Evaluation of clinical, laboratory, radiographical and histopathological characteristics in patients with spinal tuberculosis in the context of HIV infection: An analysis of 52 patients from a South African tertiary hospital

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Background. South Africa (SA) has the highest prevalence of people with tuberculosis (TB) and HIV coinfection globally. People living with HIV have an increased risk of TB infection, and are more likely to develop extrapulmonary TB. Approximately 10 - 20% of extrapulmonary TB accounts for skeletal TB, with spinal involvement in 50 - 60% of instances. Previous studies have shown highly heterogenic results regarding the effect of HIV status on clinical and laboratory characteristics in patients with spinal TB (STB).
Objective. To describe the clinical, laboratory, radiographical and histopathological characteristics of patients diagnosed with STB stratified by HIV status.
Methods. Data from patients who were treated for STB at the Division of Orthopaedic Surgery, Groote Schuur Hospital, SA, between 2013 and 2016 were analysed. We compared clinical, laboratory, radiographical and histopathological parameters of STB patients with HIV infection to those without HIV infection. To assess differences in means between the two groups, an independent samples *t*-test was used for normally distributed continuous data, and a χ^2 test for categorical data. To assess correlations between continuous data groups, the Pearson correlation coefficient was used.
Results. We assessed 52 patients with STB (mean (standard deviation (SD) age 38 (15.2) years, range 17 - 80 years), of whom 55.8% were female, and 59.6% HIV infected. Five (9.6%) patients were identified with multidrug-resistant TB of the spine, with four (19.0%) in the HIV-infected cohort and one in the HIV-uninfected cohort (p=0.058). Significantly more STB patients without HIV infection presented with neurogenic symptoms (29%, p=0.029). The mean (SD) overall erythrocyte sedimentation rate was 69.3 (35.9) mm/h, with no significant difference between HIV-infected and HIV-uninfected patients (p=0.086). The rate of vertebral collapse was higher in the HIV-infected cohort (39% v. 67%, p=0.048). HIV-infected patients showed a higher count of involved vertebrae (mean 3.0 v. 3.85; p=0.034). There was no correlation between CD4 count and the number of involved vertebrae. The mean (SD) number of granulomata per low-power field was 10 (12.6), with no difference between the two cohorts. However, we found a positive correlation between granuloma count and CD4 cell count in HIV-infected STB patients (Pearson 0.503, p=0.02), with significantly higher formation of granulomata at a CD4 cell count >400 cells/μL (p=0.045).
Conclusion. In our cohort, HIV-infected patients with STB were more likely to present with vertebral collapse, and more vertebrae on average were diseased compared with HIV-uninfected patients with STB. CD4 cell count may affect granuloma formation, and it seems that HIV infection has a negative effect on cellular immunoresponse in STB, which emphasises the need for early antiretroviral therapy initiation.

Keywords: spinal tuberculosis, tuberculous spondylodiscitis, Pott's disease, cohort study, South Africa

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Tuberculosis (TB) remains a serious global health concern. In 2022, an estimated 10.6 million people fell ill with TB, of whom 1.3 million died, including 167 000 individuals living with HIV.[1] Globally, the highest numbers of TB cases have been reported from South-East Asia (44%), followed by Africa (24%) and the Western Pacific (18%.)[2] TB is considered the 'illness of the poor', and is transmitted through droplets containing *Mycobacterium tuberculosis* (Mtb).[3,4] TB is the leading cause of death due to an infectious disease worldwide, and the leading cause of death in people living with HIV.[5,6] There were ~39 million people living with HIV globally in 2022, of whom 20.8 million lived in sub-Saharan Africa.[7] South Africa (SA) is the most affected country, with >10% of the population infected with HIV.[7] HIV causes immunosuppression with depletion and dysfunction of CD4 cells, macrophages and monocytes, which increases the risk of primary and reactivated TB.[8,9] Patients with TB/HIV co-infection are more likely to develop extrapulmonary TB (EPTB).[10-14] Extrapulmonary disease may occur during any stage of HIV infection, but risk increases with advanced stage of immunosuppression.[10,11,15,16] Overall, EPTB occurs in 15 - 20% of immunocompetent TB patients, and in >50% of patients with TB/HIV co-infection.[17] Approximately 10 - 20% of EPTB manifests as skeletal TB, with spinal involvement in more than half of these patients.[18-22] Spinal TB (STB), also called Pott's

disease, usually results in local back pain, neurological deficit, spinal instability and constitutional symptoms. Duration from initial symptoms to diagnosis can take several years.[4,19,23-25] The influence of HIV infection on tissue samples and laboratory markers from patients with STB has been well studied; however, the results of these previous studies are highly heterogeneous.[26] Further, studies examining the effect of concomitant HIV infection on radiographical parameters such as degree of vertebral collapse and spinal distribution of diseased vertebrae are inconsistent.[27,28] Therefore, the aim of this study was to describe the clinical, radiographical and histopathological characteristics of patients diagnosed with STB stratified by HIV status to better understand the influence of HIV infection on STB.

Methods

Study design and cohort

This was a retrospective cohort study. All patients >16 years old and being treated for STB at the Division of Orthopaedic Surgery, Groote Schuur Hospital, Cape Town, SA, from January 2013 to December 2016 were included in this analysis. The laboratory reports, including HIV-1/2 Ab/Ag ELISA, microbiology and histology were accessed through the National Health Laboratory System. Patients' demographic data as well as clinical assessments were retrospectively accessed through the patients' clinical files. Magnetic resonance imaging (MRI) was assessed for number of involved vertebrae, vertebral collapse, abscess formation and abscess location. Histopathological specimens were assessed for granuloma type, granuloma formation count and degree of inflammation. Degree of inflammation was defined as 0 (0 inflammatory cells per low-power field), 1 (1 inflammatory cell per low-power field) or 2 (≥2 inflammatory cells per low-power field).

Patients treated at this academic hospital are mostly from low-income households, and often live in densely populated areas or informal settlements with high TB and HIV incidence.

Definition of spinal tuberculosis

STB was defined as a positive TB spinal tissue culture (mycobacteria growth indicator tube (MGIT)) or positive GeneXpert for Mtb (GeneXpert MTB/RIF assay, USA), or acid-fast bacilli on microscopy with apparent Langerhans cells or granulomatous infection. Patients with no tissue diagnosis, no alternative diagnosis, MRI findings suggestive of STB (Fig. 1) and clinical improvement on TB treatment were considered as cases of STB.[29]

Statistical analysis

Data are presented as frequencies (%) and means (standard deviations (SD)). To assess differences in means between the two groups, an independent samples *t*-test was used for normally distributed continuous data, and a χ^2 test for categorical data. To assess differences in means between the two groups, the Mann-Whitney *U*-test was used for not normally distributed continuous data (Shapiro-Wilk ≤0.05). To assess correlations between continuous data groups, the Pearson correlation coefficient was used. The level of statistical significance was set at $p<0.05$. All statistical analyses were performed in SPSS Statistics version 29.0 for Mac OS (SPSS, USA).

Ethical approval

The study was approved by the Human Research Ethics Committee of the Faculty of Health Sciences, University of Cape Town (ref. no. HREC 597/2015). The study adhered to the ethical principles for medical research involving human subjects outlined in the Helsinki Declaration of 1975 (revised 2013).[30]

A study protocol was prepared for ethical approval. No registration of the protocol was done.

Results

Study cohort

In total, 57 patients were recruited into the STB cohort (Table 1). Five were excluded from the final analysis due to unknown HIV status or missing CD4 cell count values. The HIV-uninfected cohort, designated 'STB^{HIV-}', comprised 59.6% (*n*=31) of patients; 40.4% (*n*=21) of the patients were included in the HIV-infected cohort, designated as 'STB^{HIV+}'.

Demographics and comorbidities

Table 1 summarises the demographic characteristics and comorbidities of the STB cohort, stratified by HIV status. Overall, 44.2% (*n*=23) of the patients were male. The mean (SD) age of the cohort was 38 (15.2) years (range 17 - 80), with no significant difference between STB^{HIV-} and STB^{HIV+}. Overall, 9.6% of patients were identified with multidrug-resistant (MDR)-STB, 19.0% STB^{HIV+} and 3.2% STB^{HIV-}. A total of 76.2% of STB^{HIV+} patients were receiving antiretroviral therapy (ART) at time of presentation. Thirteen patients received TB treatment before undergoing spinal surgery, whereas 33 patients received TB treatment afterwards. In six cases, the timing of TB treatment start was undocumented.

Neurological deficit and neurogenic symptoms[31,32]

A total of 65% of patients presented with at least one neurological symptom. This included either sensory loss, radicular pain, limb weakness or inability to walk (Table 2). No significant differences were detected between the two cohorts except for neurogenic symptoms, which were more common in the STB^{HIV-} cohort. Six (66.7%) of the nine patients with neurogenic symptoms suffered from either urinary or stool incontinence, or both.

Laboratory results

Table 3 summarises the key laboratory results. The mean (SD) overall erythrocyte sedimentation rate (ESR) was 69.3 (35.9) mm/hr, with no significant difference between STB^{HIV-} and STB^{HIV+}. No statistical difference between the groups was found regarding white cell count. CD4 cell count in STB^{HIV+} ranged from 10 to 900 CD4 cells/μL.

Table 4 summarises spinal tissue microbiology. Microbiological results were available in 43 of 52 patients (82.7%). A total of 35/43 patients (81.4%) with tissue microbiology had a positive MGIT culture result for Mtb, whereas 40/43 (93.0%) had a positive Xpert result. No difference was found between the STB^{HIV-} and STB^{HIV+}.

Radiology

Table 5 summarises the MRI findings. The mean (SD) count of involved vertebrae was 3.40 (2.35), without significant differences between STB^{HIV-} and STB^{HIV+}. Half of the patients suffered from vertebral collapse. The rate of collapse was significantly higher in STB^{HIV+} (39% v. 67%, $p=0.048$). Spinal abscess formation was similar in both groups. There was no correlation between CD4 cell count and the number of involved vertebrae.

Histopathology

Table 6 summarises the histopathological findings. The predominant granuloma type was caseous (48.1%), followed by solid cellular (44.2%), suppurative and solid fibrous (each 1.9%). There was no statistical difference in granuloma formation between STB^{HIV-} and STB^{HIV+}. The mean (SD) number of granulomata per low-power field at (×40 magnification) was 10.2 (12.6), with no difference between the two cohorts. Of the spinal tissue samples, 73.1% showed high-grade inflammation (inflammatory cells easily visible at ×40 magnification), 7.7% showed moderate inflammation (inflammatory

Table 1. Demographic characteristics and clinical findings of the spinal TB cohort

Characteristic	All (*N*=52)	STB^{HIV-} (*n*=31)	STB^{HIV+} (*n*=21)	*p*-value
Demographics				
Male, *n* (%)	23 (44.2)	14 (45.2)	9 (42.9)	>0.99
Mean (SD) age (years)*	37.7 (15.2)	37.8 (17.6)	37.7 (11.3)	0.380
Country of birth, *n*	Congo (2), Malawi (1), Somalia (3), South Africa (36), Zimbabwe (5), n/a (5)			n/a
HIV infected, *n* (%)	21 (40.4)	n/a	21 (100)	n/a
ART at presentation, *n* (%)	n/a	n/a	16 (76.2)	n/a
MDR-TB, *n* (%)	5 (9.6)	1 (3.2)	4 (19.0)	0.058
TB treatment start, *n* (%)				
Pre-spinal surgery	13 (25.0)	6 (19.4)	7 (33.3)	n/a
Post-spinal surgery	33 (63.5)	22 (80.0)	11 (52.4)	n/a
Timing unknown	6 (11.5)	3 (9.7)	3 (14.3)	n/a
Comorbidities, *n* (%)				
Hypertension	4 (7.7)	3 (9.7)	1 (4.8)	n/a
Diabetes	4 (7.7)	0	4 (12.0)	n/a
Hypothyroidism	1 (1.9)	1 (3.2)	0	n/a
Epilepsy	1 (1.9)	0	1 (4.8)	n/a
Asthma	1 (1.9)	0	1 (4.8)	n/a

TB = tuberculosis; STB^{HIV-} = spinal TB, HIV uninfected; STB^{HIV+}= spinal TB, HIV infected; SD = standard deviation; n/a = not applicable; ART = antiretroviral therapy; MDR-TB = multidrug-resistant TB.
*Not normally distributed data (Shapiro-Wilk ≤0.05).

Table 2. Neurological presentation of the spinal TB cohort

Presentation	All (*N*=52)	STB^{HIV-} (*n*=31)	STB^{HIV+} (*n*=21)	*p*-value
Sensory or motor neurology, *n* (%)				
Any neurological symptom	34 (65.4)	20 (64.5)	14 (66.7)	0.873
Sensory loss	3 (5.8)	2 (6.5)	1 (4.8)	0.798
Pain with radiation in lower limbs	7 (13.5)	4 (12.5)	3 (14.3)	0.886
Any limb weakness	21 (40.4)	11 (35.5)	10 (47.6)	0.382
Unable to walk (due to pain or weakness)	6 (11.5)	4 (12.9)	2 (9.5)	0.708
Neurogenic symptoms, *n* (%)				
Any neurogenic symptoms	10 (19.2)	9 (29.0)	1 (4.8)	0.029*
Urinary retention	2 (3.8)	2 (6.5)	0	0.235
Urinary incontinence	1 (1.9)	1 (3.2)	0	0.406
Bowel constipation	1 (1.9)	1 (3.2)	0	0.406
Bowel incontinence	2 (3.8)	1 (3.2)	1 (4.8)	0.777
Urinary and bowel incontinence	4 (7.7)	4 (12.9)	0	0.087

TB = tuberculosis; STB^{HIV-} = spinal TB, HIV uninfected; STB^{HIV+}= spinal TB, HIV infected.
*$p<0.05$.

Table 3. Laboratory results of the spinal TB cohort

Haematology, mean (SD)	All (*N*=47)	STB^{HIV-} (*n*=28)	STB^{HIV+} (*n*=19)	*p*-value
ESR, mm/hour*	69.3 (35.9)	62.2 (34.8)	80.7 (35.6)	0.086
White cell count, cells × 10^9/L†	8.0 (3.1)	8.6 (3.4)	7.1 (2.4)	0.143
CD4 count, cells/mm3	n/a	n/a	362.3 (219.5)	n/a

TB = tuberculosis; SD = standard deviation; $STBHIV^-$ = spinal TB, HIV uninfected; $STBHIV^+$= spinal TB, HIV infected; ESR = erythrocyte sedimentation rate.
Values were missing in five patients (3 STB^{HIV-}; 2 STB^{HIV+}).
*Normally distributed data (Shapiro-Wilk ≥0.05).
†Not normally distributed data (Shapiro-Wilk ≤0.05).

cells easily visible at ×100 magnification) and 19.2% had a low-grade inflammation (inflammatory cells not visible at ×100 magnification). There was no significant difference between STB^{HIV-} and STB^{HIV+}. In the STB^{HIV+} cohort, a significantly higher formation of granulomata at a CD4 cell count value of 400 CD4 cells was found (stepwise Student's *t*-test $p=0.045$; Shapiro-Wilk ≥0.05). We also found a positive correlation between granuloma count and CD4 cell count (Pearson 0.503, $p=0.02$) (Fig. 2), but no correlation was found between granuloma count and ART administration. Furthermore, there was no correlation between the amount of inflammation and ART administration or CD4 cell count, respectively.

Discussion

The aim of the present study was to identify the epidemiology, clinical findings, radiographical findings and laboratory parameters among patients with confirmed STB, stratified by their HIV status

Table 4. Microbiology of the spinal TB cohort

Microbiology, *n* (%)	All (*N*=43)	STB^{HIV-} (*n*=27)	STB^{HIV+} (*n*=16)	*p*-value
Spinal tissue-sample MGIT culture positive	35 (81.4)	23 (85.2)	12 (75.0)	0.442
Spinal tissue sample GeneXpert positive	40 (93.0)	24 (88.9)	16 (100)	0.282
Spinal tissue sample MGIT and GeneXpert discordance	11 (25.6)	7 (26.0)	4 (25.0)	>0.99

TB = tuberculosis; STB^{HIV-} = spinal TB, HIV uninfected; STB^{HIV+} = spinal TB, HIV infected; MGIT = mycobacteria growth indicator tube.

Table 5. Magnetic resonance imaging findings of the spinal TB cohort

Radiological finding	All (*N*=50)	STB^{HIV-} (*n*=30)	STB^{HIV+} (*n*=20)	*p*-value
Involved vertebrae, mean (SD)*	3.40 (2.35)	3.00 (2.38)	3.85 (2.28)	0.034†
Vertebral collapse, *n* (%)	26 (50.0)	12 (38.7)	14 (66.6)	0.048†
Abscess formation, *n* (%)	36 (69.2)	22 (70.9)	14 (66.6)	0.767
Mediastinal involvement, *n* (%)	1 (1.9)	1 (3.2)	0	>0.99
Abdominal involvement, *n* (%)	2 (3.8)	1 (3.2)	1 (4.8)	>0.99

TB = tuberculosis; STB^{HIV-} = spinal TB, HIV uninfected; STB^{HIV+} = spinal TB, HIV infected; SD = standard deviation.
*Not normally distributed data (Shapiro-Wilk ≤0.05).
†$p<0.05$.

Table 6. Histopathological findings of the spinal TB cohort

Finding	All (*N*=52)	STB^{HIV-} (*n*=31)	STB^{HIV+} (*n*=21)	*p*-value
Predominant type of granuloma, *n* (%)				
Caseous	25 (48.1)	15 (48.4)	10 (47.6)	>0.99
Solid fibrous	1 (1.9)	0	1 (4.7)	0.404
Suppurative	1 (1.9)	1 (3.2)	0	>0.99
Solid cellular	23 (44.2)	13 (41.9)	10 (47.6)	0.779
n/a	2 (3.8)	2 (6.4)	0	0.509
Amount of inflammation by LPF, *n* (%)				
Low-grade	10 (19.2)	6 (19.4)	4 (19.0)	0.920
Moderate	4 (7.7)	2 (6.5)	2 (9.5)	0.920
High-grade	38 (73.1)	23 (74.2)	15 (71.4)	0.920
Granuloma count per LPF, mean (SD)	10.2 (12.6)	12.1 (14.7)	7.4 (8.0)	0.185

TB = tuberculosis; STB^{HIV-} = spinal TB, HIV uninfected; STB^{HIV+} = spinal TB, HIV infected; n/a = not applicable; LPF = low-power field; SD = standard deviation.

in a country with a high disease burden, to gain further insight into the influence of HIV status on STB disease burden. To our knowledge, this is the second largest sample size of TB spine cases with regard to HIV status reported yet.[20,33] Almost half of our study population was HIV infected, reflecting a higher incidence of STB in people living with HIV than reported in the literature.[34,35] Almost 10% of the observed patients had MDR-TB, which is consistent with a reported prevalence of 5.8 - 11.8% in SA.[29,36] A total of 34 patients presented with neurological symptoms of varying severity, including limb weakness, sensory loss and radiating pain to the lower limb. A previous study has shown that HIV-uninfected patients with STB have higher rates of collapsed vertebrae than HIV-infected patients, which could explain the significantly higher incidence of neurogenic symptoms in the present STB^{HIV-} group.[27] The mean ESR in our study was 69.3 mm/hr among all patients. There was a trend towards higher ESR (p=0.086) and lower white cell counts (p=0.113) in STB^{HIV+}, which is consistent with findings from previous studies.[27,37] Previous studies investigating the correlation between HIV and spinal infections have found very low CD4 counts in STB. A case series conducted in the USA investigating six HIV-infected patients with STB reported a mean CD4 cell count of 57.2 cells/μL, whereas another study from SA reported mean counts of 424 CD4 cells/μL.[38,39] We report a mean CD4 cell count of 362/μL among the 21 HIV-infected patients, of whom 16 received ART. Another study reported a mean CD4 cell count of 496 cells/μL in HIV-infected patients with STB, where none of the assessed patients were receiving ART.[40] We did not assess the CD4 cell counts of the HIV-uninfected cohort, but believe that there is a significant difference between the two groups, as reported in a previous study from the Eastern Cape Province in SA.[35]

Data on the vertebral involvement in STB are inconsistent. A larger study including 597 STB patients reported on average 2.7 involved vertebrae.[41] Another smaller study reported a mean number of 3.2.[42] We report a mean count of 3.40 involved vertebrae among all assessed patients, with significantly more involved vertebrae in the STB^{HIV+} group, which is inconsistent with two previous studies showing no difference between immunocompetent and immunocompromised patients regarding the number of vertebrae involved.[28,43] We detected significantly more collapsed vertebrae in STB^{HIV+}, which is consistent with findings from investigations by Marais *et al.*[28] (274 patients), but contrary to findings from Anley *et al.*[27] (50 patients).[27,28] HIV has a negative impact on granuloma formation in TB, and therefore compromises the patient's immunity towards Mtb.[44] Our histological analysis revealed predominantly caseous and solid cellular granulomata, with no difference between STB^{HIV-} and STB^{HIV+}. Danaviah *et al.*[35] reported similar findings of granuloma organisation, and described a shift towards CD8 cells in HIV-infected patients, with STB as a compensation mechanism for

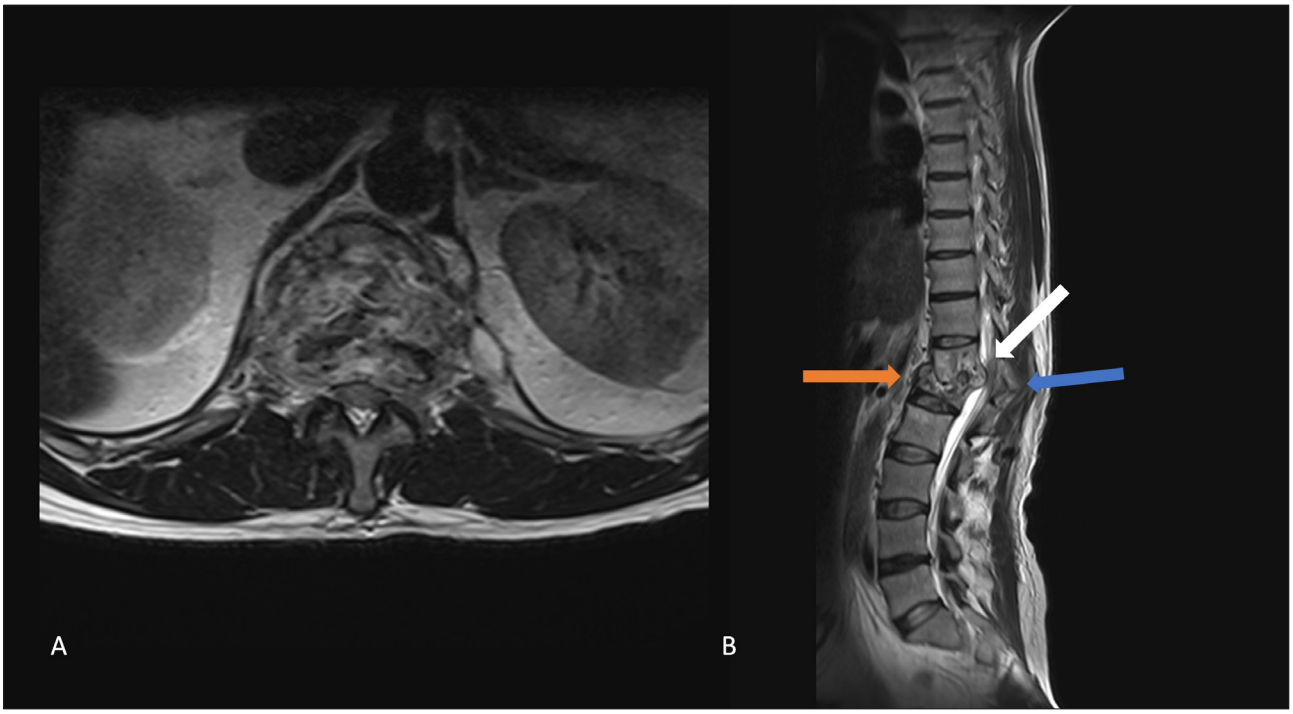

Fig. 1. Magnetic resonance imaging findings suggestive of spinal tuberculosis. T2-weighted image showing typical vertebral collapse of Th12/L1 vertebrae with gibbus formation and central canal stenosis. A: transversal view. B: sagittal view; white arrow = central canal stenosis; orange arrow = vertebral collapse of Th12/L1; blue arrow = gibbus formation.

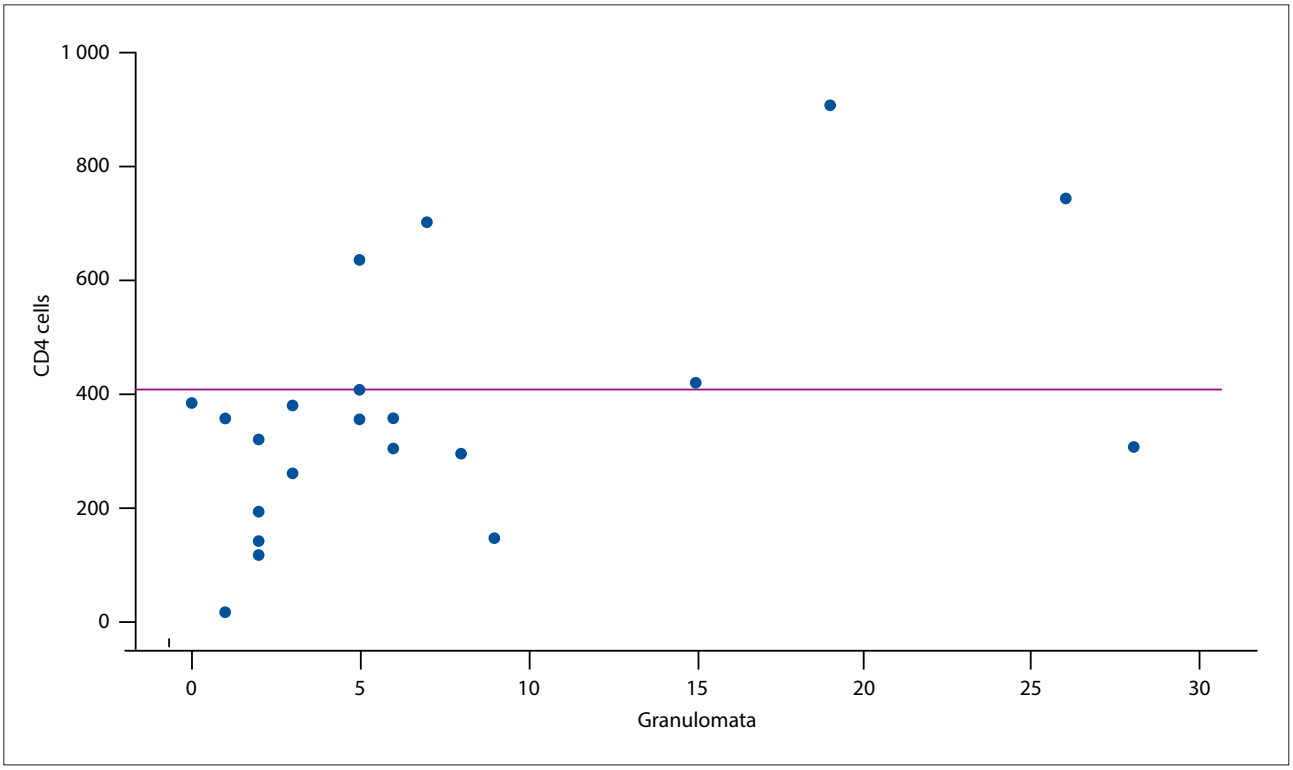

Fig. 2. Scatter plot showing the distribution granuloma count depending on CD4 cell count; purple line = cut-off value (400 CD4 cells/mm³).

the depletion of CD4 cells.[30] We observed a trend towards a decreased grade of inflammation and fewer granulomata in STB^{HIV+}, which seems logical, since inflammation and formation of granulomata is T-cell dependent, and cellular immunoreaction is impaired in patients living with HIV.[45] Our results showed a significant positive correlation between CD4 cell count and the observed number of granulomata at a cut-off of 400 CD4 cells. Several studies have focused on the question of whether CD4 cell counts are affecting TB granuloma formation.[5] To our knowledge, only one study focused on the histopathological features of HIV-infected STB patients, but did not examine the correlation between CD4 cell count and the number of granulomata.[30] An Italian study focusing on pulmonary

TB found a reduction of granuloma count associated with HIV infection, which is consistent with our findings.[46] A study conducted in Zimbabwe investigating pleural TB did not find any significant difference of granuloma formation or count between HIV-infected and uninfected patients.[47] A systematic review conducted in 2016 assessing the interaction of HIV infection and granuloma formation in TB patients revealed no significant change of granuloma formation in HIV-infected TB patients. However, most of the reviewed studies, apart from two, reported slight reduction of granulomata, and only one of the studies showed statistical significance.[48] Therefore, to our knowledge, with this study, we provide evidence of the first significant positive correlation between CD4 count and the number of granulomata in patients with STB and concomitant HIV infection.

Study limitations

Unfortunately, time of HIV diagnosis and time of ART initiation were not recorded, which leaves us unable to explain our findings regarding CD4 cell count and timing of ART initiation. Furthermore, this lack of information does not allow us to understand the dynamics between HIV infection, ART effectiveness and the development of spinal TB. Further, we were not able to assess the duration from spinal infection to tissue sampling. The more frequently seen abscess formation within the STB^{HIV-} could be due to long-existing TB infection before sampling. Another hypothesis is that abscess formation is a result of immunological activation, which is decreased in HIV-infected patients. In addition, we believe that some of our non-significant findings are due to the rather small sample size of our study population. Furthermore, in this retrospective folder analysis, clinical findings were not standardised, and could be biased depending on the degree of rigorous note making of the clinicians. Future studies, including the Spinal TB X cohort that we initiated in 2022, will focus on the mechanism of granuloma and abscess formation, mechanism of bony destruction and spread of the disease, as well as the role of CD4 cells in STB, based on a larger sample size.[49]

Conclusion

In our cohort, HIV-infected patients with STB were more likely to present with vertebral collapse, and had on average more involved vertebrae compared with HIV-uninfected patients. CD4 cell count seems to play a role in STB granuloma formation, and therefore lower CD4 cell counts may affect the spread of the disease to multilevel vertebral disease. Our results confirm the negative effect of HIV infection on the cellular immunoresponse in patients with STB, which emphasises the need for early ART in HIV-infected patients with STB.

Data availability. Data are available from the corresponding author on request.

Declaration. None.

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Author contributions. JS: conceptualisation, initial draft, analysis, editing/rewriting; ML: data curation, editing/rewriting; SC: data curation, editing/rewriting; RD: editing/rewriting; MH: data curation, editing/rewriting; FT: editing/rewriting, supervision.

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Conflicts of interest. None.

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