Host-directed therapy in diabetes and tuberculosis comorbidity, towards global TB elimination

Steven G Smith , Ruth Bowness , Jacqueline M. Cliff

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Highlights

- Host-directed therapy could enhance TB treatment outcomes and reduce post-TB lung morbidity
- People with type 2 diabetes are more susceptible to TB disease and to poor TB treatment outcomes, and stand to benefit even more from host-directed therapy
- Treatments should be aimed at reducing the excessive inflammatory response whilst maintaining effective immunity

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Steven G, Smith,[1] Ruth Bowness[2] and Jacqueline M. Cliff[1]

[1]Centre for Inflammation Research and Translational Medicine, Department of Biosciences, Brunel University of London, United Kingdom

[2]Centre for Mathematical Biology, Department of Mathematical Sciences, University of Bath, Bath, BA2 7AY, United Kingdom

Corresponding Author: Dr Jackie Cliff, Centre for Inflammation Research and Translational Medicine, Department of Biosciences, Brunel University of London, Kingston Lane, Uxbridge, Middlesex, UB8 3PH. jacqueline.cliff@brunel.ac.uk

Abstract

Host-directed therapy could potentially revolutionise tuberculosis control, as adjunct to traditional antibiotics for the treatment of tuberculosis disease, and as a strategy to prevent disease progression following *Mycobacterium tuberculosis* infection. The growing type 2 diabetes pandemic is hampering tuberculosis control worldwide, as people with diabetes have an increased risk of developing tuberculosis disease as well as worse treatment outcomes. Pulmonary tuberculosis is characterised by an inflammatory response which can cause alveolar tissue destruction and cavitation, and this inflammation is exacerbated in people with tuberculosis-diabetes comorbidity. Thus, the reduction of the inflammatory response is a key goal of host-directed therapy to dampen immunopathology, but it is vital that the inflammatory response is not suppressed too much or the immune system will not be able to react to *Mycobacterium tuberculosis* and mycobacterial replication will intensify. Furthermore, the type I interferon response and host cell metabolism are further dysregulated in tuberculosis-diabetes comorbidity, likely contributing to poor treatment outcomes. Achieving the right balance in terms of modulating the inflammatory and immune responses, both quantitatively and temporally, is more complex in tuberculosis-diabetes comorbidity and this population should be included specifically in clinical trials of new regimen. In this regard, mathematical modelling has a key role in elucidating which biological pathways should be targeted in different people. Host-directed therapy for people with tuberculosis-diabetes comorbidity will reduce immunopathology and post-tuberculosis lung disease, as well as boost microbiological cure and treatment outcomes, and thus help in the fight towards global tuberculosis elimination.

Introduction

The global effort to control and eliminate tuberculosis (TB) is being substantially thwarted by the rising type 2 diabetes mellitus (T2DM) pandemic. Of the approximately 10 million people who fell ill with TB in 2023, almost 400,000 cases were attributable to diabetes [1], the majority of whom had T2DM. An estimated 537 million people worldwide currently have diabetes, and this is anticipated to rise to 783 million by 2045 [2], with the greatest rises predicted in sub-Saharan Africa (SSA) and Asia, geographically overlapping with countries with the highest TB prevalence. Both TB and T2DM are more prevalent in rapidly urbanised areas and are driven by socioeconomic factors. People with T2DM are more likely to be infected with *Mycobacterium tuberculosis (Mtb)* and ~3 times more likely to develop TB disease [3]: pre-diabetes also confers susceptibility. In some parts of Southern Africa over 50% TB patients are HIV-positive, which greatly increases the risk of TB disease: the rising T2DM prevalence in SSA means growing overlap between all three conditions, compounding TB control challenges [4]. Current treatment for drug-sensitive TB disease is based on 6-month combination therapy with four antibiotics (isoniazid, rifampicin, pyrazinamide and ethambutol), with an overall success rate of ~85% worldwide in terms of microbiological cure. However, there are long-term sequelae post-TB including lung scarring and reduced respiratory capacity, and TB survivors have greater all-cause mortality. Lung pathology in severe pulmonary TB is largely due to excessive inflammatory host responses, aimed at eliminating *Mtb* bacilli but causing damage to the lung architecture including necrosis, cavitation and fibrosis. People who are comorbid with TB and T2DM (TB-DM) are more likely to fail TB treatment or suffer TB-relapse after treatment completion [5], likely partly due to altered TB drug pharmacokinetics including reduced or delayed rifampicin plasma concentration [6, 7], while drug-drug interactions, such as rifampicin-induced liver cytochrome P450 metabolism of oral diabetes medications enhances hyperglycaemia [8]. Furthermore, the inflammatory immune response is exaggerated in TB-DM causing more extensive pulmonary cavitation [9] with more lower lobe involvement, and increased

haemoptysis and fever [10]. Hypertension is also linked with increased TB risk, possibly via impaired lung endothelial function.

Progress towards the WHO's End TB strategy targets of 95% reduction in TB deaths and 90% reduction in TB incidence rate by 2035 from the 2015 baseline has been slow, and better tools including better treatments are required if TB is going to be eliminated globally. Traditional TB treatments focus on killing *Mtb* bacilli, but the global rise of drug-resistant TB, with approximately 400,000 rifampicin-resistant or multidrug-resistant cases in 2023 underscores the need for novel therapeutic approaches . Resistance to second- and third-line TB regimens such as linezolid, bedaquiline, and delaminid has already been reported. Drug-resistance, especially to first-line drugs, occurs more frequently in people with TB-DM [11-13], necessitating strategies that go beyond antibiotics. In this context, host-directed therapy (HDT) has emerged as a promising alternative, aiming to modulate the host immune response to *Mtb***.** Current HDT strategies and opportunities have been extensively reviewed [14, 15], with proposed treatments mainly aimed at the reduction of inflammation. In considering HDT, the right balance must be struck between an effective pro-inflammatory response which enables robust anti-*Mtb* immunity and microbial killing and the reduction of chronic pathological inflammation. In this regard, the perturbed responses in people with TB-DM relative to uncomplicated TB should be considered: hence this review is focused on implications of HDT for the TB-DM population (Figure 1).

Immunological perturbation in TB-DM

People with T2DM have chronic subclinical inflammation, affecting both innate and adaptive arms of their immune response to *Mtb* infection [16, 17]. T2DM is a metabolic disorder whereby a loss of cellular response to insulin (insulin resistance) particularly in skeletal muscle, liver and adipose tissue, causes a compensatory rise in insulin production by pancreatic β-islet cells followed by a reduction in insulin as the β-islet cells become exhausted. It is characterised by hyperglycaemia and dyslipidaemia, and can lead to cardiovascular complications, kidney disease and peripheral neuropathy. People with pre-

diabetes (PDM) have moderately impaired glucose tolerance and intermediate hyperglycaemia, and have increased risk of developing T2DM [2]. TB disease can drive hyperglycaemia, due to inflammation-induced insulin resistance, which often but not always resolves upon TB treatment [18, 19].

A complex interplay of cellular and humoral responses determines whether someone becomes infected following *Mtb* exposure, and whether an infection remains quiescent or whether there is bacterial replication leading to incipient (slow/intermittent *Mtb* replication, non-infectious, no signs/symptoms), subclinical (replicating *Mtb*, potentially infectious, unrecognised signs/symptoms) or TB disease (active *Mtb* replication, often infectious, signs/symptoms) [20]. T2DM has different effects in people with TB disease and with TB Infection (TBI: defined as persistent immune response to stimulation with *Mtb* antigens with no evidence of clinically manifest TB disease [21]). T2DM affects the immune response to *Mtb* and can drive progression along the spectrum to TB disease. The function of alveolar macrophages, the first host cells which interact with *Mtb,* is impaired in T2DM causing reduced capacity to phagocytose and to contain *Mtb,* and altered cytokine expression related to epigenetic modification [22]: this also occurs in primary monocyte-derived macrophages (MDMs). Diabetes causes delayed monocyte recruitment to the infected lung and delayed T-cell priming in lymph nodes, together impairing initial granuloma formation People with TBI with T2DM have lower *Mtb*-specific T-cell responses including lower Th1, Th17 and Th2 cells and IL-10 production [23], and the extent of dysregulation correlates with the degree of hyperglycaemia [24]. They also have reduced NK cell cytokine responses to stimulation with *Mtb*-derived antigens [25]. However, the pro-inflammatory Th1 and Th17 responses [26] and NK cell TNF and IL-17 responses [27] are enhanced in TB-DM comorbid patients compared to uncomplicated TB disease, likely reflecting excessive bacterial replication and progressive disease, although cytotoxic marker expression is reduced in $CD8^+$ T cells and NK cells. Excessive pro-inflammatory cytokines are detectable in serum

and bronchoalveolar lavage in TB-DM. Similar perturbations occur in PDM for both *Mtb*-infection and TB disease [28].

Blood transcriptomics studies have consistently revealed a neutrophil-driven type I interferon (IFN-I) response in uncomplicated TB which resolves during successful TB treatment [29]. In TB-DM, the inflammatory response is elevated relative to uncomplicated TB [30], and remains persistently high during TB treatment [19, 31]: addressing the delayed resolution of inflammation in TB-DM is a key HDT goal. Importantly, the IFN-I response is relatively reduced in TB-DM comorbid patients at TB diagnosis but does not resolve normally, remaining elevated into the treatment continuation phase whereas resolution of inflammation-related gene expression is temporally normal [19]. Thus, the IFN-I and systemic inflammatory responses are not coupled. TB patients with intermediate hyperglycaemia/PDM have transcriptomic profiles similar to TB-DM, indicating enhanced susceptibility [30]. Blood transcriptome perturbation is inversely correlated with HDL cholesterol and indicates targeting opportunities for HDT [32].

Host-directed therapy for tuberculosis: inhibition of inflammation

The only clinically proven HDT for TB is corticosteroids which are effective for TB-meningitis [33]; however trials for use in pulmonary TB have been disappointing, with no effect observed on sputum conversion, treatment failure or relapse rates, weight gain or hospitalisation. This is somewhat surprising, as corticosteroids have successful wide application as anti-inflammatory medications in diverse conditions. Most trials were performed before the introduction of rifampicin [34] and newer treatment strategies could conceivably enhance efficacy, although side-effects must be managed [35]. The adjunctive administration of prednisolone for disseminated TB in HIV^+ individuals is currently in clinical trial [36], and corticosteroids play an important role in TB-Immune Reconstitution Inflammatory Syndrome treatment.

Hence researchers are searching for alternative ways to reduce the inflammatory response to ameliorate lung immunopathology [15]. Upon infection, *Mtb* migrates to lung interstitial spaces where an inflammatory response is triggered leading to production of pro-inflammatory cytokines interleukin-1, IL-6 and TNF and chemokines [37, 38], driving the infiltration of monocytes, neutrophils, fibroblasts and lymphocytes. A granuloma develops, which can be beneficial to the host by containing the bacilli in a dormant phase with fibrotic encasement and calcification, but which alternatively can become over-inflammatory, caseous and liquefied due to necrotic cells, and harbour extracellularly replicating bacilli leading to cavity formation, dissemination and transmission. In mouse models of T2DM, the IL-6 response to *Mtb* infection is exacerbated, and is driven by NK cell:$CD11c^{+}$ cell crosstalk, such that inhibition of NK cells or IL-6 increases survival [39]. Cavities, a post-primary TB feature, are associated with spread from lower to upper lung lobes, erosion of alveolar structure and can prevent antibiotics from reaching *Mtb*, rendering treatment less successful. The host requires the correct degree of inflammation to permit recruitment of effector cells to kill and control mycobacteria without causing pathology: rectifying this balance is a key goal for HDT and has extra importance in TB-DM due to inherently excessive inflammation.

Host matrix metalloproteinases (MMPs) are instrumental in mediating cavitation via the degradation of collagen. MMP-1,-3,-8 and -9 are upregulated in TB patient sputum, BAL and granulomas [40], and can be activated directly by *Mtb*-components alongside a reduction in tissue inhibitors of metalloproteinases [41]. A phase II randomised control trial (RCT) with the FDA-approved non-specific MMP inhibitor doxycycline for 14 days showed that although there was no difference in bacterial burden, more treated patients had resolved pulmonary cavities with reduced IFN-I and IFN-γ and reduced collagenase activity [42]; longer-term studies are required. Cavity reduction could lead to shortened treatments by promoting antibiotic access to lesions and to improved lung function post-treatment, with greater potential for improvement in TB-DM patients as they have higher MMP upregulation, which is associated with bacterial burden, cavitation and extent of hyperglycaemia [43].

Alternative therapeutic agents are under consideration: spatial lung transcriptomics of human *Mtb*-infected lung granulomas identified target genes involved in collagen-mediated extracellular tissue remodelling, which could be negated by thrombospondin-1 in organoid-macrophage co-cultures [44].

Macrophages recognise *Mtb* via TLR2/4 binding to *Mtb*-lipoarabinomannan, driving polarisation to an M1 pro-inflammatory macrophage phenotype which is further enhanced by IFN-γ released by $CD4^+$ Th1 cells and NK cells [15]. Pro-inflammatory cytokine and chemokine production by M1 macrophages drives the recruitment of Th1 and Th17 cells alongside neutrophils, which together drive further inflammation. $CD4^+$ T cells are a necessary component of anti-*Mtb* immunity, providing an HDT opportunity. In this regard, the *Mtb* antigen-specificity, phenotype and localised recruitment to infected parenchyma are key determinants of the efficacy of infiltrating $CD4^+$ T cells. In mouse TB models, OX40 agonists promote bacterial killing and host survival via activated $CD4^+$ T cells, providing promise for HDT [45]: however, they drive further lung inflammation with larger and coalescing cellular aggregates and their use for people with TB-DM must be carefully considered due to existing enhanced inflammatory responses. Similarly 1-methyl-d-tryptophan, which inhibits the immunosuppressive molecule indoleamine 2,3 dioxygenase (IDO) expressed by macrophages and myeloid-derived suppressor cells, provides clinical, radiological and microbiological protection in macaque TB models via boosting $CD4^+$ T cell recruitment and IFNγ production [46], and is a promising TB HDT candidate, but exacerbation of the inflammatory response in TB-DM is risky. In contrast, the aminothiol cysteamine reduces the proinflammatory response in people with TBI or TB disease, including lower IFNγ, TNF and IL-2 production to *Mtb*-antigen stimulation, and may be effective adjunctive therapy in TB-DM [47].

M1 polarisation enhances the macrophage's bactericidal capacity, including the production of reactive oxygen species (ROS) and reactive nitrogen species via expression of inducible nitric oxide synthase (iNOS). ROS, produced by mitochondria, are critical for

mycobacterial killing, and enhancing this response and overcoming *Mtb's* ROS evasion strategies could be an HDT objective [15], with drugs such as vitamin D and metformin (see below) undergoing trials to boost anti-*Mtb* immunity via ROS generation; however, excessive ROS leads to oxidative stress-mediated tissue damage, ferroptosis and bacterial dissemination, so a careful balance must be achieved, particularly in people with TB-DM who have exacerbated ROS generation [48]. Boosting the host antioxidant status may ameliorate oxidative stress-induced tissue damage, and clinical trials of statins, which prevent excessive ROS production, are ongoing as adjunctive TB treatment [49]. MDMs from people with TB-DM are inherently more strongly M1-polarised, with increased IL-1β and iNOS expression [50], causing excessive neutrophil recruitment to the granuloma. The progression from an effective to a caseous, necrotic granuloma is driven by macrophage differentiation to lipid-rich foamy cells which lack anti-mycobacterial capacity. The dyslipidaemia in T2DM, with elevated triglycerides and low-density lipoprotein (LDL) and reduced high-density lipoprotein, promotes foamy cell formation.

Neutrophils are recruited to the lungs by necrotic macrophages and macrophage-derived inflammatory cytokines and by Th17 cells [51]. They are activated by *Mtb* to upregulate phagocytosis and oxidative killing via ROS. Activated neutrophils degranulate, releasing bactericidal proteases and α-defensins, and undergo necrosis leading to further inflammation driving further influx of monocytes, neutrophils and lymphocytes. Neutrophil Extracellular Traps (NETs) have been observed in necrotic lung lesions of TB patients [52] and in non-human primate models. NETs can retain bacteria in DNA strands but also contribute to lung tissue damage via degradative enzymes, and promote macrophage recruitment and pro-inflammatory cytokine secretion [53]. People with TB-DM have higher neutrophilia than uncomplicated TB, but with impaired phagocytic function [54], and neutrophils from people with T2DM are more prone to NETosis [55],: the higher but less effective neutrophil lung infiltration could be targeted by HDT. Additionally, an upregulation of low-density neutrophils (LDNs) has been described in blood during TB disease [56, 57],

LDNs reportedly have lower ability to phagocytose live *Mtb,* to mount a respiratory burst and to undergo NETosis than normal density neutrophils [56], although data remain inconclusive [57]. People with T2DM also have elevated LDNs [58], highlighting the enhanced importance of this cell subset in people with TB-DM for HDT. Neutrophils are initially beneficial, but as TB chronically progresses, their number increases and they become more necrotic, promoting *Mtb* intracellular survival in nearby macrophages. Inhibiting this positive feedback loop of inflammatory mediators is a key focus for HDT, and is more critical in TB-DM due to the over-exuberant inflammation. The “correct” inflammation response is vital, so it is sufficient but not excessive, and contributes acutely to recruitment of effector cells without driving chronic non-effective tissue destruction. Conversely, anti-inflammatory cytokines such as IL-10 and Transforming Growth Factor-β down-regulate the macrophage response, enabling *Mtb* survival and tissue damage long-term [59]: as such, they also pose targets for optimised HDT.

Lipid mediators, derived from polyunsaturated fatty acids, are central in the induction and maintenance of the inflammatory response and can have pro- or anti-inflammatory effects. Whether they are protective or deleterious depends on context: prostaglandin E2 (PGE2) confers resistance to *Mtb* in animal models by triggering initial inflammation, promoting apoptosis and containing the infection, whereas Lipoxin A4 (LXA4) promotes *Mtb* replication via necrosis induction and extracellular spread [60]. However, too much PGE2 or too little LXA4 is harmful, due to excessive inflammation. The non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen inhibit cyclo-oxygenases, which are involved in the biosynthesis of prostaglandins and other eicosanoids. Ibuprofen reduces *Mtb* burden and lung inflammation in murine models and is currently in phase IIB RCT for use as adjunctive therapy (Clinicaltrials.gov:NCT04575519). People with TB-DM have higher pro-inflammatory eicosanoids, including Leukotriene E4, PGE2 and PGD2, along with resolving mediators such as LXB4 and LX5S [60]: HDT aimed at restoring the balance should take account of the complexity of eicosanoid metabolism in different people.

The type I interferon response in TB-DM

The IFN-I response is typically evoked in viral infections where it protects against viral replication and spread to neighbouring cells in acute infection but can be harmfully immunosuppressive in chronic infection. IFN-Is include IFN-α, with 13 subtypes in humans, and IFN-β. Binding of IFN-α or IFN-β to the IFNAR-1 receptor leads to upregulated expression of several hundred Interferon-Stimulated Genes (ISGs) which encode proteins blocking viral RNA and protein synthesis: the biological outcome is dependent on the specific ISGs affected. In TB, the IFN-I response has more deleterious effects, with TB proposed to be an "interferonopathy" [61]. IFN-Is are associated with TB disease [29] and the ISG response is detectable prior to symptom development [62]. People lacking the ISG15 negative regulator of IFN-Is are highly susceptible to TB, whereas a loss-of-function mutation in the IFNAR-1 receptor confers resistance. In mouse models, the B6 strain is naturally resistant to *Mtb* and mice mount a weak IFN-I response due to a lack of the transcription factor IRF3. The harmful effects of IFN-I are probably due to antagonism of the IL-1β response via PGE2, via upregulation of the IL-1Receptor antagonist (IL-1Ra), via blockade of the macrophage response to IFN-γ preventing microbial killing and by induction of IL-10, emphasising again the necessity of the pro-inflammatory response and warning against too much inhibition via HDT. IFN-Is also drive NETosis [52]. Therapies targeting IFN-I pathways are at late stages of clinical development for autoimmune diseases such as systemic lupus erythematosus, with the anti-IFNAR-1 mAb treatment anifrolumab already licenced, and antibodies targeting the IFNAR Jak1/Tyk2 signal transduction pathway in phase III RCT [63]. Targeting IFN-Is themselves for HDT may run the risk of virus infection, and delineation of the downstream ISG pathways for specific targeting is warranted. For TB-DM, targeting the IFN-I pathway is particularly appealing, as it is involved in atherosclerosis and vascular damage.

Following phagocytosis, *Mtb* bacilli are retained in phagolysosome compartments. Mycobacterial antigens and DNA gain access to the macrophage cytosol via phagolysosome

membrane damage caused by the *Mtb* ESAT-6 secretion system-1 (ESX-1). *Mtb* infection damages mitochondria, releasing mitochondrial DNA into the cytosol. The cyclic GMP-AMP synthase (cGAS) sensor detects *Mtb*- and mitochondrial-dsDNA, and triggers IFN-I gene transcription through activation of the stimulator of interferon genes 1 (STING1) protein whilst directing *Mtb* to the autophagy bacterial degradative pathway. HDT could be aimed at boosting autophagy: in this regard, cysteamine decreases *Mtb* replication in macrophages and *in vitro* granulomas, likely via effects on autophagy and the host cell's oxidative state, and synergises with first- and second-line antibiotics [64]. *Mtb* has evolved strategies to avoid cGAS-STING1/autophagic control, including secretion of cyclic-di-nucleotide phosphodiesterase and STING1 inhibitors. cGAS- and STING1-deficient mice are more susceptible to TB, indicating the IFN-I pathway is necessary for protection: it is the extent and temporal control of the IFN-I response which determines whether it becomes pathological. Interstitial macrophages and plasmacytoid Dendritic Cells (pDCs) are the dominant producers of IFN-I in *Mtb* infection in mice and non-human primates, and pDC depletion reduces *Mtb* burden [65]. People with TB-DM initially have reduced pDCs, but later in treatment they significantly increase [66], reflecting IFN-I expression observed in transcriptomics studies [19]. pDCs can also be activated to produce IFN-I via NETs. Modulation of *Mtb* proteins secreted through ESX-1 uncouples the IFN-I response from the inflammatory response triggered through inflammasome activation, reminiscent of the uncoupling of responses observed in TB-DM blood transcriptomes described above [30]. Modulation of IFN-I pathways in TB-DM could be particularly beneficial, especially as the cGAS-STING1 pathway is also involved in T2DM pathogenesis [67], while raised oxidised LDL in TB-DM further inhibits autophagy [68].

Immunometabolic regulation and metformin

Macrophages are key effector cells for *Mtb* control. Their metabolic status is critical for their function and is modulated by T2DM. *Mtb* infection disrupts mitochondrial structure and function, including interference with mitochondrial protein expression leading to leakage

of electrons to enhance ROS production, as well as increasing mitochondrial fission and reducing fusion, associated with reduced aerobic respiration capacity and loss of the mitochondrial membrane potential [69]. *Mtb*-driven damage to the inner mitochondrial membrane is necessary for mycobacterial persistence. Increased mitochondrial permeability and ROS cause cytochrome C release inducing intrinsic apoptosis, whereas higher ROS levels cause pyroptosis or necrotic cell death and mycobacterial survival.

Mtb generally induces an initial biochemical switch to glycolysis in macrophages, enabling rapid production of ATP which is necessary for IL-1β production, followed by a switch to oxidative phosphorylation (OXPHOS), which is a more efficient ATP-generating pathway. Different metabolic changes are observed depending on the experimental setup, including the multiplicity of infection, the viability and virulence of the mycobacteria and the type of macrophage; nonetheless, it is evident that the macrophage metabolic status has profound implications for *Mtb* control, with glycolysis driving a bactericidal, pro-inflammatory M1 phenotype and OXPHOS driving a fibrotic, anti-inflammatory M2b-like response supporting *Mtb* persistence. The ER stress response drives M1 polarisation via activation of the HIF-1α transcription factor through the Akt/mTOR pathway, leading to the secretion of the pro-inflammatory cytokines TNF, IL-1β, IL-6, IL-12 [69], and inhibition of Akt/mTOR blocks the macrophage response to *Mtb*. T2DM is associated with an M1 macrophage phenotype, and TNF secreted from M1 macrophages drives insulin resistance in murine models [70]. Glycolytic flux is enhanced by translocation of GLUT-1 transporters from the cytosol to the plasma membrane enhancing glucose import in macrophages, and this is higher in TB-DM patients, as is IL-1β production [50]. Pharmacological blockade of the M1 shift reduces IL-1β and increases IL-10 production, increasing bacillary survival, whereas blockade of OXPHOS stabilises HIF-1α, promoting the pro-inflammatory response. Foamy macrophages contain accumulations of lipids covered with phospholipid monolayers, which interact with mitochondria, ER and lysosomes and modify host and *Mtb* metabolism. Disruption of both glycolysis and OXPHOS in *Mtb*-infected macrophages leads to

accumulation of di-hydroxy acetone phosphate and acetyl-co-A, which are precursors for the synthesis of the lipids in foamy macrophages [69], and people with T2DM have dyslipidaemia making them generally more prone to developing foamy macrophages: targeting lipid metabolism in TB-DM is an important research gap. The switch to M2 is similar in TB-DM and uncomplicated TB [71] and is induced by Peroxisome Proliferator-Activated Receptor-γ, a lipid-activated nuclear receptor, which increases lipid formation and provides an immune escape mechanism by inhibiting pro-inflammatory cytokines and promoting bacterial survival, and preventing the M2 switch is an opportune target for HDT. The switch to glycolysis and the mitochondrial damage induced by live *Mtb* are inhibited by IFN-I [72], again demonstrating IFN-I's key role in the host-pathogen interface, with a potential role of reduced IFN-I in TB-DM enabling the excessive initial M1 glycolytic switch.

mTOR inhibitors can induce autophagy and can also regulate immunometabolic changes, enhancing mycobacterial control. A phase II RCT of pulmonary TB patients in South Africa showed the mTOR inhibitor everolimus (a rapamycin derivative) led to significant improvement in the Forced Expiratory Volume in one second (FEV_1) when given as adjunctive therapy for 112 days [73], implying that it had promoted lung recovery. Future clinical trials should include people with TB-DM as this group was excluded.

The T2DM medication, metformin, has been hailed as potential adjunctive TB treatment for people with TB-DM, in contrast to the majority of HDTs which are being developed primarily focussing on uncomplicated TB. Metformin reduces intracellular *Mtb* growth in an AMPK-dependent manner, and its efficacy was discovered in a screen of autophagy activators [74]. Administration of metformin to healthy volunteers reduces the induction of ISGs by *Mtb* lysate *in vitro* and enhances phagocytosis, phagolysosome fusion and ROS production, enabling better *Mtb* control [75]. A systematic review of 1,109,660 participants, including 908,211 people with DM and 13,841 people with TB, showed that metformin decreases the risk of TB disease in people with DM by at least 40%, with higher efficacy at higher metformin doses [76]; metformin also protects against *Mtb* infection [77]. In

a phase IIB efficacy trial, adjunctive metformin given alongside conventional anti-TB treatment for the first 8 weeks reduced cavitation and inflammatory in both TB-DM and uncomplicated TB patients; however, there was no effect on sputum conversion [78]. Other anti-DM and anti-hyperglycaemia medications have been tested for their ability to either kill mycobacteria directly or to enhance antimicrobial activity of standard TB treatments with some promising results: for example, the sulfonylurea glyburide synergized separately with isoniazid, rifampicin, ethambutol and streptomycin in intracellular assays to promote up to 63% increased bacterial killing [10]: these results warrant further investigations *in vitro* and *in vivo*.

People with T2DM often take multiple medications, which may affect *Mtb* control and may interact with anti-TB drugs [10], so regimens should be closely managed. Rifampicin increases the metabolic clearance of some hypertensives such as verapamil rendering them less effective, so they should be replaced with alternatives where necessary. However, verapamil, a calcium channel blocker, can be beneficial in TB by activating macrophages to become bactericidal and by inhibiting *Mtb* efflux pumps thereby restoring antibiotic intra-bacterial concentrations [10]. Statins can protect against *Mtb* infection [77], and as well as reducing cholesterol and impacting on foamy macrophage generation, they promote phagolysosome fusion enhancing bacterial killing.

Vaccination as host-directed therapy

The current pipeline of new TB vaccines contains over a dozen candidates that are in either phase I, II or III clinical trials (reviewed [79, 80]. Mainly the target for these vaccines is prevention of infection, however some candidates are also under consideration as therapeutic vaccines, to be given adjunctively with anti-TB drugs to treat TB disease. Importantly, all these vaccine candidates have been designed and formulated to optimise T-cell activation, which is compromised in people with T2DM. RUTI is a vaccine candidate formed of inactive, fragmented *Mtb* material encapsulated in liposomes that demonstrated an ability to activate pathogen-specific $CD4^+$ and $CD8^+$ T-cells as well as antibody responses

in pre-clinical animal models. RUTI's therapeutic potential is enhanced by virtue of being formulated from *Mtb* cultured in conditions of oxidative stress to replicate the antigenic profile of non-replicating bacteria. Immune responses to these antigens could target difficult-to-kill *Mtb* that are responsible for unsuccessful treatment and relapse. Of the subunit vaccine category, H56:IC31 contains three *Mtb* antigens (Ag85b, ESAT6 and Rv2660c to target replicating and non-replicating bacteria) combined with a cationic peptide:TLR9 agonist adjuvant, and activates memory $CD4^+$ and $CD8^+$ T-cells and induces vaccine-specific antibodies [81], and is currently being tested against recurrence in recently treated drug-sensitive TB patients. If the definition of a therapeutic vaccine is expanded to include prevention of disease in *Mtb*-infected individuals, additional candidates can be considered. The recombinant BCG candidate VPM1002 is in phase II/III trials for the prevention of recurrence, and the MVA85A candidate has completed a small phase I trial in *Mtb*-infected people where a persistent polyfunctional T-cell response was demonstrated in response to the vaccine. The M72/$AS01_E$ subunit vaccine consists of fused antigenic proteins (Mtb32A and Mtb39A) delivered with $AS01_E$ adjuvant: a phase IIb trial in $IGRA^+$ participants demonstrated 50% vaccine efficacy for TB prevention. Given the increased risk of treatment failure or of relapse following treatment in TB-DM patients, therapeutic vaccination offers the potential to boost immune protection in these individuals. Immune responses to vaccination are generally compromised in T2DM individuals, with reduced antibody titres, lower Th1:Th2 cytokine ratios and lower $CD4^+$ and $CD8^+$ T-cell responses [82]. This will need to be considered for therapeutic vaccination for TB-DM patients, and vaccine trials should include people with T2DM: in this regard an ongoing Phase I trial (Clinicaltrials.gov:NCT06246851) seeks to understand the altered immune responses induced by aerosol BCG in T2DM and normo-glycaemic people.

Utilising mathematical modelling to optimise HDT in TB-DM

Mathematical modelling is a transformative tool for understanding host-pathogen interactions during *Mtb*-infection, offering a systematic and quantitative framework to unravel

the complex interplay between *Mtb* and the host immune system. These models integrate experimental data to simulate the dynamics of infection progression, immune responses, and environmental or genetic factors influencing disease outcomes. For instance, mathematical frameworks have been employed to study granuloma formation and function, predict conditions for *Mtb*-reactivation, and model the effects of treatment on phenotypically diverse bacterial populations [83-85]. Such efforts have proven instrumental in identifying critical immune thresholds that determine the transition between containment and active disease. Moreover, modelling facilitates the exploration of vaccine and treatment strategies *in silico*, allowing researchers to predict outcomes of interventions without the high costs and time constraints associated with clinical trials. This capability supports the optimisation of dosing regimens, evaluation of drug resistance, and design of combination therapies that maximise efficacy while minimising adverse effects. These models also bridge gaps in experimental research by integrating diverse data sources —including genomic, immunological, and clinical datasets—into coherent frameworks that enhance our understanding of TB pathogenesis and therapeutic options.

While models have addressed critical factors such as the impact of HIV on TB progression, research on other TB comorbidities such as TB-DM remains limited, representing a significant gap especially given the growing TB-DM prevalence. TB-DM presents unique immunometabolic challenges, including altered macrophage metabolism, insulin resistance, and potential shifts in bacterial phenotypes that may influence drug efficacy and resistance. Addressing these complexities within mathematical models is crucial to accurately simulating TB-DM interactions. Expanding computational tools in this area could improve predictions of treatment outcomes, particularly HDTs tailored to TB-DM patients. Furthermore, integrating immunometabolic data into these models will enable a more personalised approach to TB-DM treatment, bridging the gap between theoretical modelling and clinical application.

Outlook

Enhanced understanding of immunopathology in TB-DM will facilitate the development and selection of HDTs targeting reduction of pathological inflammation and reversal of tissue damage whilst boosting or at least maintaining innate and adaptive anti-*Mtb* immune responses: such new therapies would also be beneficial to TB patients with PDM. As well as reducing Post TB Lung Disease after “TB cure” [86], HDTs would protect against the development of resistance in new antimicrobials. The current focus is on repurposing existing FDA-approved drugs to enable rapid clinical translation, but there is a growing pipeline of alternative strategies, including cytokines such as GM-CSF [52], non-coding RNAs to target various host transcripts, and natural products [87]. Whilst HDTs optimised in uncomplicated TB may benefit people with TB-DM, particular focus should be placed on the perturbed IFN-I response to specifically address immune defects in TB-DM. Alongside mathematical modelling, improved animal models of TB-DM would facilitate prioritisation of HDT candidates. Innovative clinical trial strategies should be utilised to develop HDT alongside new antimicrobials efficiently, aiming to reduce the duration, cost and drug burden of new regimens. Treatment nebulisation may be advantageous, and drug-drug interaction and toxicity in combination use should be ascertained. More studies are needed to ascertain spatial and temporal aspects of the *Mtb*-host interaction to optimise HDT delivery and avoid the risk of worsening disease.

Combined management of TB and diabetes would facilitate better outcomes [88], and diabetes medications should be optimised to prevent impaired *Mtb* immune responses in high TB burden settings [76]. Eventually it may be possible to stratify TB patients based on the integration of patient and pathogen characteristics to optimise the HDT treatment regimen and duration: this would include T2DM status and extent of control, as well as extent of cavitation, culture conversion status and potentially a pharmacokinetic/pharmacodynamic analysis of HDT and anti-*Mtb* drugs to address the impact of vasculature complications on dosing in TB-DM. T2DM drives TB disease

development from *Mtb*-infection and vice versa, hence intervention with prophylactic treatment should be considered at early points in both conditions, and HDT to prevent irreparable damage should be included.

Ethical Statement

Not Applicable.

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Conflict of Interest

None.

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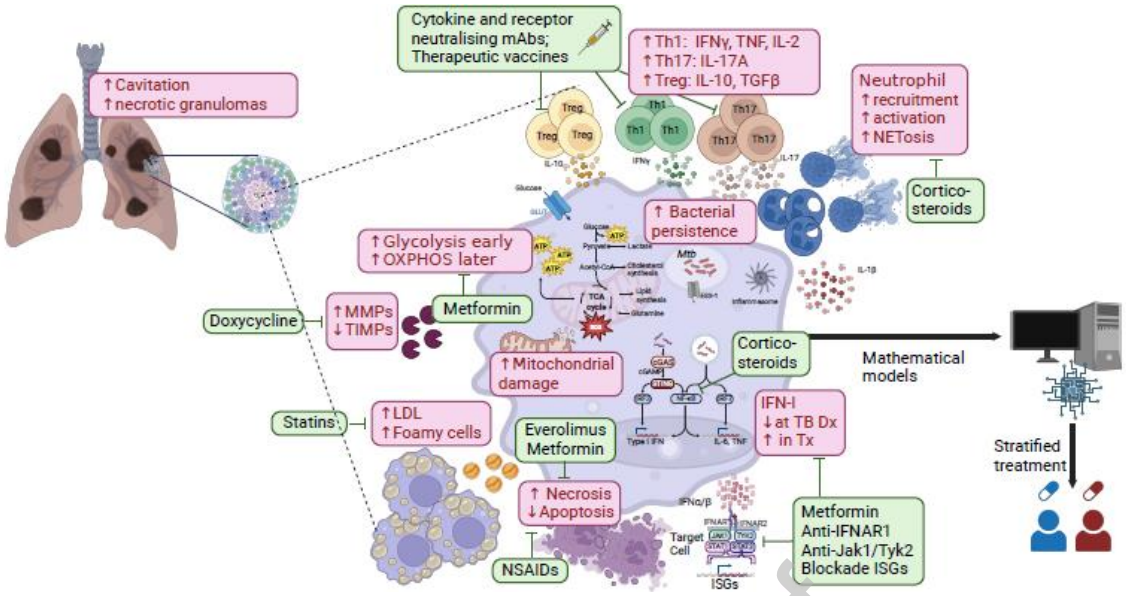

Figure 1: Impact of type 2 diabetes on host-directed therapy options for pulmonary tuberculosis. A robust multifactorial immune response during active TB is shown, with a central *Mtb*-infected macrophage. There is an initial upregulation of the glycolysis pathway followed by a switch to oxidative phosphorylation. *Mtb* antigens and DNA leave the phagolysosome via the *Mtb* ESX-1 secretion pathway and activate the host cGAS-STING pathway, leading to expression of Type I IFN via the IRF3 transcription factor, and of IL-6 and TNF via IRF7, with NF-κB in both cytokine expression pathways. The inflammasomes are activated by *Mtb* leading to release of active IL-1β following cleavage. Neutrophils are recruited, activated and release NETs. MMPs are made by the host, and cause damage to the lung architecture. Red text in red boxes shows differences in people with TB-DM co-morbidity relative to uncomplicated TB. Green text in green boxes shows potential host-directed therapy, including therapeutic vaccination. There are many potential HDT targets for people with TB-DM, and the large amount of data being generated from *in vitro* and *in vivo* models as well as clinical trials should be mined to optimise HDT interventions, including their concentration, duration and timing, to be used adjunctively with antibiotic treatment, eventually in a patient-centred stratified manner. *Figure created in https://BioRender.com.*

Abbreviations:

cGAS: cyclic GMP-AMP synthase

Dx: TB diagnosis

ER: Endoplasmic reticulum

ESAT-6: Early Secreted Antigenic Target

ESX-1: ESAT-6 secretion system-1

HDT: Host-directed therapy

iNOS: inducible nitric oxide synthase

IFN-I: type I interferon

IFNAR: Interferon α/β receptor

IRF: Interferon regulatory factor

ISGs: Interferon-stimulated genes

LDL: low density lipoprotein

LXA4: Lipoxin A4

mAb: monoclonal antibody

MDMs: Monocyte-derived macrophages

MDR: Multi-drug resistance

MMP: matrix metalloproteinase

Mtb: Mycobacterium tuberculosis

mTOR: Mammalian target of rapamycin

NETs: Neutrophil extracellular traps

OXPHOS: oxidative phosphorylation

PDM: Prediabetes mellitus

RCT: Randomised Controlled Trial

PG: Prostaglandin

ROS: reactive oxygen species

RR: Rifampicin-resistance

RX: TB treatment

STING: Stimulator of interferon genes

T2DM: Type 2 diabetes mellitus

TCA: Tricyclic acid cycle

TIMP: Tissue inhibitor of metalloproteinase

Declaration of Interest Statement

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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☐ The authors declare the following financial interests/personal relationships

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