Acute acalculous type, AIDS related
Splenomegaly	AIDS, Trauma, Abscess

The impact of the HIV pandemic on surgical outcomes remains controversial; there are no prospective trials in the current literature and most retrospective studies are small and yielded conflicting results. [9-12,16-18] Early reports showed high mortality rates of 55% to 70% in AIDS patients undergoing emergency surgery. Based on the data available then, surgeons tended to be more conservative with HIV+ patients and avoided major surgical interventions. [76,77] However, there is now emerging evidence to suggest that the post-operative morbidity and mortality in HIV+ patients compare favourably to HIV- patients, and that the standard surgical therapy should be equally afforded to both groups. [16-18,78]

The main limitation of the old studies was that most investigators failed to make a clear distinction between the surgical risk in HIV+ patients and AIDS patients. This argument has been well substantiated by Harris et al [76], who showed that when an AIDS-related condition is the primary indication for emergency surgery, the morbidity increases by four-fold and the mortality rises from 15% to 44%. However, more than two thirds of HIV+ patients who undergo abdominal surgery for an acute abdomen do not have any AIDS-related pathology. Therefore, the data cannot be used to guide the standard of surgical care for all HIV+ patients. [79,80]

Studies investigating the relationship between HIV status and GIT surgery outcomes have yielded contradictory data with regards to morbidity, mortality and hospital stay. [6-12] Intra-abdominal malignancy is associated with a high incidence of wound breakdown. [13] Anorectal procedures are also predisposed to poorer outcomes, and late mortality is related to the progression of HIV infection rather than the primary

surgical pathology. ^[81] Irrespective of aetiology, GIT bleeding is a poor prognosticator of both in-hospital and long-term mortality. ^[82,83]

Following major abdominal surgery, HIV+ patients should be considered for ICU care. In a South African study, Bhagwanjee et al ^[84] showed no increase in the ICU and total hospital stay, albeit the higher incidence of septic shock in HIV+ patients. Predictors of long-term survival after ICU admission include mechanical ventilation and albumin levels. ^[85]

Establishing whether CDC clinical stage or CD4⁺ count are prognosticators after abdominal surgery in the HIV+ has been a futile endeavour so far; the literature comprises mainly of retrospective series with conflicting results. ^[6,10,11,16,86] Some studies showed higher morbidity with advanced clinical stages of the disease ^[80,81], whilst others showed no difference. ^[87-89]

CD4⁺ count is still regarded by many as a valid predictor of outcome in HIV+ patients undergoing abdominal surgery. CD4⁺ helper T lymphocytes are important role players in the initial infection with the virus and play a vital role in wound healing. ^[28,29,38,39]

Many surgeons still advocate a CD4⁺ count >200 cells/ μ l before operating on an infected patient. ^[16] In a prospective cohort study, ČaČala et al ^[17] showed that HIV status did not influence the outcome of general surgical procedures, and CD4⁺ count was not a prognosticator of total hospital stay, hospital mortality and severity of post-operative sepsis. However, in a recent large retrospective study investigating the effects of HIV status on the outcomes of surgical sepsis, Green et al ^[6] determined that there was a significantly higher mortality of 60% in patients who had a CD4⁺ count <200 cells/ μ l versus 2% in the CD4⁺ count >200 cells/ μ l group. In emergency surgery patients, a lower CD4⁺ count is associated with increased post-operative septic complications and longer hospital stay ^[10]. Xia et al ^[11] have gone on to further suggest that a CD4/CD8 ratio \leq 0.15 is a useful predictor of post-operative sepsis in HIV+ patients undergoing major abdominal surgery.

Early immunological restoration with HAART will be therapeutic strategy chosen by clinicians in the future. ^[34] HAART controls the disease progression by suppressing the viral load ^[30-33]. This would theoretically lead to better operative outcomes in those undergoing abdominal surgery. ^[16]

1.6 Appendicitis in the Human Immune Deficiency Virus-infected patient

Appendicitis is a global disease. [55] Baker et al [90] described the first case of appendicitis in a HIV+ patient in 1986. The early medical literature is limited to case reports describing HIV-related opportunistic infections such as TB, KS and Cytomegalovirus as aetiological agents of appendicitis. [91-94] A rising incidence of appendicitis in the developing world has been partly attributed to the HIV/AIDS crisis. [55,95] HIV+ patients are more susceptible to developing appendicitis; the incidence of appendicitis is three to four-fold higher than in the general population. [73,95] There are a number of postulates for this observation. The high incidence of associated opportunistic infections seen with HIV and the fragile appendiceal vasculature have certainly impacted upon the aetiology and epidemiology of appendicitis. [3,6,73,95,96] Aldeen et al [71] hypothesised that acute appendicitis could be a manifestation of the Immune Reconstitution Inflammatory Syndrome (IRIS) after the initiation of HAART. The restoration of lymphatic tissue architecture through hyperplasia and B-cell stimulation within the appendix account for the pathophysiology of appendicitis in these cases. HAART agents such as Indinavir may also be responsible for the formation of appendiceal abscesses. [71,73] The last theory pertains to the massive T-cell depletion that occurs early in the GIT despite HAART. It is associated with dysbiosis of microbiota, increased gut permeability and bacterial translocation. [36-40,97]

Appendicitis is a common surgical emergency in the HIV+ patient. [3,70-74,78,98-102] In a large cohort of patients at a South African hospital, Green et al [6] showed that appendicitis was the cause of surgical sepsis in 26% of HIV+ patients. The diagnosis of appendicitis in the HIV+ patient remains challenging. Opportunistic infections like TB and AIDS-related malignancies such as KS and lymphoma will frequently mimic the clinical presentation of appendicitis. Whilst an appendectomy will assist the surgeon in confirming the diagnoses and direct further therapy, the associated post-operative morbidity and mortality have raised concerns. [3,6-13,98,101,102]

The effect of HIV infection on appendicitis and the surgical outcomes thereof have not been studied enough; there are only six published reports in the current literature. [3,78,98,100-102] Paradoxically, only two of these reports are from Sub-Saharan Africa where HIV is highly prevalent. [3,101] The studies addressing surgical outcomes of appendicitis in HIV+ and HIV- patients are summarised in *Table 6*.

Table 6: Studies addressing surgical outcomes of appendicitis in HIV+ and HIV- patients

Study	Year	Country	Period (years)	Number of patients	Significant Study findings
Bova et al ^[100]	1998	Australia	10	HIV- (60) HIV+ (26)	Significant delay in presentation to hospital in the HIV+ group Higher post-operative morbidity rate in HIV+ group
Giiti et al ^[101]	2010	Tanzania	1	HIV- (173) HIV+ (26)	HIV+ patients older and have less leukocytosis Peritonitis more common in HIV+ group with increased rates of Surgical Site Infection and lengthier hospital stay
Masoomi et al ^[102]	2015	US	3	HIV- (572444) HIV+ (800)	Patients with AIDS had lengthier hospital stay, higher post-operative complication and mortality rates Laparoscopic appendectomy in AIDS patients has lower morbidity, mortality and shorter hospital stay compared to open appendectomy
Kitaoka et al ^[98]	2015	Japan	6	HIV- (212) HIV+ (6)	CD4 ⁺ count lower in HIV+ patients with complicated appendicitis
Gigabhoy et al ^[3]	2016	South Africa	1	HIV- (36) HIV+ (14)	Higher laparotomy rate in HIV+ patients
Smith et al ^[78]	2016	US	8	HIV- (337514) HIV+ (794)	Longer and more expensive hospital stay in AIDS patients Higher risk of post-operative infections in AIDS patients

The prevalence of HIV in patients undergoing appendectomy in Sub-Saharan Africa is not negligible. Gigabhoy et al ^[3] recently showed that the HIV prevalence in patients undergoing appendectomy at King Edward VIII Hospital in Durban is 28%. In a Tanzanian study conducted at a major referral centre, the prevalence was found to be 13.1%. ^[101] These findings support the theory suggesting that HIV status may be a risk factor for appendicitis. ^[3,6,71,73,95,96] HIV+ patients presenting with appendicitis are also older than their seronegative counterparts. A large study that interrogated the Nationwide Inpatient Sample (NIS) in the US showed that AIDS patients undergoing appendectomy were significantly older than the control group. ^[78] These findings are echoed in both papers emanating from Africa. ^[3,101]

Failure to mount an immune response can manifest clinically by the absence of pyrexia and abdominal signs in early appendicitis. Two studies have convincingly shown that pre-operative leukocytosis is seen less frequently in HIV+ patients. ^[100,101] Localised right iliac fossa tenderness is not common in those infected with the virus, and 57% of these patients have peritonitis on presentation. ^[3] The absence of these clinical signs explains the significant delay to hospital presentation, and the subsequent high post-operative morbidity and mortality that ensue. A higher laparotomy rate in these patients is also ascribed to the high perforation rates and peritonitis that occur secondary to delays in presentation. ^[3,78,100,101] Most studies show that there is a higher incidence of post-operative complications and a lengthier hospital stay in the HIV+ group. ^[78,98,100-102] The morbidity relates predominantly to Surgical Site Infections, and is less commonly seen when a laparoscopic approach is used. ^[102]

It is still not clear whether CD4⁺ count, Viral Load (VL) and clinical stage influence the surgical outcomes of appendectomy in HIV+ patients. The CD4⁺ count is low in patients with appendiceal perforation and those undergoing laparotomy ^[3,6] Although a decreased viral load is associated with a decreased occurrence of appendicitis ^[95], there is currently no evidence to show that it can be used as a reliable post-operative prognosticator. The interrogation of large databases to elucidate whether HIV status influences surgical outcomes of appendectomy is only helpful to a certain extent. This is because data is extracted via the International Statistical Classification of Diseases and Related Health Problems (ICD) system. Individual patient characteristics such as CD4⁺ count, CD4/CD8 ratio, VL and the presence of opportunistic infections are not easily gathered and therefore cannot be analysed. ^[78,102]

The current data does provide some direction regarding the issue, but there is a need for a large multi-centre prospective study in Sub-Saharan Africa to investigate the effect of HIV status on the surgical outcomes of appendicitis.

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CHAPTER TWO:
PUBLICATION-READY MANUSCRIPT

A STUDY COMPARING OUTCOMES OF APPENDECTOMY BETWEEN HIV-
INFECTED AND HIV-NEGATIVE PATIENTS

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ABSTRACT

Background: The high prevalence of Human Immunodeficiency Virus (HIV) has added a new dimension to the management and outcomes of many general surgical conditions in South Africa. However, there is a paucity of data describing the impact of HIV status on surgical outcomes in our setting. Appendicitis is the most common gastrointestinal emergency, and its surgical outcomes in areas of high HIV prevalence are poorly described in the literature. Thus, the aim of this study is to describe and compare the outcomes of appendectomy between HIV-infected (HIV+) and HIV-negative (HIV-) patients.

Methods: This is a retrospective cohort study of patients undergoing appendectomy at a large regional hospital over a 12-month period. Demographic data, duration of pre-hospital symptoms, HIV status, surgical approach, operative findings, histopathology reports, hospital stay and complications were recorded. Data for the HIV+ and HIV- patient cohorts were then described, analysed and compared.

Results: The study group comprised 134 patients; 18 (13.4 %) tested positive for HIV. HIV+ patients were significantly older (mean age of 29.3 vs. 20.3 years, $P= 0.002$) and had longer duration of pre-hospital symptoms (mean of 3.94 vs. 2.57 days, $P= 0.03$). Postoperative complications (44.4 % vs. 17.2 %, $P= 0.03$) and lengthier hospital stays (7.28 days vs. 5.95 days, $P= 0.004$) were also more frequently seen in the HIV+ patients. There were no differences in appendiceal rupture rates, operative approaches, histopathological findings and mortality.

Conclusion: HIV infection is common in patients admitted with clinical features of acute appendicitis in South Africa. Presentation in HIV+ patients was delayed, and surgery was associated with significant postoperative morbidity and longer hospital stay.

Introduction

The Human Immune Deficiency Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS) pandemic has added a new dimension to the epidemiology, clinical presentation and outcomes of a wide array of surgical conditions in South Africa. ^[1-7] Thirty-seven million people are infected with HIV worldwide, the majority of whom (25.8 million) live in Sub-Saharan Africa. South Africa has the highest number of people living with HIV globally; the national prevalence is 12% and 6.4 million people live with the disease. Residents of rural informal areas are at higher risk of getting infected, with KwaZulu-Natal being the top high prevalence province in South Africa at 16.9%. Our study was conducted in the Northern Cape province, where the HIV prevalence is 7.4%. ^[8]

South Africa currently boasts the largest Highly Active Antiretroviral Therapy (HAART) program in the world. Three million patients are on treatment and the annual intake includes a further 600 000. Improved life expectancy with HAART and the increasing HIV prevalence in South Africa over the past decade are both significant contributors to an epidemiological transition witnessed by surgeons. ^[8-14] The latter now frequently manage the longterm sequelae of HIV infection such as Gastrointestinal (GIT) lymphoma, abdominal Tuberculosis (TB), Kaposi's Sarcoma (KS) and HIV vasculopathy, as well as the complications of HAART-induced pancreatitis and lipodystrophy. ^[15-19] This epidemiological transition has also translated in medical and surgical cohorts across the country. HIV is the second most common chronic disease in South Africa after hypertension (Table 1). ^[20-24] In the large multi-centre prospective South African Surgical Outcomes Study, Biccard et al showed that HIV/AIDS was present in 13.2% of patients undergoing surgery in South Africa (Table 2). ^[25]

Abdominal pain is a common complaint; 10% to 15% of HIV-infected (HIV+) patients will experience a severe episode at least once during the course of their illness. Establishing whether patients need conservative therapy coupled with further investigations versus urgent surgical intervention is often a challenge for the general surgeon in South Africa. ^[26] The complexities lie primarily with the interpretation of conflicting findings and investigations, and a high incidence of opportunistic infections. Moreover, emergency surgery in the AIDS patient is associated with significant morbidity and mortality. ^[27-30]

Appendicitis is a global disease. ^[34] Baker et al ^[35] described the first case of appendicitis in a HIV+ patient in 1986. The early medical literature is limited to case reports describing HIV-related opportunistic infections such as TB, KS and Cytomegalovirus as aetiological agents of appendicitis. ^[36-39] A rising incidence of appendicitis in the developing world has been partly attributed to the HIV/AIDS crisis. ^[40] HIV+ patients are more susceptible to developing appendicitis; the incidence of appendicitis is three to four-fold higher than in the general population. ^[26] There are a number of postulates for this observation. The high incidence of associated opportunistic infections seen with HIV and the fragile appendiceal vasculature have certainly impacted on the aetiology and epidemiology of appendicitis. ^[40] Aldeen et al ^[41] hypothesised that acute appendicitis could be a manifestation of the Immune Reconstitution Inflammatory Syndrome (IRIS) after the initiation of HAART. The restoration of lymphatic tissue architecture through hyperplasia and B-cell stimulation within the appendix account for the pathophysiology of appendicitis in these cases. HAART agents such as Indinavir may also be responsible for the formation of appendiceal abscesses. ^[40] The last theory pertains to the massive T-cell depletion that occurs early in the GIT despite HAART. It is associated with dysbiosis of microbiota, increased gut permeability and bacterial translocation. ^[42]

Appendicitis is a common surgical emergency in the HIV+ patient. ^[3,31,43-47]

In a large cohort of patients at a South African hospital, Green et al ^[6] showed that appendicitis was the cause of surgical sepsis in 26% of HIV+ patients. The diagnosis of appendicitis in the HIV+ patient remains challenging. Opportunistic infections like TB and AIDS-related malignancies such as KS and lymphoma will frequently mimic the clinical presentation of appendicitis. Whilst an appendectomy will assist the surgeon in confirming the diagnoses and direct further therapy, the associated post-operative morbidity and mortality have raised concerns. ^[43-47]

The effect of HIV infection on appendicitis and the surgical outcomes thereof have not been studied enough; there are only six published reports in the current literature. ^[3,31,43,45-47] Paradoxically, only two of these publications are from Sub-Saharan Africa where HIV is highly prevalent. ^[3,46] The studies addressing surgical outcomes of appendicitis in HIV+ and HIV- patients are summarised in Table 3. The aim of this study is to describe and compare the outcomes of appendectomy between HIV-

infected (HIV+) and HIV-negative (HIV-) patients in a setting where HIV is significantly prevalent.

Patients and Methods

The Human Research Ethics Committee of the Faculty of Health Sciences at the University of Cape Town granted ethical approval for this study (HREC REF: 341/2015). Patients subjected to appendectomy following a clinical diagnosis of acute appendicitis from March 2010 to March 2011 at Kimberley Provincial Hospital were included in this retrospective study. Standard demographic information, time from onset of symptoms to hospital admission, HIV status, medical comorbidities, details of surgical approach, operative findings, histopathology reports, duration of Intensive Care Unit (ICU) admission, total hospital stay and post operative complications were documented. When a patient was known to be HIV-infected, the CD4⁺ count and the HAART regimen were recorded.

Surgical approach

Following initial assessment, a clinical diagnosis of acute appendicitis and informed consent, patients were taken for surgery. Prophylactic antibiotics were administered in all cases. Patients with localised right iliac fossa tenderness were approached through a McBurney or Lanz incision. An exploratory midline laparotomy was performed for generalized peritonitis. At the time of this study, laparoscopy had been newly introduced at Kimberley Provincial Hospital; laparoscopic appendectomy was thus attempted only in a limited number of cases. Conversion from a McBurney incision, Lanz incision or a laparoscopic approach to a laparotomy was necessary when diffuse peritonitis was noted intraoperatively or when the appendectomy could not be completed safely through the initial surgical approach. All resected appendices were sent for histopathological assessment.

Post operative care and follow up

Antibiotics were stopped within 48 hours of appendectomy for uncomplicated appendicitis and continued for five days in cases of rupture or diffuse peritonitis. HIV testing was offered to all patients; pre-test and post-test counseling were conducted irrespective of the test result. In the event of a positive result, the patient was immediately referred to the Infectious Diseases Clinic. On discharge from hospital, all patients were entered into a four-week follow-up program, and issued with a summary note detailing medical problems, treatment administered and a list of instructions to be followed. In particular, patients were advised to return to the unit

immediately in the event of persistent abdominal pain, pyrexia and wound sepsis. Readmitted patients underwent complete clinical, biochemical and radiological evaluation as necessary.

Statistical analysis was performed using the Chi-Squared or Fisher's exact test for non-continuous variables, and non-parametric ANOVA and Wilcoxon ranked sum test for continuous variables. A P value less than 0.05 was considered statistically significant.

Results

One hundred and thirty-nine patients were subjected to appendectomy from March 2010 to March 2011. Five patients were excluded from the study; three did not consent to HIV testing and two had incomplete medical records.

The study sample thus comprised 134 patients. There were 86 males (64.2 %) and 48 females with a mean age of 21.5 years (range: 4 – 64). Eighteen patients were HIV+; 16 were diagnosed during the present hospital admission and two patients were known to be HIV+ on HAART. A CD4⁺ count was available in 13 of these 16 patients; the mean count was 260 cells/ μ L (range: 12 – 1129). HIV+ patients were older (mean age of 29.3 years vs. 20.3 years, $P = 0.002$) and experienced symptoms for longer (mean of 3.94 days vs. 2.57 days, $P = 0.03$) before presenting to hospital (Table 4). There was no difference in the signs and symptoms experienced by both patient groups (Table 5).

A laparotomy was more frequently performed in the HIV+ patient (72.2% vs. 41.3%, $P = 0.03$) (Table 6). The postoperative complication rate was higher in HIV+ patients (44.4% vs. 17.2 %, $P = 0.03$); the predominant complication was Surgical Site Infection (SSI) (Table 7). There was no difference in the mortality. Although the total hospital stay was longer for HIV+ patients (7.28 days vs. 5.95 days, $P = 0.004$), ICU stay was similar in both patient groups.

The appendiceal perforation rates and negative appendectomy rates were similar in the HIV+ and HIV- groups, 38.9% vs. 31.0% ($P = 0.69$) and 27.8% vs. 12.9% ($P = 0.20$) respectively.

Discussion

The HIV/AIDS pandemic has significantly impacted upon the South African surgical landscape. Atypical presentations and outcomes associated with increased morbidity and mortality are now well recognized amongst many general surgical conditions.^[1-7] This study was conducted in the Northern Cape province of South Africa, where the HIV prevalence is 7.4%. An HIV seroprevalence of 13.4% in this cohort of patients is not negligible and is comparable to data from other Sub-Saharan centres. Gigabhoy et al^[3] recently showed that the HIV prevalence in patients undergoing appendectomy at a large tertiary urban hospital is 28%. In a Tanzanian study conducted at a major referral centre, the prevalence was found to be 13.1%.^[46] These results support the theory that HIV status may be a risk factor for appendicitis.^[26,40,41]

The mean age was significantly higher in the HIV+ group than in the seronegative patients (29.3 vs. 20.3 years). This finding is echoed in both papers emanating from Africa,^[3,46] which suggest that the HIV+ patient develops appendicitis at a more advanced age. A large study that interrogated the Nationwide Inpatient Sample (NIS) in the US also showed that AIDS patients undergoing appendectomy were significantly older than the control group.^[31] Crum-Cianflone and colleagues^[40] propose that biological and epidemiological factors account for this observation. HIV seropositivity imparts an increased risk of developing appendicitis because the fragile vasculature of the appendix is more predisposed to disease. Furthermore, opportunistic infections and IRIS secondary to HAART render HIV+ patients more prone to developing appendicitis. Most importantly in South Africa, HIV seroconversion tends to occur in early adulthood and predominantly affects the young. The South African National HIV prevalence, Incidence and Behaviour Survey in 2012 showed that 25.2% adults belonging to the 25 to 49-year age group were HIV+; these data mirror the prevalence of HIV seen in patients with appendicitis.^[3]

In this study, the mean CD4⁺ count was 260 cells/ μ L and was recorded in 81% (13 patients) of the HIV+ cohort. Because of the small subgroup numbers, it was not statistically feasible to correlate the CD4⁺ count with appendiceal perforation or post-operative morbidity and mortality. A Viral Load (VL) was not routinely performed for budgetary reasons. In our setting, the VL is used to gauge therapeutic response to HAART and determine the presence of viral resistance. Establishing whether CD4⁺ count or VL should be routinely done in the HIV+ undergoing abdominal surgery has been a futile endeavour so far. We remain unconvinced of their use as surgical prognosticators since the literature comprises mainly of retrospective series with

conflicting results. ^[48-51] Some studies show higher morbidity with advanced clinical stages of the disease ^[52,53], whilst others conclude there is no difference. ^[50] It is well established that CD4⁺ helper T lymphocytes are important role players in the initial infection with the virus and play a vital role in wound healing. ^[54-56] This is why the CD4⁺ count is regarded by many as a predictor of outcome in HIV⁺ patients undergoing abdominal surgery.

Some surgeons will still advocate for a CD4⁺ count >200 cells/ μ l before operating on an infected patient. ^[48-50] In a prospective cohort study, ČaČala et al ^[51] showed that HIV status did not influence the outcome of general surgical procedures, and CD4⁺ count was not a prognosticator of total hospital stay, hospital mortality and severity of post-operative sepsis. However, in a recent large retrospective study investigating the effects of HIV status on the outcomes of surgical sepsis, Green et al ^[6] determined that there was a significantly higher mortality of 60% in patients who had a CD4⁺ count <200 cells/ μ l versus 2% in the CD4⁺ count >200 cells/ μ l group. In emergency surgery patients, a lower CD4⁺ count is associated with increased post-operative septic complications and longer hospital stay ^[43,48,49]. Xia et al ^[49] have gone on to further suggest that a CD4/CD8 ratio \leq 0.15 is a useful predictor of post-operative sepsis in HIV⁺ patients undergoing major abdominal surgery.

Delayed presentation to hospital occurred more frequently in the HIV⁺ patient cohort (3.94 vs. 2.57 days, P = 0.03). Failure to mount an immune response can manifest clinically by the absence of pyrexia and abdominal signs in early appendicitis.

Localised right iliac fossa tenderness is not common in those infected with the virus ^[3] and pre-operative leukocytosis is also less frequently observed. ^[46]

Many have suggested that the absence of these clinical signs, symptoms and laboratory findings contribute to the delay in hospital presentation, and the subsequent higher morbidity seen in HIV⁺ patients. Although the delay in presentation is well documented in this study, there were no difference in the clinical signs and symptoms exhibited by both patient groups.

A recent systematic review conducted by Yang et al confirmed that appendicitis trends in South Africa are consistent with those seen in other newly industrialised countries. ^[57] However, appendicitis in South Africa has a far more serious clinical course when compared to developed countries, mainly because of longer delays in getting definitive surgical care. A high perforation rate of 36% and the need for

laparotomy in 18% to 60% of patients drive the high post-operative morbidity seen in these patients. ^[58] Up to 30% of patients will require Temporary Abdominal Closure (TAC) at their initial surgery because of four quadrant peritonitis, diffuse soiling of the abdomen and the need for relook laparotomies. Furthermore, 11% of patients will require admission to the Intensive Care Unit and 29% will require a second surgical intervention. ^[58] The laparotomy rate was higher in HIV+ patients (72.2% vs. 41.3%, P=0.03). Previous authors have ascribed this operative approach to the high rate of perforation and peritonitis, that occur due to the delay in presentation of these patients. ^[3,46] Most studies show that there is a higher incidence of post-operative complications and a lengthier hospital stay in the HIV+ group. ^[3,31,46] The morbidity relates predominantly to Surgical Site Infections, and is reduced with a laparoscopic approach. ^[31,47] The post-operative morbidity was higher in those infected with the virus (38.9% vs. 14.7%, P=0.03) in this study. SSI was the most common complication and septic shock was documented in a single patient. These findings are in keeping with previous studies that have investigated the effect of HIV on appendicitis. ^[3,46,31,47] In spite of these correlations, the impact of the HIV pandemic on surgical outcomes remains controversial; there are no prospective trials in the current literature and most retrospective studies are small and yielded conflicting results. ^[59-61] Early reports showed high mortality rates of 55% to 70% in AIDS patients undergoing emergency surgery. Based on the data available then, surgeons tended to be more conservative with HIV+ patients and avoided major surgical interventions. ^[50] However, there is now emerging evidence to suggest that the post-operative morbidity and mortality in HIV+ patients compare favourably to HIV- patients, and that the standard surgical therapy should be equally afforded to both groups. ^[62,63]

The principal flaw in the old studies was that most investigators failed to make a clear distinction between the surgical risk in HIV+ patients and AIDS patients. This argument has been well substantiated by Harris et al ^[29], who showed that when an AIDS-related condition is the primary indication for emergency surgery, the morbidity increases by four-fold and the mortality rises from 15% to 44%. However, more than two thirds of HIV+ patients who undergo abdominal surgery for an acute abdomen do not have any AIDS-related pathology. Therefore, the data cannot be applied to all HIV+ patients.

There was a single mortality in the HIV+ group. This was a 26-year-old pregnant woman who had a laparotomy for perforated appendicitis in the presence of abdominal TB. She was ventilated for one day in the ICU and demised of septic shock. The two deaths in the HIV- were also attributed to septic shock secondary to diffuse peritonitis. The mortality was similar in both patient cohorts. Whether HIV+ patients undergoing emergency abdominal surgery are at risk for increased mortality is still highly debatable. A careful literature search yielded contradictory data with regards to mortality. [64-71] There is some data to suggest that anorectal procedures are predisposed to poorer outcomes, and late mortality is related to the progression of HIV infection rather than the primary surgical pathology. [64,70,71] Irrespective of aetiology, GIT bleeding is another poor prognosticator of both in-hospital and long-term mortality. [65,66]

Following major abdominal surgery, HIV+ patients should be considered for ICU care. In a South African study, Bhagwanjee et al [62] showed no increase in the ICU and total hospital stay, albeit the higher incidence of septic shock in HIV+ patients. Predictors of long-term survival after ICU admission include mechanical ventilation and albumin levels. [63]

Post appendectomy, the HIV+ patients stayed longer in hospital (7.28 vs. 5.95 days, $P=0.004$); an observation made by two large national database studies previously. [31,47] The length of hospital stay in this study relates mainly to the post-operative complications of SSIs and persistent pyrexia. Cases of SSIs were managed in hospital until all wounds were fully consolidated. This is mainly because of the geography of the Northern Cape province; a large number of our patients come from rural areas and access to healthcare facilities can be difficult.

A prolonged post-operative pyrexia was noted in two HIV+ patients; the septic work-up was negative in both. It is interesting to note that previous authors have made similar observations but could not assign a specific aetiology to them. [40,46]

Conclusion

This retrospective study investigated the effect of HIV status on the surgical outcomes of appendectomy in the Northern Cape Province of South Africa. The HIV prevalence in those undergoing appendectomy in South Africa is not negligible. Furthermore, these patients present in a delayed fashion to hospital and require more extensive surgery than their seronegative counterparts. Findings of higher post-operative complication rates in those infected in the virus are in keeping with previous reports.

The effect of CD4+ count, VL and Clinical Stage on surgical outcome is still controversial. It is vital to understand that this study was conducted in a single province of South Africa where the HIV prevalence is 7.4%, and only provides a snapshot of the effect of HIV on a common GIT surgical emergency. The HIV infection rate in appendicitis patients was nearly double the population rate at 13.4%, suggesting that HIV infection might be a risk for developing acute appendicitis. Although the current data does provide some direction regarding the issue, there is need for a large multi-centre prospective study in Sub-Saharan Africa to investigate the effect of HIV status on the surgical outcomes of appendicitis.

Table 1: Prevalence of chronic medical conditions in South Africa ^[20-24]

Chronic Medical Condition	Prevalence in South Africa (%)
Hypertension	30.4
HIV	12.2
Asthma	8.1
Diabetes	7.0

Table 2: Comorbid conditions in patients recruited for South African Surgical Outcomes Study ^[25]

Comorbid disease	N (%)
HIV/AIDS	509 (13.2)
Chronic Obstructive Pulmonary Disease/Asthma	240 (6.2)
Diabetes	225 (5.8)
Coronary Artery Disease	160 (4.1)
Congestive Cardiac Failure	55 (1.4)

Table 3: Studies addressing surgical outcomes of appendicitis in HIV+ and HIV- patients

Study	Year	Country	Period (years)	Number of patients	Significant Study findings
Bova et al ^[45]	1998	Australia	10	HIV- (60) HIV+ (26)	Significant delay in presentation to hospital in the HIV+ group Higher post-operative morbidity rate in HIV+ group
Giiti et al ^[46]	2010	Tanzania	1	HIV- (173) HIV+ (26)	HIV+ patients older and have less leukocytosis Peritonitis more common in HIV+ group with increased rates of Surgical Site Infection and lengthier hospital stay
Masoomi et al ^[47]	2015	US	3	HIV- (572444) HIV+ (800)	Patients with AIDS had lengthier hospital stay, higher post-operative complication and mortality rates Laparoscopic appendectomy in AIDS patients has lower morbidity, mortality and shorter hospital stay compared to open appendectomy
Kitaoka et al ^[43]	2015	Japan	6	HIV- (212) HIV+ (6)	CD4 ⁺ count lower in HIV+ patients with complicated appendicitis
Gigabhoy et al ^[3]	2016	South Africa	1	HIV- (36) HIV+ (14)	Higher laparotomy rate in HIV+ patients
Smith et al ^[31]	2016	US	8	HIV- (337514) HIV+ (794)	Longer and more expensive hospital stay in AIDS patients Higher risk of post-operative infections in AIDS patients

Table 4. Demographic and Clinical Characteristics of patients undergoing appendectomy during study

Demographic / Clinical Characteristics	HIV+ (n=18)	HIV- (n=116)	P Value
Gender (number)			
Male	11	75	-
Female	7	41	
Age (years)			
Mean	29.3	20.3	0.002
Range	13-30	4-64	
Delay (days)			
Mean	3.94	2.57	0.003
Range	0-14	0-15	
ICU Stay (days)			
Mean	1	3	0.71
Range	1-1	3-6	
Total Hospital Stay (days)			
Mean	7.28	5.95	0.004
Range	3-19	1-53	
Mortality			
Number	1	2	> 0.05
Rate (%)	5.56	1.72	

Table 5. Individual clinical and haematological characteristics in HIV- and HIV+ patients

Clinical and Laboratory Parameters	HIV+ (n=18) N (%)	HIV- (n=116) N (%)	P Value
Symptoms			
Migratory Right Iliac Fossa Pain	67 (58)	13 (72)	
Nausea / Vomiting	95 (83)	16 (89)	
Anorexia	96 (83)	15 (83)	
Signs			
Right lower quadrant pain	108 (94)	17 (94)	> 0.05
Rebound tenderness	86 (75)	16 (89)	
Elevated temperature	64 (56)	11 (61)	
Laboratory Findings			
Leucocytosis	93 (81)	11 (61)	

Table 6. Surgical approaches in HIV+ and HIV- patient cohorts

Surgical Approach	HIV+ (n = 18) Number (%)	HIV- (n = 116) Number (%)
Minor		
McBurney Incision	4 (22.2)	44 (37.9)
Lanz Incision	0	17 (14.7)
Laparoscopic	1 (5.56)	6 (5.17)
Laparoscopic converted to McBurney Incision	0	1(0.862)
Total	5 (27.8)	68 (58.7)
Major		
Laparotomy	11 (61.1)	41 (35.3)
McBurney Incision converted to laparotomy	0	5 (4.31)
Lanz Incision converted to laparotomy	0	2 (1.72)
Laparoscopic converted to laparotomy	2 (11.1)	0
Total	13 (72.2)	48 (41.3)
P Value	0.03	

Table 7. Complications documented in HIV- and HIV+ patient cohorts

HIV Status	Post-operative Complications	Number of Complications (%)
HIV+ (n=18)	Surgical Site Infection	3
	Persistent Post-operative Pyrexia	2
	Intraabdominal Abscess	1
	Septic Shock	1
	Morbidity Rate	7/18 (38.9 %)
HIV- (n=116)	Surgical Site Infection	9
	Intraabdominal Abscess	3
	Ileus	2
	Septic Shock	2
	Nosocomial Pneumonia	1
	Morbidity Rate	17/116 (14.7 %)
	P Value	0.03

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PROTOCOL AND ETHICS APPROVAL:

A STUDY COMPARING OUTCOMES OF APPENDECTOMY BETWEEN HIV-INFECTED AND HIV-NEGATIVE PATIENTS

SYNOPSIS

Kimberley Hospital is a large regional facility, providing surgical services to the entirety of the Northern Cape. Appendicitis remains the most common surgical pathology encountered by surgical centres worldwide. In South Africa, the presentation and the outcome of this disease has been influenced by delayed presentation and comorbidities. Fatalities are not infrequent, and comorbidities are often the culprit factors. The effect of HIV/AIDS on the surgical management of appendicitis has not been described before.

Research setting:

This chart review will be conducted in the Surgical Unit at Kimberley Hospital. Folders of patients who have undergone surgery for appendicitis will be drawn from the department surgical log for the period February 2010 to February 2011.

Study Aim:

The aim of this retrospective study is to describe and compare the outcomes of appendectomy between HIV-infected and HIV-negative patients from a one a large regional surgical unit.

Study Objectives:

1. To describe the demographics of patients presenting to a large regional surgical unit with clinical features of appendicitis
2. To describe the history and presentation of such patients on arrival to hospital
3. To detail the associated comorbidities in these patients
4. To evaluate the short and long-term morbidity of admitted patients
5. To compare the outcomes in HIV-infected and HIV-negative patients

Study Design:

This will be a review of all patients who have undergone surgery for appendicitis at Kimberley Hospital for the period February 2010 to February 2011. Since this is a chart review, only patients who have been tested for HIV at some point will be included. Test results will be drawn from the patient files.

Inclusion / Exclusion Criteria:

All patients who underwent surgery for a clinical diagnosis of appendicitis at Kimberley Hospital and who were tested for HIV.

Study Participants:

Study participants will be identified from the surgical log at the Department of General Surgery at Kimberley Hospital.

Protection of Study Participants:

Study parameters will be drawn from retrieved patient files and entered into data collection sheets, which will be kept with the lead investigator. At no point will photos of patients be included in this study. All data collection sheets will be destroyed at the end of the study.

Expected Benefits:

It is expected that at the end of the study, we will be able to describe the full range of presentations for patients with appendicitis in the Northern Cape. This should allow us to establish whether HIV status affects the outcomes of appendectomy.

RESEARCH PROTOCOL

Purpose of study:

The purpose of this study is to describe our experience with the management of patients with appendicitis at Kimberley Hospital. Our objectives will be to:

1. To evaluate the presentation of appendicitis at Kimberley Regional Hospital
2. To describe the demographics of these patients
3. To describe the presentation of such patients on arrival to hospital
4. To detail the associated comorbidities in these patients
5. To evaluate the short and long-term morbidity of admitted patients
6. To compare outcomes in HIV-infected and HIV-negative patients

Background:

The Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS) pandemic has added a new dimension to the management and surgical outcomes of acute appendicitis.¹⁻⁷ A rising incidence of this common gastrointestinal surgical emergency in the developing world has been attributed to the HIV/AIDS crisis in Sub-Saharan Africa.² HIV-infected (HIV⁺) patients are more susceptible to developing appendicitis than the general population. Postulates for this include a high incidence of opportunistic infections, a dampened immune response and the emergence of appendicitis as a manifestation of the Immune Reconstitution Inflammatory Response (IRIS), with the advent of Highly Active Antiretroviral Therapy (HAART).^{2,8-9}

An estimated 10 to 15 % of HIV⁺ patients will experience severe abdominal pain during their illness. The diagnosis of appendicitis in these patients is challenging.

Opportunistic infections including Cytomegalovirus and Tuberculosis, and AIDS-related malignancies such as Kaposi's Sarcoma and lymphoma will frequently mimic the clinical presentation of acute appendicitis. Whilst an appendicectomy will confirm the diagnoses of these related infections and malignancies, surgical outcomes of appendicectomy in HIV⁺ patients have been associated with high rates of morbidity and mortality.^{1,2,4,8}

Despite an estimated national HIV prevalence of 12.2 %, there are no published reports describing the surgical outcomes of acute appendicitis in the HIV-infected population in South Africa.¹⁰ Studies comparing surgical outcomes in HIV-infected and HIV-positive patients are few and have emanated from Northern America and Europe.⁹ Thus, the aim of this study is to describe and compare the surgical outcomes of acute appendicitis in HIV⁺ and HIV-negative (HIV⁻) patients following appendectomy.

Methods:

This will be a review of all patients treated at Kimberley Hospital for appendicitis from February 2010 to February 2011. Study participants will be identified from the Department of Surgery's Surgical Log. Study parameters will be drawn from retrieved patient files and entered into data collection sheets, which will be kept with the lead investigator only at all times. At no point will photos of patients be included in this study. All data collection sheets will be destroyed at the end of the study. Data will be entered into Microsoft Excel and Descriptive Statistics used to compute the results.

Potential Benefits:

It is expected that at the end of the study, we will be able to describe the full range of presentations for patients with appendicitis in the Northern Cape. This should allow us to establish whether HIV has an effect on the surgical outcomes of appendicitis.

Informed Consent Process:

No additional consent will be required. All patients grant consent according to standard procedures at Kimberley Hospital.

Privacy and Confidentiality:

At no times will patient names be documented during the study; only file numbers will be used. At no point will photos of patients be included in this study. All data collection sheets will be destroyed at the end of the study.

References:

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Department of Surgery

Departmental Research Committee

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26th May 2015

Dr S Sobnach
Department of Surgery
Division of General Surgery
Groote Schuur Hospital
University of Cape Town

Dear Dr Sobnach,

RE: PROJECT 2015/034

PROJECT TITLE: A study comparing outcomes of appendectomy between HIV-infected and HIV-negative patients

The above proposal was reviewed by the Department of Surgery Research Committee and I am pleased to inform you that the committee approved the study.

Please use the above project number in all future correspondence.

Yours sincerely

signature removed

**DR T PENNEL
CHAIRMAN: RESEARCH COMMITTEE**



UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee



Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • Facsimile [021] 406 6411
Email: sumayah.eriefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

12 February 2016

HREC REF: 341/2015

Prof D Kahn
Department of Surgery
J45, OMB

Dear Prof Kahn

**PROJECT TITLE: A STUDY COMPARING OUTCOMES OF APPENDECTOMY BETWEEN HIV-
INFECTED AND HIV-NEGATIVE PATIENTS (MMed-candidate-Dr S Sobnach)**

Thank you for your response letter to the Faculty of Health Sciences Human Research Ethics Committee (HREC) dated 11 February 2016.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 28th February 2017.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

We acknowledge that the following student, Dr Sanju Sobnach will also be involved in this study.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

signature removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.

Institutional Review Board (IRB) number: IRB0001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH)

HREC 341/2015

From: **sanju sobnach** sanjusobnach@yahoo.com
Subject: Fwd: Sobnach: Confirmation of Approval of Study Proposal
Date: 24 June 2016 at 11:43 PM
To: sanju sobnach sanjusobnach@yahoo.com



Sent from my iPhone

Begin forwarded message:

From: Vuyi Mgoqi <vuyi.mgoqi@uct.ac.za>
Date: 21 June 2016 at 1:56:19 PM SAST
To: "sanjusobnach@yahoo.com" <sanjusobnach@yahoo.com>
Cc: Delawir Kahn <delawir.kahn@uct.ac.za>
Subject: Sobnach: Confirmation of Approval of Study Proposal

Dear Dr Sobnach

Candidature Approval (SBNSAN003)

Degree	MMed in Surgery
Title	A study comparing outcomes of appendectomy between HIV-infected and HIV-negative patients
Department	Surgery
Supervisor	Prof Delawir Kahn
Ethics Approval	341/2015

I am pleased to advise that the Chair of the Dissertations/Doctoral & Masters Committee has approved your candidature for the above degree on behalf of the Committee. Formal approval was obtained by publication in the Dean's Circular, PG-Med June 2016.

☐


Yours sincerely

☐

Vuyi Mgoqi

☐

☐

 **Vuyiseka Mgoqi** | Receptionist: PG Academic Administration | Faculty of Health Sciences | University of Cape Town | Room N2.19, Wernher & Beit North, Health Sciences Campus, Anzio Rd, Observatory, 7925 | ☎ +27 21 406 6751 | 📠 021 261 5584 | 🕒 Office Hours: 08h30 - 16h30 Unavailable Hours: 13h00 - 13h30

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DATA COLLECTION SHEET

DEMOGRAPHICS

Folder no:

Age:

Gender:

Date of onset of symptoms:

Date of admission:

Date of discharge:

ICU Stay:

Ward:

HIV Data

HIV Status:

CD4 count:

WHO Stage:

HAART: Yes/No

Bactrim prophylaxis: Yes/No

COMORBIDITIES

VITALS ON ADMISSION

BP: P: T:

INVESTIGATIONS

WCC:

AXR:

CXR:

U/S:

CT:

ESR:

CRP:

Urine Dipstix:

Sputum:

OPERATIVE APPROACH:

OPERATIVE FINDINGS:

HISTOLOGY CODE:

PUS SWAB:

OUTCOME (e.g. Uneventful, wound sepsis, death):

LONG TERM FOLLOW UP (e.g. Clinic Visit at 6 weeks):

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Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, and will delay publication.

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Named authors must consent to publication. Authorship should be based on substantial contribution to:

- (i) conception, design, analysis and interpretation of data;
- (ii) drafting or critical revision for important intellectual content; and
- (iii) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to www.icmje.org).

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Authors must declare all sources of support for the research and any association with a product or subject that may constitute conflict of interest.

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Qualification, affiliation and contact details of ALL authors must be provided in the manuscript and in the online submission process.

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Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dl). Litres is denoted with a lowercase 'l' e.g. 'ml' for millilitres). Units should be preceded by a space (except for %), e.g. '40 kg' and '20 cm' but '50%'. Greater/smaller than signs (> and 40 years of age'. The same applies to \pm and $^{\circ}$, i.e. '35 \pm 6' and '19 $^{\circ}$ C'.

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Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'. Figure legends: Fig. 1. 'Title...' All illustrations/figures/graphs must be of **high resolution/quality**: 300 dpi or more is preferable but images must not be resized to increase resolution. Unformatted and uncompressed images must be attached as

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Journal references: Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. *Stat Med* 1998;289(1):350-355. [<http://dx.doi.org/10.1000/hgjr.182>] [PMID: 2764753]

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9. The research was approved by a Research Ethics Committee (if applicable)
10. Any conflict of interest (or competing interests) is indicated by the author(s).

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