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The Immunopathogenesis of Tuberculous Pericarditis

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Corresponding Author:	Patrick James Howlett, Mb ChB BSc Imperial College London London, UNITED KINGDOM
First Author:	Patrick James Howlett, Mb ChB BSc
Order of Authors:	Patrick James Howlett, Mb ChB BSc
	Elsa Du Bruyn, Mb ChB
	Hazel Morrison, Mb Chb
	Isiguzo C Godsent, MBBS PhD
	Katalin A Wilkinson
	Mpiko Ntsekhe, Mb ChB PhD
	Robert J Wilkinson, Mb ChB MA PhD FRCP
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Suggested Reviewers:	Maghdi Yacoub Professor m.yacoub@imperial.ac.uk Expert in Pericardial disease
	Daniel Faria danielfaria8@gmail.com
	Andrew Wragg Andrew.wragg2@nhs.net
	Helen Fletcher Helen.Fletcher@lshtm.ac.uk Expert in TB immunology
	Gerhard Walzl gwalzl@sun.ac.za

The Immunopathogenesis of Tuberculous Pericarditis

Patrick Howlett*[a,b], Elsa Du Bruyn[b,c], Hazel Morrison[d], Isiguzo C Godsent[b,e], Katalin A Wilkinson[b,c,e], Mpiko Ntsekhe[b,c], Robert J Wilkinson[b,c,e,g]

a. National Heart & Lung Institute, Imperial College London, Guy Scadding Building, Cale Street, London, SW3 6LY
b. Department of Medicine, University of Cape Town, Observatory 7925, Republic of South Africa
c. Wellcome Centre for Infectious Diseases Research in Africa, Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Observatory 7925, Republic of South Africa
d. The Jenner Institute, University of Oxford, Old Road Campus Research Build, Roosevelt Dr, Oxford OX3 7DQ, United Kingdom
e. Francis Crick Institute, 1 Midland Rd, London NW1 1AT
f. Department of Medicine, Federal Teaching Hospital Abakaliki, Nigeria
g. Department of Infectious Diseases, Imperial College London, W2 1PG, United Kingdom

Corresponding author: Patrick Howlett
National Heart & Lung Institute
Faculty of Medicine
Imperial College London
Guy Scadding Building,
Cale Street, London, SW3 6LY

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Abstract

Tuberculous pericarditis is a severe form of extrapulmonary tuberculosis and is the commonest cause of pericardial effusion in high incidence settings. Mortality ranges between 8-34%, and it is the leading cause of pericardial constriction in Africa and Asia. Current understanding of the disease is based on models derived from studies performed in the 1940-50s. This review summarises recent advances in the histology, microbiology and immunology of tuberculous pericarditis, with special focus on the effect of Human Immunodeficiency Virus (HIV) and the determinants of constriction.

Keywords

Tuberculosis; Pericardial; HIV; Pathogenesis; Immunology; Constriction

1. Background

Tuberculosis (TB) is the leading cause of death from an infectious disease worldwide[1]. The World Health Organization (WHO) estimates that there were 1.3 million TB deaths in Human Immunodeficiency Virus (HIV) uninfected individuals and 300,000 HIV-TB co-infected deaths in 2017. Extrapulmonary TB (EPTB) contributes 15% of the global TB incidence[1] and presents diagnostic and therapeutic challenges. Pericardial involvement is present in 1-2% of TB cases[2]; it is a severe form of extrapulmonary TB and the most common cause of pericardial disease in Africa[3]. In high TB incidence settings, TB accounts for 65% of large pericardial effusions in those who are HIV uninfected [4], rising to over 90% of clinically significant pericardial effusions in HIV infected persons, [5,6]. By contrast, in non-endemic countries, less than 5% of pericarditis occurs as a result of TB[7].

Mortality generally occurs early in the disease [8], and ranges from between 8-17% in those uninfected by HIV, rising up to 34% in HIV co-infected persons[9,10]. Tuberculous pericarditis (TBP) also carries a significant morbidity. Although constriction in those with TBP is relatively rare, it represents the most common cause of constrictive pericarditis in Africa and Asia[11,12]. Drivers of adverse outcomes remain poorly described but may relate to diagnostic delays and uncertainty, high bacillary burden, presentation with cardiac tamponade and poor penetration of anti-mycobacterial drugs into the pericardium, with the risk of progression to constriction remaining high despite standard treatment[13]. Better understanding of the mechanisms underlying the disease is essential to improving both diagnostic and treatment outcomes, in particular to guide the prescription of adjunctive anti-inflammatory therapy.

2. Clinical Presentation

While TBP classically presents with a pericardial effusion, termed ‘effusive’ pericarditis, a broad range of clinical presentations may be observed. Presentation is often insidious, with non-specific symptoms including fever, weight loss, night sweats and fatigue. Cough, dyspnoea and chest pain may become prominent [14]. Clinical signs include tachypnoea, sinus tachycardia, pulsus paradoxus, pericardial rub, muffled heart sounds, raised jugular venous

pulse, increased cardiac dullness, hepatomegaly and ascites[11,14]. 10% of patients present with cardiac tamponade[15], necessitating urgent pericardiocentesis. Up to 50% of patients may present with features of both tamponade (caused by a compressive pericardial effusion) and constrictive physiology (caused by a non-compliant inflamed oedematous visceral pericardium), with venous pressure remaining elevated despite pericardiocentesis. This is termed 'effusive-constrictive' pericarditis[16–19].

In those with TBP who survive beyond the standard period of therapy with antituberculous medication, the natural history of the disease is either "cure" or the development of constrictive pericarditis (CP) in a minority (incidence 3.16-4.75 per 100 patient years.)[8,20]. A subset of patients appear to "skip" the effusive phase TBP and present with evidence of CP[11].

Plain chest radiograph shows an enlarged, globular cardiac shadow in most of those with TBP at presentation. Chest radiographic features of active pulmonary TB are seen in up to 30% and pleural effusions in 40-60%[11]. Echocardiography allows non-invasive confirmation of a pericardial effusion. Fibrinous strands are suggestive but not pathognomonic for TB pericardial effusion[21]. A definitive diagnosis of TBP relies on isolating *Mycobacterium tuberculosis* (Mtb) bacilli from pericardial fluid or tissue samples. Pericardiocentesis, where possible, is indicated in all persons with suspected TBP for diagnostic purposes but may also provide therapeutic benefit in those with large effusions. Those with TBP characteristically have a lymphocyte-rich exudative pericardial effusion with high protein content and raised adenosine deaminase (ADA) levels[11].

Microscopy of pericardial fluid for Mtb has low sensitivity at 0-42%[2,8,13,22–24] compared to composite clinical and culture reference standards. Conventional culture techniques have a sensitivity of between 50 to 65% (see Table 1) compared to clinical reference[7,8,22–27]. Obtaining pericardial tissue increases culture sensitivity rates and is particularly important in non-TB endemic areas. Histological examination may show acid-fast bacilli and granulomatous inflammation (see Table 2). The rapid nucleic acid amplification test, Xpert® MTB/RIF (Xpert), has a diagnostic sensitivity of 66% with a specificity of 96% when compared to culture in TBP[28]. In the absence of microbiological confirmation of Mtb, a diagnosis of probable TBP can be made when pericardial fluid is suggestive (lymphocytic, exudative effusion and a raised ADA), when there is an otherwise unexplained pericardial effusion and

Mtb has been isolated from elsewhere in the body, or where there is a good clinical response to antituberculous treatment[11].

3. Histopathology

Four stages of TB pericarditis have been proposed, based on case series presented in the 1940-50s[29]. An initial 'dry stage' in which patients present with an acute pericarditis syndrome progresses to an 'effusive stage' (the most common at presentation) characterised by a sero-sanguinous pericardial effusion. The effusion then organises in an 'absorptive stage', during which caseous granulation and fibrin deposition occurs to form a thickened pericardium. This is the precursor to the final 'constrictive stage', during which the visceral and parietal pericardium become fibrosed and calcified, leading to the clinical syndrome of constrictive pericarditis. Since it was originally proposed, this model has been widely cited[11,30,31]. However, little has been done to advance the model, most importantly to take into account the effect of HIV. Even at the time it was proposed, limitations were identified; patients can present at any stage, progress at different rates, skip stages, or not progress at all[29].

The spread of Mtb to the pericardium has been proposed as predominantly being through the breakdown of adjacent lymph nodes[32]. Computerized tomography (CT) imaging of the chest detected mediastinal lymphadenopathy (defined as >10 mm) in all of a series of 22 HIV uninfected patients starting treatment for TB pericarditis. Most commonly involved were the aortopulmonary (16 patients), paratracheal (12 patients), pre-tracheal (7 patients) and then hilar nodes (4 patients)[33]. Alternative pathways of pericardial involvement include haematogenous spread, typically thought to occur more commonly in advanced HIV[31] and, less commonly, direct spread from infected pleura[11]. Although there is no direct evidence for haematogenous spread, this hypothesis appears plausible as TB bacteraemia amongst HIV infected adults presenting with features of sepsis ranges between 9%[34] and 43%[35] and is more prevalent at lower CD4 counts[36,37]. A systematic review and meta-analysis of autopsies in HIV infected adults and children found disseminated TB (>1 organ involvement) in 87.9% of deaths; however only one included study reported involvement of the pericardium in a single patient[38]. In a sub study involving 70 consecutive patients with

culture positive pericardial fluid TB, the majority of whom were HIV infected (67%), 17% of the participants had evidence of TB outside of the pericardium[24]. Participant CD4 counts were not provided. A South African autopsy study examined 50 adults with a pre-mortem diagnosis of TB who died during hospital admission. Twelve out of 47 HIV infected cadavers had evidence of pericarditis. Only one of these was reported as confirmed tuberculous pericarditis, with the remainder reported as adhesive or non-specific. However, this was based purely on microscopy and likely significantly underestimated the true prevalence[39].

Histology may be obtained by open surgical procedure or percutaneous pericardial biopsy. Several case studies and series of almost exclusively HIV-uninfected adults and children report the presence of granulomas, with or without the presence of acid fast bacilli (AFB), in those patients biopsied and ultimately diagnosed with TB (see Table 1). The most comprehensive study reporting histological findings on pericardial tissue, obtained via open biopsy, found granuloma in both HIV infected (13/20, 60%) and uninfected participants (2/5, 40%)[40] but it was underpowered to demonstrate significant difference in the yield of histology. A lower prevalence of granulomas in HIV co-infected persons, especially in those with low CD4 counts, was reported in a meta-analysis of granuloma formation in TB across all sampled body sites. The authors found a reduction in quantity of granuloma in those co-infected with HIV, compared to those HIV un-infected (RR: 0.82, 0.65-1.03), and poor quality of granuloma formation, especially in those with CD4+ counts <50 mm^3[41].

4. Microbiology

As previously outlined, the identification of Mtb in pericardial fluid is challenging, with low sensitivity of direct microscopy, PCR, and culture alone when compared to composite (clinical and microbiological) reference standards (see Table 2). There is some debate however regarding whether these difficulties reflect a paucibacillary process or, potentially, do not accurately represent a dynamic continuum of high and low bacterial burden affected by stage of disease and immune response[37,42].

A comprehensive microbiological comparison of sputum and multiple extrapulmonary TB samples has reported that pericardial fluid is relatively paucibacillary, compared to expectorated sputum[24]. The median time to culture positivity (TTCP) using liquid culture medium was significantly lower in expectorated sputum (8 days, IQR 6-13) compared to pericardial fluid (22, IQR 15-32 days). Pericardial fluid TTCP was broadly similar to that of cerebrospinal fluid (21, IQR 18-33 days). On PCR using GeneXpert, the median cycle threshold (Ct) values were significantly lower for expectorated sputum samples (22.4 (IQR 18.1–28.4)than pericardial fluid (28.6 (IQR 26.1–31.2)), consistent with a greater mycobacterial load in sputum. In a univariate analysis, no association was found between HIV status and TTCP in pericardial fluid samples[24]. No difference was found in TTCP or Ct value of pericardial fluid of HIV positive participants in those with CD4+ >200 cells/μl, compared to those with CD4+ counts ≤200 cells/μl. However, it should be noted that only patients who were culture positive to begin with were included in the substudy, thus not excluding the likelihood of an association between HIV status, CD4 cell depletion and culture positivity.

A further microbiological study of participants from the Investigation of the Management of Pericarditis (IMPI) study registry used two previously described methods of converting TTCP to a standard measure of bacterial load – the number of colony forming units/ml (CFU/ml) – in 70 pericardial fluid compared to 18 sputum samples. The first model did not take treatment duration into account, while the second did (assumed 3 days completed). Using the first model, the authors found TTCP to be shorter (12 vs 22 days), and the bacillary burden significantly higher (mean difference 2.22 ± 0.34 $\log_{10}$CFU, $p<0.001$) in sputum samples versus pericardial fluid samples. When initiation of treatment was accounted for, the median bacillary load in pericardial fluid was reported to be greater than sputum[13]. There are several methodological concerns in this study including the low number of sputum samples used for comparative analysis, the assumptions used in the second modelling method of timing to initiation of treatment, and incomplete presentation of results. While ATT initiation rapidly reduces bacterial load in sputum, with the greatest reduction in the first three days[43] preliminary evidence suggests that the penetration of the key sterilizing ATT in the pericardium is poor and that rapid reduction in bacterial load may not occur.

Despite the possibility of a larger mycobacterial load than previously suspected, it is likely that pericardial fluid is relatively paucibacillary when compared to sputum. However bacterial load remains significant and importantly is a determinant of mortality[13]. In a similar fashion to pleural TB, in which pleural biopsy improves diagnostic yield over pleural fluid sampling[44,45], the pericardium may be a richer source of Mtb than the accompanying fluid, as identified in the only study which routinely compared the two sites[26].

5. Immunology

5.1. Innate immune response

Neutrophils are important mediators of the innate immune response to Mtb, with a neutrophil-driven interferon-inducible transcriptional signature characterising active pulmonary TB from latent TB and other diseases[46]. Their role appears to change during the disease course. While they may be protective during early infection[47], higher neutrophil counts in blood during disease are associated with higher sputum bacillary load[48] and worse outcome[49]. Higher numbers in blood and bronchoalveolar lavage fluid (BALF) are associated with greater lung damage[50,51].

A recent transcriptomic analysis of HIV-infected and HIV-uninfected individuals with TBP found significant co-expression of neutrophil associated genes in pericardial fluid, with evidence of a degree of congruence in measured proteins[52]. Significantly greater transcript abundance of the neutrophil chemotactic factor interleukin 8 (IL-8) and cathelicidin antimicrobial peptide (CAMP) gene products were demonstrated in pericardial fluid compared to blood, with significantly higher IL-8 concentration being demonstrated at the protein level. Neutrophils are efficient producers of cathelicidin in response to Mtb infection, and it is thought that this antimicrobial peptide may have a role to play in the early immune response to Mtb[53]. Cathelicidin's roles are broad and complex with both pro- and anti-inflammatory properties dependent on concentrations and presence of other factors. At high concentrations common in infection, they have been found to induce IL-1β[54]. Furthermore, elevated peripheral blood neutrophil counts are shown to be an independent predictor of mortality in a study including pulmonary (49%) and extrapulmonary TB patients (51%)[49].

Overall peripheral blood neutrophil counts are lower in TB versus non-TB effusions. In tuberculous effusions, peripheral blood absolute neutrophils counts are lower in HIV infected compared to non-infected individuals although frequency (%) is similar[22,55]. In tuberculous effusions compared to effusion of non-TB origin, pericardial fluid is lymphocyte predominant[22,42] whereas neutrophil predominant effusions are more likely to point towards an aetiology other than TB. In HIV-infected individuals the frequency of neutrophils in pericardial fluid appears slightly higher than in non-HIV infected individuals (HIV- 28.4%, SD 22.5% vs. HIV+ 35.9%, SD 29.2%), however despite marked depletion of the CD4+ T cell subset in these individuals their effusions remain lymphocyte dominated[22]. Pericardial fluid monocyte counts appear similar between tuberculous and non-tuberculous effusions, and HIV and non-HIV infected individuals[22]. Although fibroblasts have been implicated in the pathology behind radiation induced pericardial fibrosis, and pericardial manifestations of systemic sclerosis, no direct links have been made in tuberculous pericarditis, although raised mRNA collagen transcripts have been reported [52,56].

Overall, further study is required to elucidate whether neutrophils are a correlate of bacillary load in the pericardium and hence severity of disease, and/or whether their early active participation in the immune response is required for immune mediated Mtb clearance.

5.2. Adaptive immune response

5.2.1. The role of Interferon Gamma (IFN-γ) and other pro-inflammatory mediators

CD4+ T cells and in particular a functional Th1 response characterized by IFN-γ production is required for control of Mtb infection[57]. This is supported by the fact that the aforementioned transcriptomic TB signature was dominated by both IFN-γ and type I IFN-αβ signalling[46], thus adding to the knowledge that IFN-γ is an important component of the immune response to Mtb[46,58]. There is however also evidence that excessive amounts of IFN-γ can be detrimental in Mtb infection[59,60] and that IFN-γ independent pathways of CD4 T cell mediated Mtb control exists[61,62].

Unstimulated pericardial fluid from TBP patients has a higher IFN-γ concentration than that of non-TB pericarditis patients and as such has been suggested as a diagnostic tool [22,42]. However, despite its excellent sensitivity (95.7%, 95% CI 88.1 to 98.5) and specificity (96.3%, 95% CI 81.7 to 99.3), and superior accuracy for the diagnosis of microbiologically confirmed TBP compared to the ADA assay and the Xpert MTB/RIF test, financial and technical constraints have thus far limited its widespread use[23]. It remains to be seen whether higher IFN-γ concentration in pericardial fluid is associated with higher bacterial load and adverse clinical outcome in those with TBP.

Stimulation with Mtb specific antigens led to similar increases in IFN-γ concentrations in pericardial fluid of both HIV-infected and HIV-uninfected patients with TBP[42]. Although the source of IFN-γ has been presumed to originate from a mixture of natural killer (NK), CD4+ and CD8+ cells, a recent transcriptomic analysis has found that the corresponding pericardial fluid mRNA for IFN- γ was reduced by comparison with blood. The authors also found that a corresponding mRNA signature did not reflect raised protein concentrations of IL-1β[52]. They hypothesised that this difference may be the result of differentiated antigen-specific T cells that enter the pericardium, release IFN-γ and die, thus possibly activating the inflammasome pathway, leading to pyroptosis and the release of IL-1β. To investigate this hypothesis, the authors compared cell death enrichment factors in pericardial fluid from TBP patients to that of asymptomatic individuals undergoing cardiac surgery and found significantly increased concentrations of cytoplasmic histone-associated DNA fragments (mono- and oligonucleosides) in those with TBP[52].

Providing further support for compartmentalized, inflammation-induced pyroptosis in the pericardial fluid, a more recent study found that prednisolone treatment – an adjunctive medication to TB therapy in TBP shown to reduce mortality in HIV uninfected participants in a randomised controlled trial[8] – is associated with a trend toward lower concentration of inflammatory mediators: IL-1β concentrations were reduced in saliva fluid by 24 hours of treatment, IL-8 concentrations were reduced in saliva and pericardial fluid by 24 hours treatment, and IL-6 concentration reduced in plasma by 8 hours of treatment[63]. Both of these studies involving pericardial fluid are limited by small sample sizes, which in particular impair the ability to compare responses in HIV infected and uninfected individuals. This would

be of interest given the suggestion of reduced granuloma formation and constriction in HIV-infected individuals with TBP[16,40] and theoretical basis for reduced regulation of fibrogenesis as fewer IL-13 secreting CD4 T cells are present[64]. The pro-inflammatory cytokine IL-1β is associated with a greater extent of lung involvement in pulmonary TB[65], fibroblast activation[66], recruitment of neutrophils[67], and activation of matrix metalloproteinases (MMPs)[68,69].

Interleukin-22 (IL-22) is produced by cells from both the innate (innate lymphoid and NK cells) and adaptive immune system (Th1, Th17 and Th22) and binds to its receptor, IL-22R1, expressed on epithelial and stromal cells. IL-22 may play a protective role in TB through its induction of epithelial cell healing and stimulation of antimicrobial peptide production[70–72]. Evidence from animal models indicates that IL-22R1 is upregulated by Mtb infected macrophages and that IL-22 can reduce Mtb growth by the increased expression of antimicrobial peptides such as calgranulin A[73–76]. Human studies have found significantly higher frequencies of Mtb-specific IL-22 producing CD4+ T cells and soluble IL-22 in serum in persons with latent TB infection when compared to active TB disease[77–79]. Elevated IL-22 concentration is found in BALF and pleural fluid of patients with TB [80–82]. Soluble levels of IL-22 are higher in pericardial fluid of those with TBP than matched serum samples, and higher than serum samples from healthy controls in whom IL-22 is largely undetectable. In the same study, pericardial fluid samples from participants with TBP also had higher IL-22 concentrations than pleural fluid samples from those with no pericardial involvement ([83]). It is thought that the higher concentration of IL-22 found at the site of disease reflects the migration of IL-22 producing Mtb-specific cells to the site of infection. IL-22 concentration in serum and pericardial fluid correlated positively with matrix metallopeptidase 9 (MMP-9) blood levels. MMP-9 has been implicated in macrophage recruitment and hence development of well organised granulomas at disease site, extracellular matrix remodelling, and maintenance of mucosal barrier integrity in the gut and lung[84–87]. The correlation between IL-22 with MMP-9 concentrations in pericardial fluid and blood suggest that increased IL-22 at the TB disease site may be involved in the healing/regeneration response, rather than an anti-microbial response[83]. IL-22 is a regulator of keratinocyte mobility, epidermal differentiation and wound healing, while the success of Mtb as pathogen is partially dependent on its destruction of the extracellular matrix, a process mediated by

MMPs. While MMP generation is generally tightly regulated[88], neutrophils are the only source of stored MMPs, specifically MMP-8 and -9, without synthesising tissue inhibitors of metalloproteinases (TIMPs), allowing for the unrestrained effect of MMPs[89].

5.2.2. N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP)

Ac-SDKP is an immunomodulatory and angiogenic peptide associated with reduced cardiac fibrosis and inflammation in animal models[90]. In rat models, Ac-SDKP inhibited IL-1β mediated MMP-2 and -9 activation, also increasing the activity of TIMP-1 and TIMP-2[91]. Depressed levels of Ac-SDKP were found in pericardial fluid of patients with TB, compared to healthy controls undergoing coronary artery bypass surgery. Some of the protective anti-inflammatory[92]) and anti-fibrotic[93] effects of ACE-inhibitor treatment in humans are mechanistically linked to increased Ac-SDKP concentrations, observed during ACE inhibitor treatment[90]. Angiotensin converting enzyme (ACE) is raised in miliary tuberculosis[94]. On a population scale, there is evidence to suggest ACE inhibitors are associated with a reduced risk of tuberculosis, however the mechanism is unclear across all studies ages and subgroups[95]. This raises the potential use of ACE inhibitors as a possible therapy to prevent fibrosis and constriction in patients with pericardial TB, once the acute cardiac compressive effects of the effusion have been dealt with.

5.2.3. T cell response and HIV infection

One comprehensive study of the T cell response to Mtb in TBP has investigated the functionality and phenotype of T cells in pericardial fluid and blood, in HIV infected and uninfected individuals[42]. The authors reported a higher frequency of Mtb antigen ESAT-6 specific IFN-γ producing T cells in the pericardial fluid of HIV uninfected individuals. The authors also found a trend towards lower numbers of antigen-specific T cells at the disease site in HIV-1-infected patients, together with lower concentrations of secreted IFN- γ, suggesting that HIV-1 decreases the T-cell responses at the site of disease. Investigation by multicolour flow cytometry indicated that CD4 T cells were the predominant lymphocytes found in the pericardial fluid of HIV uninfected individuals, whereas CD8 T cells predominated in HIV coinfected individuals. This difference could be explained by preferential depletion of

CCR5+ memory T cells, which were found at significantly higher frequency in pericardial fluid of HIV uninfected individuals when compared to HIV infected individuals (see Figure 1.). The CCR5 receptor, in addition to the CD4 receptor, is used by CCR5-tropic HIV strains to gain cellular entry and its presence on cells in HIV/TB co-infected participants may explain the elimination of these cells by HIV mediated killing[96]. HIV viral load was increased in pericardial fluid, and CD4+ memory T cells from pericardial fluid of HIV-1 infected patients were of a less differentiated phenotype (CD4+CD28-CD45RA-). There was a significant negative correlation between viral load and the predominant (less differentiated) memory T cell subset (CD4+CD28-CD45RA-). CD4+ cells in HIV infected individuals also exhibited a more polyfunctional cytokine expression (TNF, IL-2 and IFN-γ) than HIV uninfected participants, consistent with a less differentiated CD4 T cell response. This observation in HIV infected persons is supported by BALF studies showing a similar depletion of polyfunctional Mtb-specific CD4 T cells[97,98]. The less differentiated CD4+ T cell phenotype found in the HIV coinfected individuals may be less efficient to contain *Mtb* replication[42].

5.3. The immunology of pericardial constriction

Given the histological and immunological differences already described, a difference in pathogenesis and potentially rates of constriction according to HIV and degree of immunosuppression may be expected. This view is supported by one small prospective observational study that found, in a multivariable model, clinical features of HIV infection at presentation were associated with reduced odds of constriction at either 3 or 6 months follow-up (0.14, 95% CI 0.02–0.87, P = 0.035)[99]. Although of clinical interest, this study was limited by few participants consenting to HIV serological testing (55%) and the absence of echocardiography data to confirm clinically diagnosed constriction.

A further study used the gold standard diagnosis of effusive-constrictive pericarditis (ECP) by performing right heart catheterisation in persons presenting with definite or probable TB and examining the immunological profile of the pericardial fluid[16]. In contrast to the previously reported study on the determinants of constriction[99], the primary outcome in this study was the presence of ECP at the time of presentation with TBP as opposed to the development of constriction over time. The authors found that, in a multivariable model, HIV-infection was

not associated with the presence of ECP, however a right atrial pressure > 15 mmHg (OR 48, 95%CI: 8.7-265; P<0.0001) and serum IL-10 > 200 pg/ml (OR 10, 95%CI: 1.1-93; P=0.04) were associated with ECP. Univariate analysis found that patients with ECP were significantly younger (29.0 yrs, 95% CI 26.0-34.5 vs 37.0 ys 95% 29.0-53.0) and had raised TGF-β blood concentration. TGF-β was absent in the pericardial fluid of both groups. Both groups had raised IFN-γ concentrations in pericardial fluid but this was higher in the group with ECP. The study reports significantly higher rates of ECP (52.9%, 95% CI 41.2-65.4) compared to previously reported rates of between 2-14.8%[8,100]. However, follow-up data was not available to identify in which patients the initial findings of ECP translate to long-term clinical evidence of constriction. The paper raises questions regarding the presence and role of IL-10 as an early signal of fibrosis in those with evidence of constrictive physiology at presentation[101,102]. Longer term outcomes of those identified with ECP could help further describe the role of IL-10 in the development of fibrosis and ultimately constriction. Finally, and giving indirect support to the hypothesis the constrictive immunopathology may not differ by HIV status, the limited transcriptomic signature of pericardial fluid previously described did not differ according to HIV status[52].

6. Management

Pericardial fluid concentrations of 3 of the 4 standard drugs used to treat PTB (rifampicin, pyrazinamide and ethambutol) are well below the minimum inhibitory concentration (MIC) of typical clinical *Mtb* isolates and may contribute to higher bacillary load and poor outcomes[13]. A thickened pericardium due to significant fibrosis or, particularly given the rapid clearance of rifampicin from the pericardial fluid, efflux mechanisms may contribute to lower concentrations[103]. There has long been debate about the merits of adjunctive corticosteroids in TBP. A recent large randomised controlled trial in African patients with TBP showed no improvement in the composite primary endpoint of death, cardiac tamponade or constrictive pericarditis with prednisolone versus placebo. It did show decreased rates of pericardial constriction with prednisolone but also significantly increased rates of cancer in HIV co-infected persons[8]; adjunctive corticosteroids are currently recommended in HIV uninfected patients with TBP[104]. The same trial evaluated the use of *M Pranii* as an immunomodulator adjunct and found this also resulted in no significant difference in the

same composite primary endpoint compared to placebo. Increased rates of cancer, in particular HIV-related cancer, were also seen in the *M Pranii* arm compared to placebo[8]. Increased rates of HIV-related cancers may be reduced with more widespread antiretroviral treatment (ART) coverage than was available at the time of this study.

The use of intra-pericardial fibrinolytics has been reviewed, finding a low certainty of evidence for efficacy and safety ([105]). Theoretical benefits include improved evacuation of pericardial fluid by breaking down fibrin strands and loculations, in turn augmenting removal of inflammatory mediators and potentiating the penetration of antituberculous drugs. Their use is currently under study in the second investigation of the management of pericarditis (IMPI-2) trial https://clinicaltrials.gov/ct2/show/NCT02673879).

7. Conclusions

Despite being a severe form of tuberculosis, we have a limited understanding of the immunopathology of TB pericarditis. The four-stage model of pathogenesis, while developed through years of experience with patients with TBP, predates the arrival of HIV and is therefore relatively simplistic. In the development of new models, two main outcomes of clinical concern exist; mortality and constriction. Mortality is associated with HIV coinfection and with a higher Mtb bacillary load, which are mechanistically linked (see Figure 1). The exact mechanisms of mortality however are not well described but likely related to haemodynamic compromise due to cardiac tamponade and inadequately treated mycobacterial infection due to low drug concentration. Future intervention trials should focus on alternative mycobactericidal regimes with greater pericardial penetration or higher doses of rifampicin. Diagnostics remains a challenge, however newer high sensitivity lipoarabinomannan based testing[106] on pericardial samples may represent a cost-effective approach, especially in HIV infected individuals in whom mortality is highest. Constriction represents a more challenging target. On the basis of this review, we propose a potential model (see Figure 2) in a which a compartmentalised response leads to pericardial fibrosis that may be tested in further studies. Steroids have been shown to be effective in HIV uninfected populations, and with the more widespread use of ART, re-examining their use in HIV infected patients may be beneficial. Low dose ACE inhibitors represent a potential therapeutic option, for use following

the acute illness when hypotension would not permit administration. Improved mycobactericidal regimes may lead to reduced constriction through reduced antigen load and subsequent inflammation.

Conflict of interest: The authors have no conflict of interest to declare.

Figure 1. Compartmentalised response of HIV in Mtb infection of pericardium, leading to impaired T cell response

Mtb antigen promotes an influx of MTb specific CD4 T cells into the pericardium. These cells express CCR5 that allows homing of antigen specific cells to disease sites. HIV gains access to these cells via the CCR5 receptor and induces apoptosis, leading to reduced frequency of CD4 T cells. This results in a less differentiated, more polyfunctional CD4 T cell response at the disease site. There is further release of HIV during apoptosis, leading to increased viral load in the pericardial space.

Figure 2. Proposed mechanism of pericardial constriction and therapeutic targets

1. Pericardial Mtb infection from either breakdown of lymph nodes or haematogenous spread from visceral and parietal pericardium.
2. Macrophage phagocytosis of Mtb antigen complexes promotes recruitment of Mtb specific CD4/CD8 cells, and further macrophage recruitment.
3. Mtb specific CD4 T cell secrete IFN-γ and produce IL-10. Natural killer cells contribute to the production of IFN-γ.
4. Macrophages produce IL-8.
5. Increased IL-8 promotes neutrophil chemotaxis.
6. IFN-γ promotes the recruitment of neutrophils. Increased IFN-γ is linked with increased IL-1β through a process of cell death and IL1β release. IL-10 is linked with constriction, however a pathway is unclear.
7. Increased numbers of neutrophils contribute to the production of IFN-γ. Neutrophils are the only store of MMP-9 that is unable to synthesise tissue inhibitors of metalloproteinases (TIMPs).
8. IL-1β has been linked to increased MMP activation. IL-1β has also been linked to increased neutrophil recruitment and fibroblast activation in tuberculosis outside the pericardium.
9. *Mtb* is partially dependent on MMP associated extracellular matrix destriction; MMP-9 is associated with extracellular remodelling.
10. Reduced Ac-SDKP is linked with increased IL-1β. Angiotensin converting enzyme breaks down Ac-SDKP. Increased ACE levels are reported in military tuberculosis.

11. Both IL-1β mediated fibroblast activation and MMP-9 mediated extracellular remodelling contribute to increased pericardial fibrosis.
12. Steroid administration is linked to reduced IL-8 in pericardial fluid and IL-1β in saliva.
13. ACE-inhibitors reduce angiotensin converting enzyme, therefore reducing the breakdown of Ac-SDKP.
14. IL-22 is produced by both the adaptive and innate immune system and its function is upregulated by *Mtb* infected macrophages. It is a regulator of keratinocyte mobility, epidermal differentiation and wound healing, and it thought to be involved in the regeneration and healing response to *Mtb*.
15. Compartmentalised response to HIV. Resulting in; fewer CD4 T cells, reduced differentiation of CD4 T cells and less polyfunctional cytokine expression. How HIV infection may alter the mechanism and incidence of fibrosis is unclear.

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Figure 1

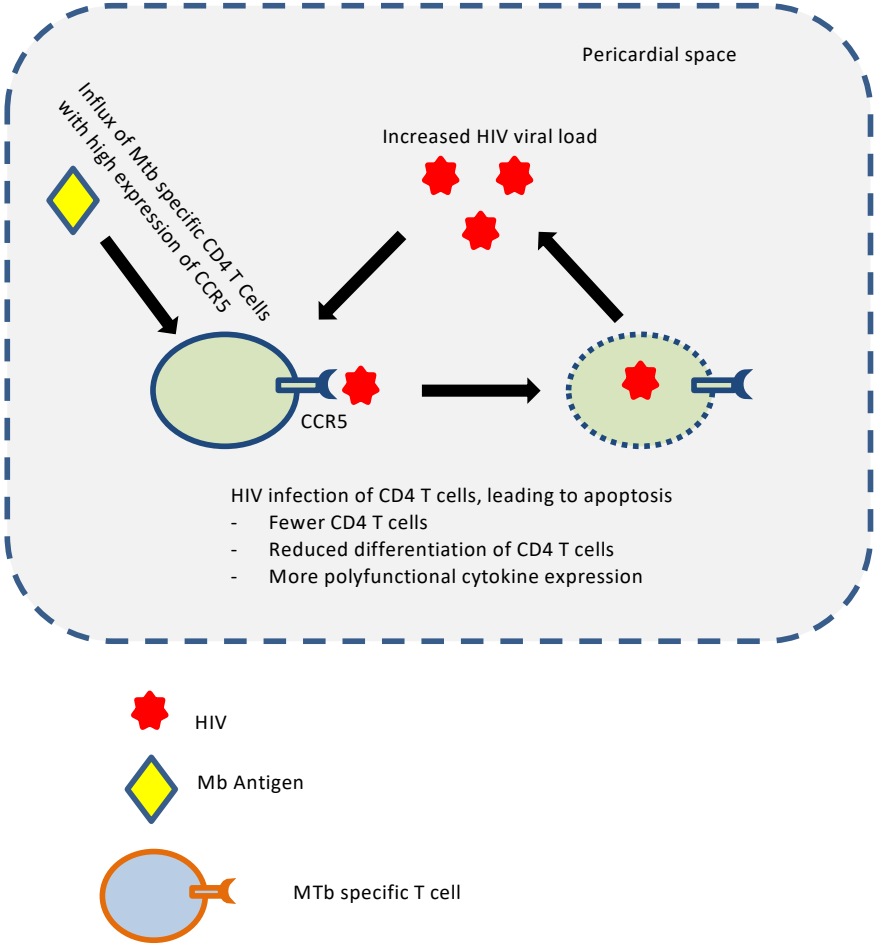
Pericardial space
Influx of Mtb specific CD4 T Cells with high expression of CCR5
Increased HIV viral load
CCR5
HIV infection of CD4 T cells, leading to apoptosis
- Fewer CD4 T cells
- Reduced differentiation of CD4 T cells
- More polyfunctional cytokine expression
HIV
Mb Antigen
MTb specific T cell

Figure 2

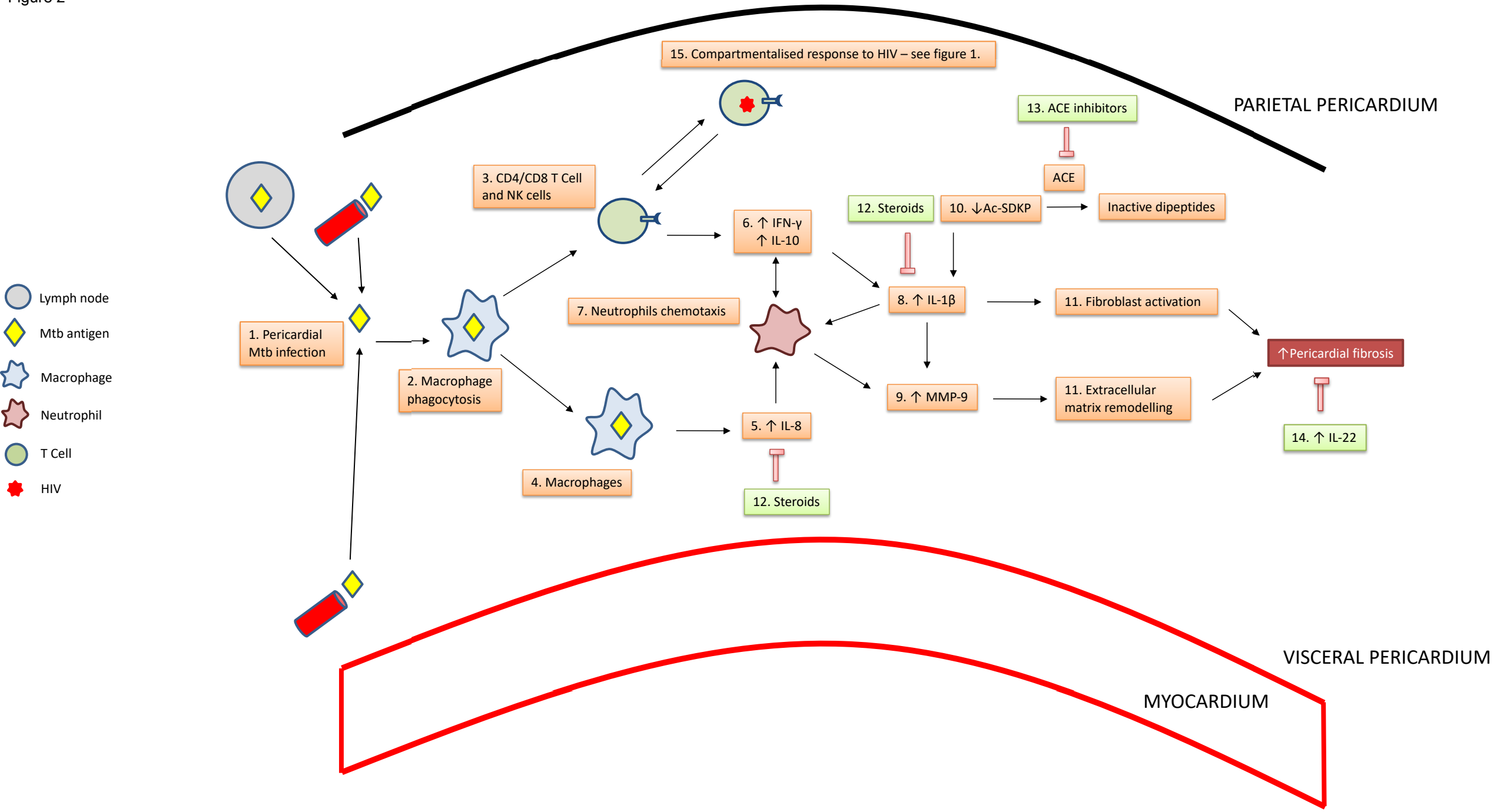
15. Compartmentalised response to HIV – see figure 1.
PARIETAL PERICARDIUM
13. ACE inhibitors
ACE
3. CD4/CD8 T Cell and NK cells
12. Steroids
10. ↓Ac-SDKP
Inactive dipeptides
6. ↑ IFN-γ ↑ IL-10
7. Neutrophils chemotaxis
8. ↑ IL-1β
11. Fibroblast activation
1. Pericardial Mtb infection
2. Macrophage phagocytosis
9. ↑ MMP-9
11. Extracellular matrix remodelling
↑Pericardial fibrosis
5. ↑ IL-8
14. ↑ IL-22
4. Macrophages
12. Steroids
VISCERAL PERICARDIUM
MYOCARDIUM
Lymph node
Mtb antigen
Macrophage
Neutrophil
T Cell
HIV

Table 1

Study	Number of patients in study biopsied	HIV-uninfected/Unknown	HIV positive	Pericardial fluid microbiology findings
Fowler 1991[1]	3/19	1/3 AFB+ 1/3 Culture 1/3 Granuloma	NA	Unclear
Ceglieski 1997 [2]	15/19	13/15 Granuloma	NA	PCR 12/15 (80%) Liquid media 8/15 (53%) Solid media 14/15 (93%)
Quale 1987 [3]	11/17	8/11 Granuloma or AFB	NA	NA
Uthaman 1997[a][4]	7/19	7/7 granuloma 5/7 +ve culture 4 /7+ve AFB	NA	Paediatric series. Fluid positive culture in 2/7 with granuloma
Cherian 2004[5]	18/19 (1 pleural biopsy)	16/18 granuloma 8/18 AFB	NA	1 further pt granuloma negative, fluid +ve culture 1 nonspecific
Trautner 2001[6]	9/10 (1 pericardial fluid sample)	5/7 granuloma - 2/5 AFB+ 1/7 chronic inflammation/fibrosis - 1/1 AFB+	2/2 granuloma - 1/2 chronic inflammation (CD4+ 272 cells/mm^3) No AFB+	Fluid culture +ve 6/10 (3 HIV+/ 3 HIV-)
Reuter 2006[7]	25/25 biopsies	13/20 Granuloma - 4/13 necrotising and AFB+ - 7/13 necrotising and AFB- - 2/13 non-necrotising 2/20 Fibrotic 5/20 Serofibrinous	2/5 Granuloma - 1/2 Necrotising AFB- (CD4+ >200 cells/mm^3) - 1/2 Non-necrotising (CD4+ >200 cells/mm^3) 1/5 Serofibrinous (CD4+ >200 cells/mm^3) 1/5 Purulent and AFB+ (CD4+ 39 cells/mm^3) 1/5 Serous (CD4+ 44 cells/mm^3)	Not reported

Table 1. Histology characteristics of TB pericarditis

[a] Patient age range 2-20 years

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Table 2

Study (n)	AFB smear microscopy Sensitivity	GeneXpert/PCR Sensitivity	GeneXpert/PCR Specificity	Culture Sensitivity	Notes
Fowler 1973, n=13 [1]	HIV unknown 5/12 (41.6%)	-	-	-	Reporting of culture results not clear
Trautner 2001, n=9 [2]	-	-	-	HIV- 3/6 (50%) HIV+ 3/3 (100%)	Not stated AFB performed. Single PCR positive reported
Sagrista 1988, n=13 [3]	-	-	-	HIV- 4/11 (36%)	-
Ceglieski 1997 n=19 [4]	-	HIV unknown 2/13 (15%)	HIV unknown 3/3 (100%)	HIV unknown Liquid media 15/28 (54%) Solid media 13/28 (46%)	PCR of histology sample PCR Sens 12/15 (80%) Spec 3/4 (75%) AFB and GeneXpert compared against culture reference standard
Reuter 2006 n=162 [5]	HIV unknown 3/118 (2.5%)	HIV unknown 10/33 (30%)	HIV unknown 15/15 (100%)	HIV unknown 91/118 (77%)	Total of 162 cases in series. 32 identified from sputum, 16 positive pericardial biopsy. 16 positive culture/histology other body site. AFB and GeneXpert compared against culture reference standard
Mayosi 2006 n=185 [6]	HIV- 4/33 (12%) HIV+ 3/20 (13%)	-	-	HIV- 4/10 (40%) HIV+ 3/7 (43%)	Large series 185 patients – few with reported diagnostics. Clinical diagnosis of HIV used
Pandie 2014 n=74 [7]	HIV unknown 1/74 (1.3%)	HIV- 3/14 (21%) HIV+ 41/55 (75%)	HIV+ 13/13 (100%) HIV+ 5/5 (100%)	HIV unknown 49/74 (66%)	Total of 74 cases in series – all had PC fluid sent.
Theron 2014, n=85 [8]	HIV unknown 1/46 (0.2%)	HIV unknown 27/46 (59%)	HIV unknown 61/85 (72%)	HIV unknown 46/131 (35%)	AFB and GeneXpert compared against culture reference standard
Mayosi 2014, n= 1400 [9]	HIV unknown 23/1377 (1.6%)	-	-	228/1172 (16%)	Reported from in IMPI randomized controlled trial

Table 2. Sensitivity and specificity of acid fast bacilli (AFB) stain, GeneXpert and polymerase chain reaction (PCR) and culture against composite (clinical and microbiological) reference standards for TB pericarditis diagnosis unless otherwise specified. Notes: AFB, Genexpert, Histology – sensitivity and specificity compared to TB culture. TB culture results liquid media unless otherwise specified. Where HIV status not known, reported in table as “HIV unknown”.

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