



Compromised Gut Associated Lymphoid Tissue is a Risk Factor for Postoperative Septic Complications in HIV-Seropositive Trauma Patients

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Accepted: 27 November 2020 / Published online: 12 January 2021
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Abstract

Background The gut associated lymphoid tissue (GALT) is an important part of the immune system and compromised in HIV treatment-naïve as well as in HIV-seropositive patients on antiretroviral treatment (ART) due to HIV-induced changes. The influence of the impaired GALT on the postoperative complication rate after surgery for penetrating abdominal trauma has not been investigated and the hypothesis that the HIV-induced changes of the GALT contribute to septic complications postoperatively was tested.

Material and methods This prospective study included patients who required a small bowel resection due to abdominal gunshot wounds. A bowel specimen was obtained in the index operation, and the T-lymphocytic quantity in the specimen was analyzed via immunohistochemistry to scrutinize whether these lymphocyte numbers had an impact on the postoperative outcome. Septic and postoperative complications were documented during the in-hospital course and the first month after discharge.

Results In total, 62 patients were included in the study of which 38 patients were HIV-seronegative and 24 were HIV-seropositive. HIV-seropositive patients had a significantly lower quantity of CD4 + T cells in the GALT compared to the HIV-seronegative patients ($p = 0.0001$), which was also associated with a significantly higher rate of septic complications in the postoperative course. In the HIV-seropositive group, no significant differences were detected for T-lymphocytic quantity in the GALT between the HIV-treatment naïve and antiretroviral treatment groups.

Conclusion The compromised GALT in HIV-seropositive patients may predispose these patients to postoperative septic complications. Antiretroviral therapy does not result in an adequate immune reconstitution in this tissue.

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Introduction

Acquired immunodeficiency syndrome (AIDS)-related pathologies requiring surgery have decreased markedly since the introduction of combined antiretroviral therapy (ART) [1]. Reconstitution of the immune system after starting antiretrovirals (ARVs) resulted in an increased life expectancy [2] and reduced the complication rate after surgical procedures compared to the pre-ART period [3].

However, a considerable number of HIV-seropositive patients on ARVs only show an incomplete immune recovery at the time of surgical intervention [4]. Furthermore, problems are encountered in HIV-seropositive patients requiring urgent surgery who are newly diagnosed or those who have defaulted their treatment, the latter of which is often encountered among trauma patients [5].

Current research on HIV-related changes of the gut associated lymphoid tissue (GALT) has documented a more severe decrease in CD4 + T cells compared to the peripheral blood [6]. Weakening of the local immune system due to depletion of CD4 + T cells in the lamina propria together with structural changes of the bowel seems to predispose HIV-seropositive patients to bacterial translocation [7].

This prospective study compared the postoperative course between HIV-seropositive and HIV-seronegative patients who sustained penetrating abdominal trauma and determined whether the T-lymphocytic quantity of the GALT impact on the outcome.

We hypothesized that the HIV-induced changes of the GALT contribute to septic complications postoperatively.

Material and methods

In this prospective study, we recruited HIV-seropositive and HIV-seronegative adult patients from December 2018 to March 2020 at the Chris Hani Baragwanath Academic Hospital (CHBAH) Trauma Unit in Johannesburg, South Africa, who required surgery for abdominal gunshot injuries with bowel involvement. Exclusion criteria were uncontrolled diabetes mellitus (A1C level > 7%), active tuberculosis infection, a history of prolonged steroid use, pre-existing organ failure and demise within 72 h of admission. The data collection was done independently and prospectively by the trauma research group of CHBAH.

For comparison of the bowel specimen, a control group of eleven patients was recruited. These patients underwent small bowel resection for non-traumatic indications, without physiological derangements or signs of sepsis at the time of surgery and had all a confirmed HIV-negative serostatus. For the distal small bowel specimens, patients

who underwent stoma reversal with practically no comorbidities were recruited. For the specimens of the proximal bowel, we recruited three patients who had surgery for malignancies.

The protocol was approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (clearance number M180914). Informed consent was obtained from all patients, or if the patient had a decreased level of consciousness on admission, consent was signed by the patient's next of kin.

A full thickness, non-contused specimen of the small intestine, at least 5 mm in size, was obtained by the surgical team during index laparotomy from the segment of the bowel requiring resection due to the sustained injuries without knowing the patient's confirmed HIV status yet. The entirety of the sustained intra-abdominal injuries was graded according to the penetrating abdominal trauma index (PATI) [8] which is commonly used and validated scoring system for these injuries [9].

HIV status and CD4 + T-lymphocyte count in the peripheral blood were tested in all patients. In HIV-seropositive patients, viral load, ARV treatment status, treatment duration, drug combinations and presence of AIDS-defining conditions were documented.

The follow-up of the study patients was restricted to in-hospital course and a weekly review in our trauma clinic for the period of one month after discharge from the hospital. The outcome was measured according to the number and nature of septic complications, as well as postoperative surgical complications, which were classified according to the Clavien–Dindo classification [10]. Septic complications included superficial and deep surgical site infections, septic intra-abdominal collections (diagnosed via radiological imaging or during relook), septicemia with positive blood cultures, fungemia, pneumonia and urinary tract infections. Postoperative complications according to the Clavien–Dindo classification of grades 1–2 were categorized as minor, whereas grades 3–5 were major complications. The latter division was based on grade 3 complications and higher needing invasive interventions, either surgically, endoscopically or radiologically.

Laboratory investigations of bowel tissue

Immunohistochemistry (IHC) was performed on all bowel specimens by the National Health Laboratory Service's Division of Histopathology at CHBAH. CONFIRM anti-CD4 (SP35) rabbit monoclonal primary antibody and CONFIRM anti-CD8 (SP57) rabbit monoclonal primary antibody (Roche/Ventana Medical Systems, Inc.; Tucson, Arizona) were used for IHC staining. The antibodies were

stored at 2–8 °C until used in the detection kits specific for the Ventana BenchMark XT automated slide stainer.

Light microscopic examination was performed independently by the principle investigator (MM) and a histopathologist in a blinded manner without any accompanying clinical information.

The number of CD4 + and CD8 + lymphocytes of the lamina propria, hereafter referred to as lamina propria lymphocytes (LPL), was assessed at X400 magnification within 10 non-overlapping high-power fields by manual counting with the aid of Zeiss (Zeiss Inc.; Jena, Germany) Axioscope and software and expressed as number of cells per mm².

Statistical analysis

The chi-squared test or Fisher's exact test was used, as appropriate, to assess the relationships between categorical variables according to the patients' HIV status.

The relationship between the continuous variables and HIV status was assessed by the t-test. Where the data did not meet the assumptions of these tests, a non-parametric alternative, the Wilcoxon rank sum test was used. Sample size calculations were carried out in G*Power, and a minimum sample size of 54 patients was required for determination of a large size effect [11].

Data analysis was carried out using STATA version 15.1 for Windows. *P*-values < 0.05 were considered significant.

Results

Patient recruitment, demographics and perioperative factors

During the study period, 167 patients required a laparotomy for abdominal gunshot wounds, of which 93 patients were excluded because they had no small bowel injuries, and 12 were excluded due to demise within 72 h of admission. In total, 62 patients were recruited. The demographics, injury severity, other relevant perioperative factors in the study population, as well as the injured organs, are listed in Table 1. The HIV-seropositive patients were significantly older than the HIV-seronegative patients.

Of the 24 HIV-seropositive patients, 12 patients were newly diagnosed, while 12 patients knew their HIV status. Of those who knew their HIV status, 10 (83%) were taking ARVs. The mean (\pm SD) treatment duration in the latter group was 5.5 (4.1) years. The median CD4 + T-lymphocyte count of the entire HIV-seropositive study population on admission was 338 cells/ μ l (IQR 204–471). The

median viral load was 8 010 copies/ml (IQR 368–64 450) which is equivalent to a mean (\pm SD) of 3.7 (1.6) Log copies/ml. No significant difference in the CD4 + T-lymphocyte count between HIV naïve and patients on ARVs was detected in the admission blood of the HIV-seropositive patients (HIV naïve: 320; IQR 196–440 vs. HIV treatment: 390; IQR 238–482, *p* = 0.58; data not shown). Only two HIV-seropositive patients showed clear signs of AIDS-defining conditions, both of them were treatment-naïve.

The amount of blood products, including red blood cells, fresh frozen plasma and platelets did not differ between the groups.

Comparison of lymphocyte quantity in the GALT in relation to HIV infection and treatment

The lamina propria of the HIV-seropositive patients showed a severe depletion of CD4 + T cells, with the median number (IQR) of CD4 + LPL significantly lower compared to the HIV-seronegative patients at 252 (176–413) cells/mm² vs. 905 (813–997) cells/mm², respectively (*p* = 0.0001). Conversely, the quantity of CD8 + LPL was significantly higher in HIV-seropositive (1 143; IQR 826–1 235 cells/mm²) vs. HIV-seronegative (512; IQR 410–572 cells/mm²) patients (*p* = 0.0001). In the HIV-seropositive patient group, a significantly lower CD4 + LPL count and a significantly higher CD8 + LPL count were associated with a significantly higher rate of septic complications compared to the HIV-seronegative patients (*p* = 0.002); data shown in Fig. 1 and Table 2.

Within the group of HIV-seropositive patients, there was no significant difference between the treatment-naïve and the ARV-treated patients in the number of the CD4 + LPL [treatment-naïve 229 (IQR 166–260) vs. treated 349 (IQR 225–425) cells/mm²; *p* = 0.18] and CD8 + LPL [treatment-naïve 1 175 (IQR 878–1 307) vs. treated 979 (IQR 778–1 231) cells/mm²; *p* = 0.27; data not shown].

The inclusion and analysis of the non-trauma, HIV-seronegative control group provides reference values for CD4 + LPL and CD8 + LPL. These reference values are as follows [median (IQR)]: CD4 + LPL: 1 121 (720–1 199); and CD8 + LPL: 414 (371–612) cells/mm².

Figure 2 displays microscopic images following IHC and shows the difference of the CD4 + LPL between a treatment-naïve HIV-seropositive patient (Fig. 2a) and a HIV-seronegative patient (Fig. 2b), with CD4 + T cells embrowned.

Clinical course and complications

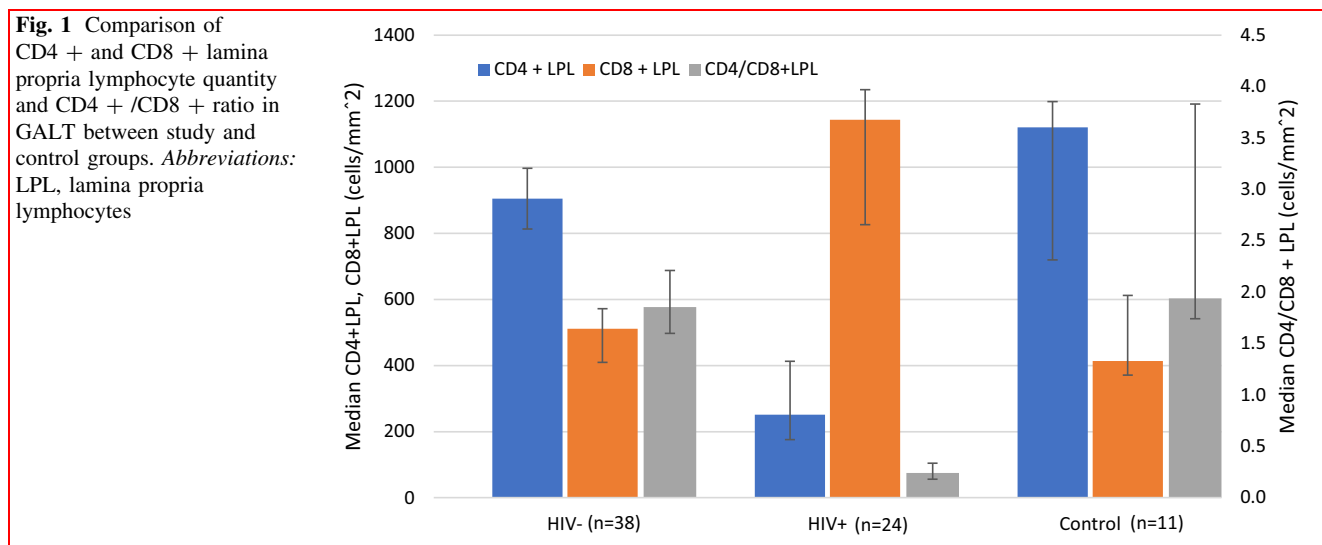
In the postoperative follow-up of the study patients, significantly more patients with septic complications

Table 1 Demographics, perioperative factors and injured organs of study patients according to HIV-serostatus

Variable	HIV-seronegative patients (n = 38)	HIV-seropositive patients (n = 24)	P value
Age, years	31 (25–40)	41 (32–47)	0.013
<i>Gender</i>			
Male	36 (95%)	22 (92%)	0.64
Female	2 (5%)	2 (8%)	
Time injury-to-operation (h)	4 (3–6)	5 (4–6)	0.51
PATI	27 (17–33)	27 (16–32)	0.79
pH, on admission	7,34 (7,26–7,43)	7,33 (7,26–7,36)	0.32
Lactate (mmol/L), on admission	4,5 (3,2–6,6)	4,7 (3,1–5,4)	0.82
Bicarb (mmol/L), on admission	21,7 (16,3–23,2)	21,9 (17,8–23,8)	0.59
BE (mmol/L), on admission	−4,1 (−8,8 to −1,0)	−4,0 (−7,4 to −1,6)	0.85
<i>Fecal contamination</i>			
Mild	5 (13%)	3 (13%)	
Moderate	10 (26%)	6 (25%)	> 0.99
Severe	23 (61%)	15 (63%)	
Colonic injury	25 (66%)	13 (54%)	0.43
Liver injury	3 (8%)	4 (17%)	0.42
Stomach injury	5 (13%)	5 (21%)	0.49
Vascular injury	11 (29%)	4 (17%)	0.37
Involvement of other organs	10 (26%)	9 (38%)	0.40
Inotrope requirement	23 (61%)	15 (63%)	> 0.99
Inotrope duration (h)	41 (7–66)	50 (24–96)	0.21
Hypotension (SBP < 90 mmHg), on admission	10 (26%)	7 (29%)	> 0.99
Damage control surgery	19 (50%)	12 (50%)	> 0.99

Continuous numerical variables presented as median (interquartile range [IQR]). Categorical variables expressed as absolute and relative frequencies (in brackets)

RBC red blood cell; FFP fresh frozen plasma; SBP systolic blood pressure



($p = 0.002$; Table 3) were observed in the HIV-seropositive group compared to the HIV-seronegative group. The higher complication rate was primarily due to superficial surgical site infections that were significantly more

common in the HIV-seropositive patients ($p = 0.005$; Table 3). HIV-seropositive patients had an anastomotic leak rate of 38%, HIV-seronegative patients leaked in 18% of the cases; this difference did not reach statistical

Table 2 Comparison of quantity of CD4 + LPL and CD8 + LPL between HIV-seronegative and HIV-seropositive patients in relation to septic complications

	HIV-seronegative patients ($n = 38$)	HIV-seropositive patients ($n = 24$)	p value
CD4 + LPL (cells/mm ²)	905 (813–997)	252 (176–413)	0.0001
CD8 + LPL (cells/mm ²)	512 (410–572)	1 143 (826–1 235)	0.0001
Patients with septic complications	20 (53%)	22 (92%)	0.002

Continuous numerical variables presented as median (interquartile range [IQR]). Categorical variables expressed as absolute and relative frequencies (in brackets)

LPL lamina propria lymphocytes; *mm* Millimeter

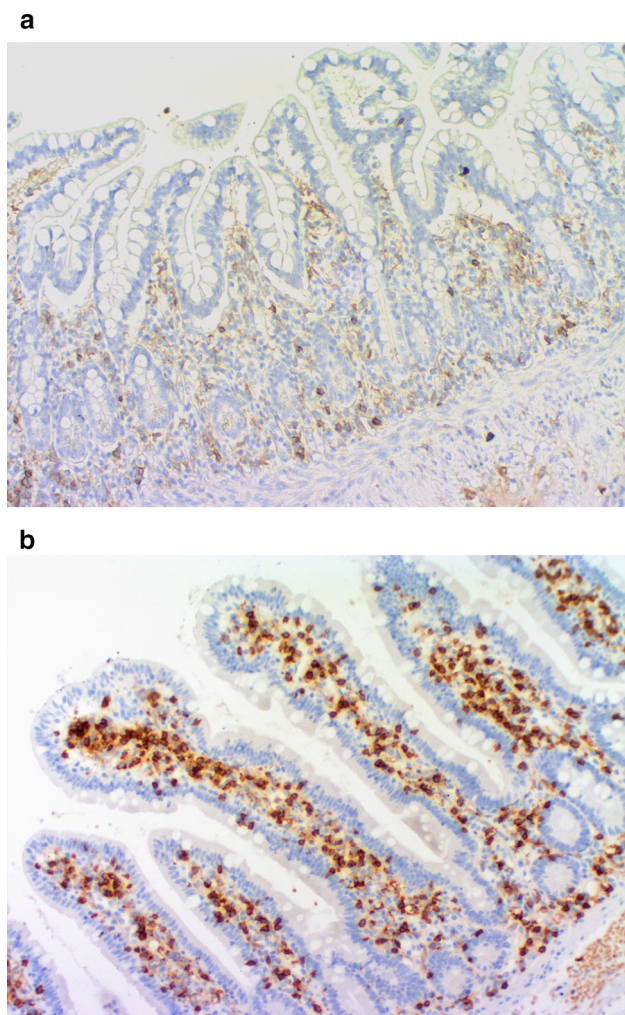


Fig. 2 Immunohistochemistry analysis of CD4 + T cells in the lamina propria of a treatment-naïve HIV-seropositive patient **a** and a HIV-seronegative patient **b**. *Specification: small bowel, × 100 magnification*

significance ($p = 0.14$). With regard to the time of diagnosing the anastomotic leak, the mean (\pm SD) time to notice this complication was significantly later in the HIV-

seropositive patients with 10.4 (1.4) days, compared to the HIV-seronegative patients [6.9 (1.6) days; $p = 0.0003$].

A sub-analysis between the treatment-naïve HIV-seropositive patients and patients on ARVs showed a similarly high complication rate in both groups, and the patients on ARVs did not have significantly fewer septic problems (Table 4).

Discussion

This study determined the T-lymphocytic quantity in the lamina propria of the GALT in the small bowel and investigated whether it has an influence on the postoperative course after penetrating abdominal trauma. Moreover, special emphasis was to investigate whether HIV-infection, and specifically, preexisting HIV-induced changes of the GALT had an impact on postoperative septic complications.

The demographic profile, perioperative factors, injury pattern and severity showed no significant differences between HIV-seropositive and HIV-seronegative patients, hence the groups were well matched, except for a significant difference in age between the two groups.

In the analysis of the GALT, we observed that HIV-seropositive patients had significantly less CD4 + T cells and significantly more CD8 + T cells in the LP compared to the HIV-seronegative study patients and the non-trauma, HIV-seronegative control group. Lower CD4 + T cells and higher CD8 + T cells were also associated with an increased rate of septic complications in this study population.

Our finding reflects Brenchley et al.'s observation in which he described a severe depletion of the mucosal CD4 + T cells after primary HIV-infection that persists for the further course of disease resulting in a severe lymphopenia [7]. The cause for this massive decrease in CD4 + LPL is still debatable and is most likely multifactorial; virus-induced Fas/FasL-mediated apoptosis, virus triggered cytolysis, lymphocyte destruction by cytotoxic

Table 3 Comparison of clinical course and complications according to HIV-serostatus

Parameter	HIV-seronegative patients (<i>n</i> = 38)	HIV-seropositive patients (<i>n</i> = 24)	<i>P</i> value*
Septic complications	20 (53%)	22 (92%)	0.002
Superficial SSI	17 (45%)	18 (75%)	0.005
Deep SSI	8 (21%)	8 (34%)	0.22
Septicemia (positive BC)	14 (37%)	14 (58%)	0.28
<i>Pneumonia</i>			
No pneumonia	29 (76%)	16 (67%)	
VAP	5 (13%)	5 (21%)	0.13
Postop pneumonia (not ventilator-associated)	4 (11%)	3 (13%)	
Septic intra-abdominal collection	16 (42%)	14 (58%)	0.30
Anastomotic leak	7 (18%)	9 (38%)	0.14
Repair break down	3 (8%)	3 (13%)	0.66
Number of relooks	1 (0–3)	1 (0–4)	0.40
ICU-LOS (in days, censored for death)	30 (15– <i>ne</i>)	18 (5–33)	0.78
Ventilatory days	6 (3–15)	4 (4–18)	0.93
<i>Renal failure</i>			
Dialysis required	5 (13%)	4 (17%)	0.67
Dialysis not required	5 (13%)	1 (4%)	
<i>Clavien–Dindo classification</i>			
0–2, minor	19 (50%)	7 (29%)	0.12
3–5, major	19 (50%)	17 (71%)	
Mortality	7 (18%)	9 (38%)	0.14

***Bold** values are statistically significant. Continuous numerical variables presented as median (interquartile range [IQR]). Categorical variables expressed as absolute and relative frequencies (in brackets)

BC blood culture; ICU-LOS intensive care unit length of stay; SSI surgical site infections; VAP ventilator-associated pneumonia; *ne* not estimable

Table 4 Sub-analysis for septic and surgical complications of HIV-seropositive patients according to treatment status

	HIV-seropositive naïve (<i>n</i> = 14)	HIV-seropositive on treatment (<i>n</i> = 10)	<i>p</i> value
<i>Number of septic complications</i>			
0	0 (0%)	2 (20%)	0.16
1 or more	14 (100%)	8 (80%)	
<i>Clavien–Dindo classification</i>			
0–2 minor	4 (29%)	3 (30%)	> 0.99
3–5 major	10 (71%)	7 (70%)	

Categorical variables expressed as absolute and relative frequencies (in brackets)

T-lymphocytes and NK-cells as well as activation-induced cell death of lymphocytes seem to play a role [12].

Among the HIV-infected patients in our study, we did not find a significant quantitative difference of CD4 + T cells in the GALT of treatment-naïve patients and patients on ARVs. The patients on treatment showed only a slightly higher CD4 + T cell count on average, indicating a partial recovery, but their numbers fell far short of the HIV-

negative study members, which confirms results of current HIV research [13].

We observed a significantly higher quantity of CD8 + T cells in the LPL of the HIV-seropositive patients compared to the HIV-seronegative patients. Despite the observation that CD8 + T cell-induced responses are essential for viral control and limit the viral replication in the acute and chronic disease phase [14, 15], the accumulation of activated CD8 + T cells in the LP also seems to have a

negative effect on the reexpansion of the CD4 + T cell pool [13, 16].

In line with the findings of the CD4 + cell count in the HIV-seropositive patients, we also did not detect a significant difference in the CD8 + T cell count between treatment-naïve and treated patients, showing again the insufficient efficacy of the ARVs in restoration of lymphocytes in the LP of the GALT, a finding broadly supported by current HIV research [17–19].

Significantly more patients in the HIV-seropositive group suffered septic complications, especially superficial surgical site infections played a major role. More than a third of the HIV-infected patients was affected by an anastomotic leak which is an unacceptably high number and makes intrinsic, systemic causes, such as an impaired GALT, likely.

Fascial as well as anastomotic healing is reparative processes involving fibroblasts that are essential for remodeling the extracellular matrix and collagen synthesis. The fibroblast function is regulated by cytokines derived from monocytes/macrophages as well as from CD4 + T-lymphocytes [20]. The severe depletion of T-lymphocytes in the GALT may result in an altered fibroblast activity which affects the collagen and proteoglycan synthesis and influences wound strength and resilience. The latter is further supported by the finding that patients who suffered from an anastomotic leak had a significant lower CD4 + T cell count in their GALT compared to patients without a leak. The observation of impaired wound- and anastomotic healing is further supported by a rat model showing that a severe decrease in CD4 + T cells resulted in weaker wounds measured with several mechanical properties [21].

The analysis of the T-lymphocytic quantity of the GALT revealed a significant association between a decreased quantity of CD4 + LPL and more septic postoperative complications. The loss of these immune cells in the GALT may therefore be a predisposing factor for propagation of enteric bacteria into the blood stream with subsequent septic events. Supporting this presumption is the impressive mouse model from Gautreaux et al. in which T cell depletion resulted in a significantly higher translocation of *E. coli* from the small bowel [22].

Identically low CD4 + T cell quantity in the GALT was documented as a common denominator in treatment-naïve as well as treated HIV-seropositive patients. There is no doubt about the beneficial role that ARVs have in the treatment and prognosis of HIV-infected patients. However, the very limited efficacy on the reconstitution of the GALT may be the “Achilles heel” in the perioperative phase. Several reports about the influence of HIV on surgical treatment documented that the treatment with ARVs did not result in better outcomes or less complications which highlights the significance of this problem [23–25].

There is a paucity of data regarding the impact of age on the GALT. Quantity of LPL does not seem to be affected, but functional changes, especially decreased Interleukin-2 production, was observed in higher age groups [26] which, in turn, could have contributed to the higher rate of septic complications in the HIV-seropositive study group that was also significantly older.

Our research project was not without limitations. The number of 62 patients only had the statistical power to determine large size effects. Hence, more subtle significant associations might have been missed, not because there is no significant relationship but because there is insufficient evidence due to the small sample size. Consecutive patient recruitment resulted in groups that were not age-matched which could have led to biased results in the comparison between HIV-seropositive and HIV-seronegative patients.

Furthermore, the vast majority of our patients were male patients, and only four female patients were recruited. This gender imbalance makes it difficult to generalize our results as the new insights gained related almost exclusively to men.

No considerations were given to the nutritional status of the patients. It is documented that hypoalbuminemia is a risk factor for impaired wound and anastomotic healing [27], hence inclusion of this variable would have improved the study design.

In conclusion, we documented in HIV-seropositive patients a significantly higher septic complication rate compared to the HIV-seronegative patients which was primarily due to superficial surgical site infections. HIV-seropositive patients had a significantly lower CD4 + T cell quantity and a significantly higher CD8 + T cell quantity in their GALT which may predispose them to postoperative septic complications. The alterations of the GALT in HIV-seropositive patients on ART were persistent and almost unchanged in terms of CD4 + T cell recovery.

Acknowledgements The contribution(s) of the following people and institutions were instrumental in the realization of this project: The team of Division of Histopathology, NHLs at CHBAH, that provided immunohistochemistry specimens and the team from the Charlotte Maxeke Johannesburg Academic Hospital, National Health Laboratory Service flow cytometry laboratory, who provided an excellent and reliable service in the blood analysis.

Funding The study was sponsored by the trauma unit of the Chris Hani Baragwanath Academic Hospital.

Compliance with ethical standards

Conflict of interest The author declares that they have no conflict of interest.

Ethical Approval Throughout the study we adhered to the ethical requirements.

Informed consent Informed consent was obtained from all individual participants included in the study.

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