

## A Study Comparing Outcomes of Appendectomy between HIV-Infected and HIV-Negative Patients

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### Abbreviations:

HIV - Human Immune Deficiency Virus  
AIDS - Acquired Immune Deficiency Syndrome  
GIT - Gastrointestinal  
KS - Kaposi's Sarcoma

### Rezumat

#### *Studiu privind compararea rezultatelor apendicectomiei la pacienții infectați cu HIV versus pacienții neinfecțați*

**Context:** Prevalența crescută a virusului imunodeficienței umane (HIV) a dobândit o dimensiune nouă în managementul și rezultatul intervențiilor chirurgicale în Africa de Sud. Cu toate acestea, în cadrul instituției noastre există puține informații care să descrie impactul infecției cu HIV asupra rezultatelor intervențiilor chirurgicale. Apendicita este cea mai frecventă urgență gastrointestinală, iar rezultatele chirurgicale ale acesteia în zonele cu prevalență mare a virusului HIV sunt descrise insuficient în literatura de specialitate. Așadar, scopul acestui studiu este de a descrie și a compara rezultatele apendicectomiei la pacienții infectați cu virusul HIV (HIV+) și la cei neinfecțați cu acest virus (HIV-).

**Metode:** Acesta este un studiu de cohortă de tip retrospectiv, pe o perioadă de 12 luni, cu pacienți care au fost supuși apendicectomiei în cadrul unui spital regional. Au fost înregistrate date demografice, durata simptomelor înainte de internare, statutul HIV, abordarea chirurgicală, concluziile intervenției, rapoartele histopatologice, informații privitoare la șederea în spital și complicațiile. Au fost descrise, analizate și comparate datele referitoare la cohortele de pacienți HIV+ și HIV-.

**Rezultate:** Grupul de studiu cuprinde 134 de pacienți; 18 (13,4%) fiind infectați cu virusul HIV. Pacienții cu HIV+ sunt semnificativ mai în vârstă (vârsta medie de 29,3 față de 20,3 ani,  $P = 0,002$ ) și au prezentat simptome pentru o perioadă mai lungă de timp înaintea internării (medie de 3,94 vs. 2,57 zile,  $P = 0,03$ ).

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Complicațiile postoperatorii (44,4% față de 17,2%,  $P = 0,03$ ) și durata mai lungă a internării în spital (7,28 zile față de 5,95 zile,  $P = 0,004$ ) au fost de asemenea mai frecvent observate la pacienții cu HIV +. Nu au existat diferențe în ceea ce privește ratele de ruptură ale apendicelui, rezultatele histopatologice și mortalitatea.

**Concluzii:** Pacienții HIV+ s-au prezentat mai târziu la spital, iar intervenția chirurgicală a fost asociată cu o rată mai ridicată a morbidității postoperatorii și o perioadă mai lungă a internării.

**Cuvinte cheie:** apendicită, HIV/AIDS, rezultate, morbiditate, mortalitate

## 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 a 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, histopathological findings and mortality.

**Conclusions:** Presentation in HIV+ patients was delayed and surgery was associated with significant postoperative morbidity and longer hospital stay.

**Key words:** appendicitis, HIV/AIDS, outcomes, morbidity, mortality

## Background

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 general surgical conditions (1). 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. This study was conducted in the Northern Cape province, where the HIV prevalence is 7.4% (2).

This high national prevalence has also translated into surgical cohorts across the country. In the large multi-centre prospective South African Surgical Outcomes Study, Biccard et al (3) showed that 13.2% of patients undergoing surgery were HIV+.

Appendicitis is a very common Gastrointestinal (GIT) surgical emergency in the HIV+ (4-9). Green et al (10) recently showed that appendicitis was the cause of surgical sepsis in 26% of HIV+ patients. Opportunistic infections such as Tuberculosis (TB) and AIDS-related malignancies such as

Kaposi's Sarcoma (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 are concerning (1,4-9).

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. Paradoxically, only two of these publications are from Sub-Saharan Africa where HIV is highly prevalent (4,6). The studies addressing surgical outcomes of appendicitis in HIV+ and HIV- patients are summarised in *Table 1*. Thus, the aim of this study is to describe and compare the outcomes of appendectomy between HIV-infected (HIV+) and HIV-negative (HIV-) patients.

## 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 completely safely through the initial surgical approach. All resected appendixes were sent for histopathological assessment.

**Table 1.** 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 (5)	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 (6)	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 (7)	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 (9)	2015	Japan	6	HIV- (212) HIV+ (6)	CD4+ count lower in HIV+ patients with complicated appendicitis
Gigabhoy et al (4)	2016	South Africa	1	HIV- (36) HIV+ (14)	Higher laparotomy rate in HIV+ patients
Smith et al (8)	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

## 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/ $\mu$ 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 2).

**Table 2.** 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	

There was no difference in the signs and symptoms experienced by both patient groups (Table 3).

A laparotomy was more frequently performed in the HIV+ patient (72.2% vs. 41.3%,  $P = 0.03$ ) (Table 4). 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 5). 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

**Table 3.** Individual clinical and haematological characteristics in HIV- and HIV+ patients

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

**Table 4.** 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

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).

This study was conducted in the Northern Cape province of South Africa, where the HIV prevalence is 7.4% (2). 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 (4) 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% (6). These results support the theory that HIV status may be a risk factor for appendicitis (11,12). Crum-Cianflone and colleagues (12) propose that biological and epidemiological factors account for this observation. HIV seropositivity imparts an increased risk of developing appendicitis because the fragile vasculature of

**Table 5.** 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

the appendix is more predisposed to disease. Furthermore, opportunistic infections and IRIS secondary to HAART render HIV+ patients more prone to developing appendicitis (13).

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, (4,6) 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 (8).

A CD4+ count was recorded in 81% (13 patients); the mean value was 260 cells/µL. 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 (14-18). Some studies show higher morbidity with advanced

clinical stages of the disease (1,14,15), whilst others conclude there is no difference (16). In a prospective cohort study, ČaČala et al (16) 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/ $\mu$ l versus 2% in the CD4+ count >200 cells/ $\mu$ l group. In emergency surgery patients, a lower CD4+ count is associated with increased post-operative septic complications and longer hospital stay (14,15,17,19). Xia et al (15) 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 (4) and pre-operative leukocytosis is also less frequently observed (6). 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. Although the delay in presentation is well documented in this study, there were no differences 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 (20). 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 (21). 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 occurred due to the delay in presentation of these patients (4,6). The morbidity relates predominantly to Surgical Site Infections, and is reduced with a laparoscopic approach (7,8). 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 (5-8). 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 (1,22-24). 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. 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 (25,26).

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. 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 (27-29). Irrespective of aetiology, GIT bleeding is another poor prognosticator of both in-hospital and long-term mortality (30,31).

Following major abdominal surgery, HIV+ patients should be considered for ICU care. In a South African study, Bhagwanjee et al (25) 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 (26).

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 (7,8). 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 (6,12).

## Conclusion

This retrospective study investigates 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 13.4%. 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%. It only provides a snapshot of the effect of HIV on a common GIT surgical emergency. 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.

## *Ethics Approval and Consent to Participate*

The Human Research Ethics Committee of the Faculty of Health Sciences at the University of Cape Town (Federal Wide Assurance Number: FWA00001637, Institutional Review Board number: IRB00001938) granted ethical approval for this study ( HREC REF: 341/2015).

*Consent for Publication:* Not applicable.

## *Availability of Data and Materials*

Please contact authors for data requests.

## *Authors' Contributions*

SS,CE and DK designed the study and drafted the manuscript. AB and JK performed the study analysis and drafted the manuscript. GV performed all the histopathological analyses and drafted the manuscript.

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*Conflicts of Interest:* None

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