



Leucocyte count and C-reactive protein cannot be relied upon in the diagnosis of acute appendicitis in HIV-infected patients

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Abstract

Background: South Africa has the highest prevalence of human immunodeficiency virus (HIV) infection in the world, and is commonly found in association with appendicitis. Atypical presentation of appendicitis in the presence of HIV infection makes clinical diagnosis of appendicitis unreliable, and inflammatory markers are commonly used as adjuncts. The aim of this study was ascertain the value of inflammatory markers in the diagnosis of appendicitis in patients with and without HIV infection.

Methods: Patients with acute appendicitis were studied and divided into HIV-infected and HIV-uninfected groups. Symptoms, and systemic and local signs were recorded. Appendiceal pathology was classified as simple or as complicated by abscess, phlegmon or perforation. Total white cell count (WCC) and C-reactive protein (CRP) were chosen as inflammatory markers. Findings were compared between the two groups.

Results: The study population consisted of 125 patients, of whom 26 (20.8 per cent) had HIV infection. Clinical manifestations did not differ statistically, and there was no difference in the incidence of simple or complicated appendicitis between the two groups. The mean CRP level was significantly higher in HIV-infected patients (194.9 mg/l versus 138.9 mg/l in HIV-uninfected patients; $P = 0.049$), and mean WCC ($\times 10^9/L$) was significantly lower (11.07 versus $14.17 \times 10^9/L$ respectively; $P = 0.010$)

Conclusion: Clinical manifestations and pathology did not differ between HIV-infected and HIV-uninfected patients with appendicitis, except that the WCC response was significantly attenuated and CRP levels were generally higher in the presence of HIV infection.

Introduction

The lifetime risk of developing acute appendicitis is estimated to be 7–8 per cent¹. As different populations adopt Western diets, such as in South Africa, the incidence of acute appendicitis increases^{2,3}.

An accurate history and careful physical examination are required to diagnose appendicitis, although clinical diagnosis alone is notoriously unreliable⁴. Various adjuncts have been devised to enhance the reliability of clinical diagnosis. Of these, the white cell count (WCC) and C-reactive protein (CRP) have proved to be the most useful. Several systems that combine clinical manifestations and inflammatory markers for the diagnosis of acute appendicitis have been developed⁵. Although meta-analyses have reported that individual descriptors have weak discriminatory power, in combination they can provide a high degree of diagnostic accuracy^{6,7}.

A majority of people living with the human immunodeficiency virus (HIV), an estimated 7 million, are in sub-Saharan Africa⁸. South Africa has the highest prevalence of HIV infection in the world⁹. The use of highly active antiretroviral therapy has led to a large population of long-term survivors of HIV infection who may be susceptible to other illnesses, including acute

appendicitis¹⁰. The incidence of acute appendicitis is increasing in South Africa^{3,11}, so acute appendicitis in HIV-infected patients is common.

Few studies of acute appendicitis in the HIV population have been published^{12–17}. HIV infection has a profound effect on immunity^{18–20}, potentially resulting in an altered response to acute appendicitis. Although changes in inflammatory markers have been used widely to improve diagnostic accuracy, their value in HIV-infected patients with acute appendicitis is unclear^{5–7}. A prospective study of patients with acute appendicitis, comparing inflammatory markers in patients with and those without concomitant HIV infection, was undertaken to address this knowledge deficit.

Methods

This was a prospective cross-sectional study of adult patients treated for acute appendicitis at Steve Biko Academic and Kalafong Hospitals in Pretoria from January 2015 to March 2017. These hospitals form part of the academic training complex of the University of Pretoria. Consecutive patients, aged 18 years or above, diagnosed clinically with acute appendicitis, who were not

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part of another study, were included and grouped according to their HIV status. Patients were excluded if they were taking immunosuppressive drugs, had other non-appendiceal pathology at surgery, or displayed different appendiceal pathology on histological examination. Clinical data, inflammatory markers and final histological findings were studied.

Ethical approval was granted by the research ethics committee of the Faculty of Health Sciences of the University of Pretoria (reference 436/2014).

The following presenting clinical features were recorded: duration of symptoms, central abdominal pain shifting to the right iliac fossa (RIF), nausea or vomiting, and anorexia. Clinical signs including pulse rate, temperature, tenderness in the RIF, and peritonism in the right lower quadrant were recorded.

Blood tests to measure WCC (with differential counts) and CRP levels were performed upon making the clinical diagnosis. HIV status was recorded, and HIV testing was performed with consent for all patients who were unaware of their HIV status after standard counselling. A cluster of differentiation 4-positive (CD4+) cell count was done for HIV-positive patients.

Routine imaging was not used, except where the diagnosis of acute appendicitis was equivocal and there was need to exclude gynaecological or urological pathology; in these cases, ultrasound imaging was usually performed.

Appendectomy was performed through a standard right iliac fossa incision, and the macroscopic appearance was recorded. All specimens were submitted for histological examination and definitive diagnosis based on the histological appearance. Appendiceal pathology data were classified by severity as simple appendicitis when histological examination showed acute inflammation with or without suppuration, or as complicated when either the macroscopic or microscopic appearance showed necrosis, perforation, a phlegmon or abscess. The appendix was reported as normal if no pathology was seen.

Statistical analysis

Analysis of the data was performed using the STATA Release 15 version 15.1 programme. HIV-infected and HIV-uninfected groups were compared for differences in clinical presentation, results of inflammatory markers, and final histology. Continuous data are presented as mean(s.d.), and categorical data as proportions. The two groups were compared using Student's *t* test or Fisher's exact test, and ANOVA for multiple variants. Specific CRP and WCC categories were analysed using logistic regression with the occurrence of acute appendicitis and HIV status as fixed factors, reporting odds ratios with 95 per cent confidence intervals. The levels of significant inflammatory biomarkers used for comparison in this study were WCC of $12 \times 10^9/l$ or higher and CRP of 25 mg/l or above. In all analyses the significance level was set at $P \leq 0.050$.

Results

A total of 150 patients with a clinical diagnosis of acute appendicitis were enrolled during the study period. One patient with a neoplasm of the appendix was excluded from analysis. Of the remaining 149 patients, 121 (81.2 per cent) had no HIV infection and 28 (18.8 per cent) were infected by HIV. Twenty-four patients (16.1 per cent) had no appendicitis at operation or on histological examination. Of these, 22 had no HIV infection and two were HIV-infected ($P = 0.252$). Of the 125 patients with appendicitis, 99 (79.2 per cent) were not infected by HIV and 26 (20.8 per cent) had HIV infection. There was no difference between the groups in the

proportion of patients with complicated appendicitis: 14 of 26 (54 per cent) for HIV-infected versus 47 of 99 (47 per cent) for HIV-uninfected patients ($P = 0.660$).

Demographic and clinical data for patients with appendicitis in the two groups are shown in Table 1. The mean age of the HIV-infected patients was marginally higher than that of the HIV-uninfected patients ($P = 0.056$). A significantly higher proportion of women compared with men who developed acute appendicitis were infected with HIV (62 versus 38 per cent respectively; $P = 0.026$).

There was no difference in the duration of symptoms at presentation between the groups. The only parameter that showed a statistically significant difference was the higher mean pulse rate in HIV-infected compared with HIV-uninfected patients (103 versus 93 beats per min respectively; $P = 0.029$) (Table 1).

A comparison of inflammatory markers in patients with acute appendicitis with or without HIV infection is shown in Table 1. The mean CRP concentration was higher in patients with HIV infection (194.9 mg/l versus 138.9 mg/l in those without HIV infection; $P = 0.049$), and WCC was lower (11.07 versus $14.17 \times 10^9/l$ respectively; $P = 0.010$). Further analysis of inflammatory markers is shown in Figs 1–3. The mean CRP level was increased in patients with appendicitis compared with that in patients with a normal appendix (150.9 versus 19.8 mg/l respectively; $P < 0.001$) and was significantly higher in the overall HIV-infected group (183.1 versus 116.4 mg/l; $P = 0.013$) (Fig. 1a,b). Mean CRP concentration was highest in complicated appendicitis (HIV infection: 243.1 mg/l versus 143.8 mg/l ($P = 0.059$) in simple appendicitis; no HIV infection: 195.3 versus 89.3 mg/l respectively; $P < 0.001$) (Fig. 1c).

There was a significant increase in mean WCC in patients with acute appendicitis compared with the value in those with a normal appendix (13.52 versus $10.16 \times 10^9/l$ respectively; $P = 0.004$) (Fig. 2a). Comparatively, mean WCC was lower in HIV-infected patients overall ($10.92 \times 10^9/l$ versus $13.46 \times 10^9/l$ in HIV-negative patients; $P = 0.023$) (Fig. 2b), and especially in those with complicated appendicitis (11.45 versus $16.00 \times 10^9/l$ respectively; $P < 0.001$); WCC was highest in patients with complicated appendicitis without HIV infection (Fig. 2c). The mean neutrophil response was comparable in HIV-infected and HIV-uninfected

Table 1 Demographics and manifestations of 125 patients with appendicitis

	HIV-negative (n=99)	HIV-positive (n=26)	P†
Age (years)*	31.5(11.4)	35.9(11.1)	0.056‡
Sex			0.026
M	63 (64)	10 (38)	
F	36 (36)	16 (62)	
Symptoms and signs			
Duration (days)*	3.8(2.6)	3.6(3.5)	0.910
Periumbilical pain	57 (58)	17 (65)	0.510
RIF pain	92 (93)	21 (81)	0.126
Nausea and/or vomiting	83 (84)	18 (69)	0.101
Anorexia	53 (54)	10 (38)	0.192
RIF tenderness	93 (94)	23 (88)	0.392
Generalized peritonitis	23 (23)	9 (35)	0.312
Pulse rate (beats/min)*	93(17)	103(21)	0.029‡
Temperature (°C)*	36.8(0.4)	36.8(0.1)	0.918
CRP (mg/l)*	138.9(123.41)	194.9(134.80)	0.049‡
WCC ($\times 10^9/l$)*	14.17(5.64)	11.07(4.29)	0.010‡

Values in parentheses are percentages unless indicated otherwise;

* values are mean(s.d.). HIV, human immunodeficiency virus; RIF, right iliac fossa; CRP, C-reactive protein; WCC, white cell count.

† Fisher's exact test, except.

‡ Student's *t* test.

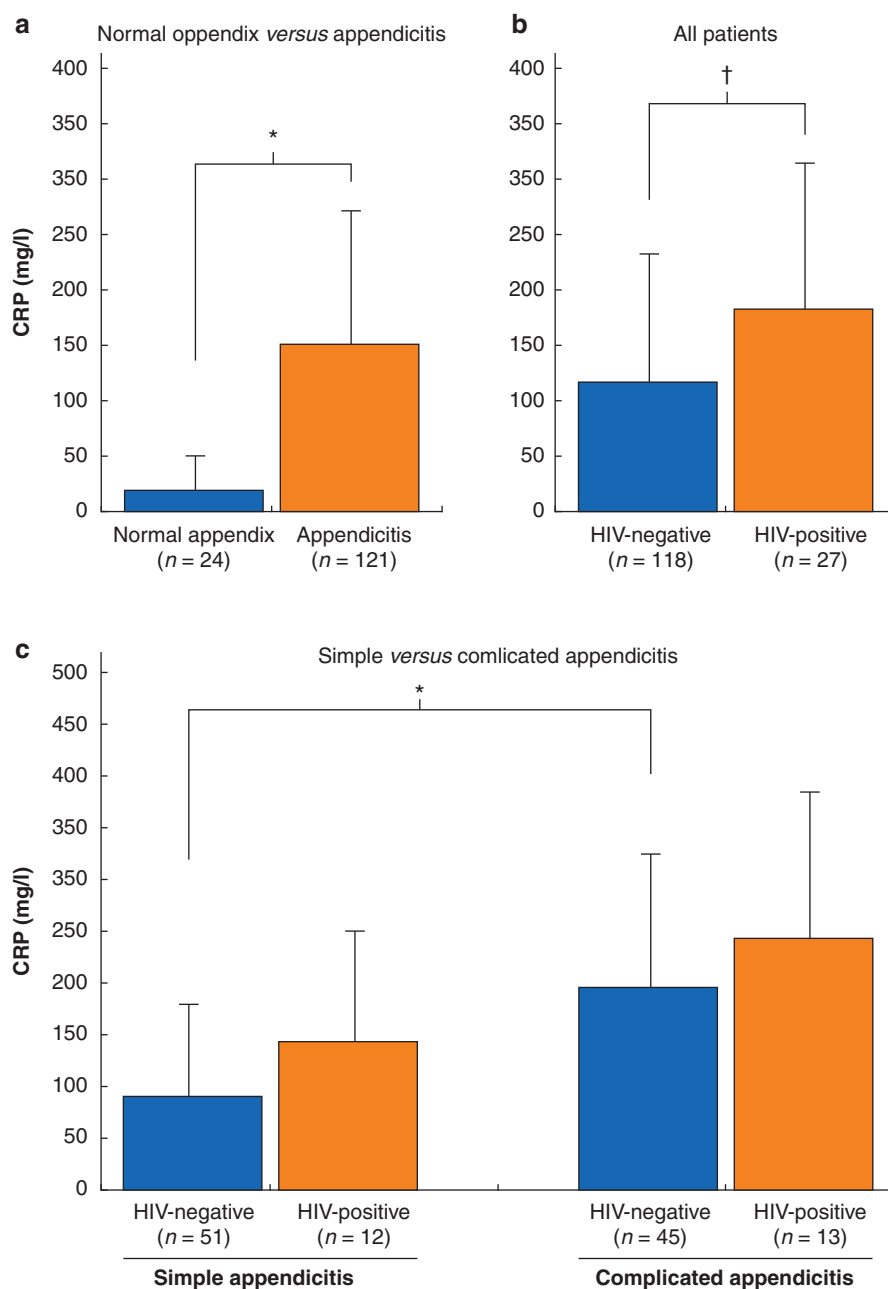


Fig. 1. Comparisons of C-reactive protein levels in patients with a normal appendix, acute appendicitis, and simple or complicated appendicitis with or without human immunodeficiency virus infection

a Normal appendix versus acute appendicitis; **b** acute appendicitis with or without human immunodeficiency virus (HIV) infection; **c** simple or complicated appendicitis with or without HIV infection. Values are mean(s.d.). CRP, C-reactive protein. * $P < 0.001$, † $P < 0.050$ (Student's *t* test).

patients (8.2 versus $10.4 \times 10^9/l$ respectively; $P = 0.095$) (Fig. 3b), but significantly lower in HIV-infected patients with complicated appendicitis (8.2 versus $12.6 \times 10^9/l$; $P = 0.046$) (Fig. 3c).

The CD4+ T-cell count was available for 23 of the 26 HIV-infected patients. The count was low in patients with HIV infection, but similar mean(s.d.) CD4+ cell counts were found in patients with simple or complicated acute appendicitis ($186(117)$ versus $195(190)$ cells/ μl respectively, $P = 0.910$; normal reference range 332 – 1632 cells/ μl). The mean(s.d.) WCC in HIV-infected patients with a low CD4+ T-cell count was $9.88(4.11) \times 10^9/l$ compared with $14.34(7.78) \times 10^9/l$ in HIV-infected patients with a high CD4+ count ($P = 0.022$). No patient was diagnosed with acquired immune deficiency syndrome.

Two (7 per cent) of 28 HIV-infected patients and 22 (18.2 per cent) of 121 HIV-uninfected patients had an incorrect clinical diagnosis of appendicitis ($P = 0.252$). Table 2 shows the analysis of the value of CRP and WCC in the diagnosis of appendicitis according to HIV status. The sensitivity of a raised CRP level was high for both HIV groups, but the specificity and negative predictive value were low for HIV-infected patients. The odds ratio of a raised CRP was high in HIV-uninfected patients.

Discussion

This study examined the value of measuring inflammatory markers in acute appendicitis in HIV-infected and HIV-uninfected

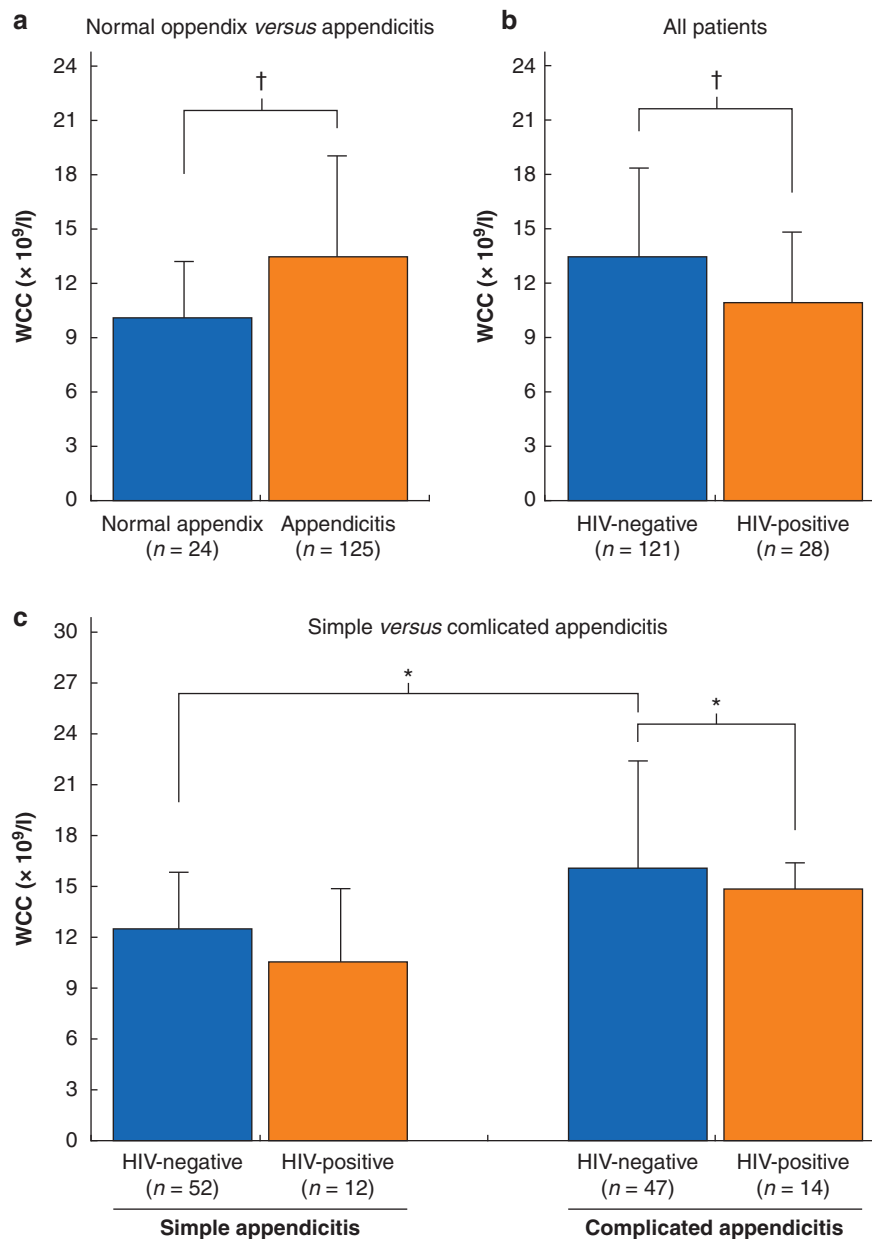


Fig. 2. Comparison of white cell count in patients with a normal appendix, acute appendicitis, and simple or complicated appendicitis with or without human immunodeficiency virus infection

a Normal appendix versus acute appendicitis; **b** acute appendicitis with or without human immunodeficiency virus (HIV) infection; **c** simple or complicated appendicitis with or without HIV infection. Values are mean(s.d.). WCC, white cell count. * $P < 0.001$, † $P < 0.050$ (Student's *t* test).

patients. The mean age of the two groups was similar, unlike in a US Veterans study¹⁶ in which HIV-infected patients were significantly younger than uninfected patients.

The preponderance of women in the HIV-infected group in the present study was not surprising. The prevalence of HIV infection is higher among women of child-bearing age in South Africa, where almost one-fifth of women aged 15–49 years are infected with HIV⁹. This is also the age range in which acute appendicitis occurs most commonly, and was reflected in the sex distribution of HIV infection in this study.

The diagnosis of acute appendicitis in this study was based on standard clinical evaluation. Clinical presentation did not differ between the two groups, as noted by others^{14,15}. The only clinical parameter that differed significantly by HIV status in the present study was a higher pulse rate in HIV-infected patients. This could

possibly reflect the somewhat more common appendicitis complications in these patients.

Acute appendicitis in HIV-infected patients has been reported^{14,15,21} to be associated with more serious complications than in HIV-uninfected patients. Although complicated appendicitis was slightly more common in HIV-infected patients in the present study (14 of 26, 54 per cent), the difference was not statistically significant. This accords with the findings of another study¹⁶, in which the incidence of complicated appendicitis was 39 per cent.

In this study, raised CRP levels were significantly higher in patients with HIV infection. It is known that there is a chronic state of immune activation in HIV-infected patients, as a result of which CRP levels are frequently increased²². In a study of 42 HIV-infected patients without additional infection of any kind, a

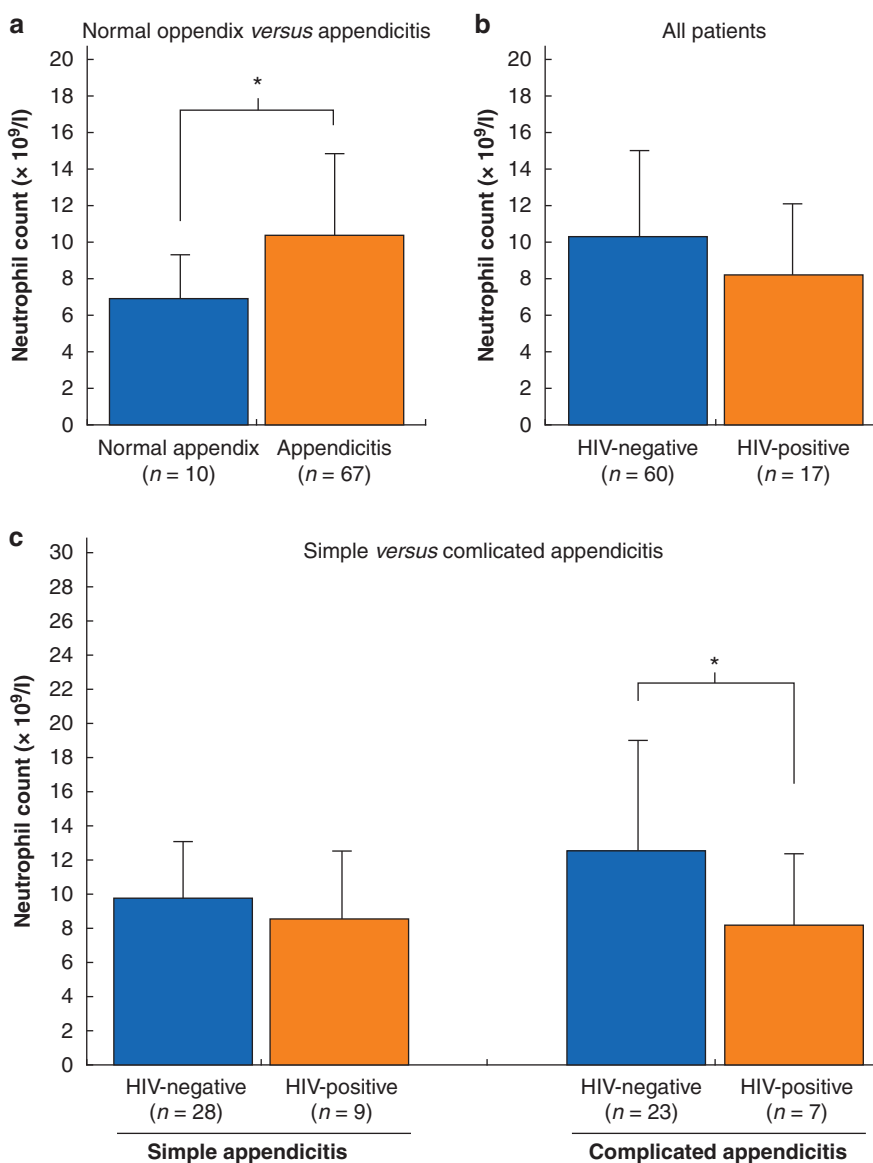


Fig. 3. Comparison of neutrophil count in patients with a normal appendix, acute appendicitis, and simple or complicated appendicitis with or without human immunodeficiency virus infection

a Normal appendix versus acute appendicitis; **b** acute appendicitis with or without human immunodeficiency virus (HIV) infection; **c** simple or complicated appendicitis with or without HIV infection. Values are mean(s.d.). * $P < 0.050$ (Student's *t* test).

Table 2 Test characteristics of biomarkers of all 149 patients by human immunodeficiency virus status

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Odds ratio (95% CI)*
CRP (>25 mg/l)					
HIV-negative (n=121)	77	77	94	44	11.90 (3.94-35.89)
HIV-positive (n=28)	84	50	96	20	5.50 (0.28-107.15)
WCC (>12 000 x10⁹/l)					
HIV-negative (n=121)	65	73	91	31	4.87 (1.74-13.58)
HIV-positive† (n=28)	–	–	–	–	–

* Values in parentheses are 95 per cent confidence intervals.

† Cannot be calculated as no patient had a white cell count (WCC) above 12 000 x10⁹/l. PPV, positive predictive value; NPV, negative predictive value; CRP, C-reactive protein; HIV, human immunodeficiency virus.

median level of 5.9 (range 0.5–108.6) mg/dl was found²³. Raised CRP concentration has been used as an adjunct in the diagnosis of acute appendicitis^{24,25}. The background of raised CRP concentration in HIV-infected patients renders it an unreliable adjunct in the diagnosis of acute appendicitis in these patients. The

specificity of a raised CRP level for appendicitis was low in the present study, as was its negative predictive value.

WCC differed significantly at presentation between HIV-infected and HIV-uninfected patients in this study. HIV-uninfected patients showed the expected increase in mean WCC, but the HIV-infected

patients had a significantly lower leucocytosis than those not infected with HIV. An attenuated WCC response in acute appendicitis has been reported in previous HIV studies^{13–15,21}. The low leucocytosis response in HIV-infected patients may be attributable to the low CD4+ cell count, as their neutrophil response was comparable to that of the HIV-uninfected group. WCC and CRP, used in acute appendicitis scoring systems^{25,26}, cannot therefore be relied on in the diagnostic workup of acute appendicitis in HIV-infected patients in South Africa.

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