



# Interaction between HIV and *Mycobacterium tuberculosis*: HIV-1-induced CD4 T-cell depletion and the development of active tuberculosis

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## Purpose of review

HIV infection is the main driver of the HIV/tuberculosis (TB) syndemic in southern Africa since the early 1990s, when HIV infection rates started to increase exponentially and TB incidence rates quadrupled simultaneously. Here, we discuss pathogenic mechanisms of HIV-induced CD4 T-cell depletion and their potential impact on immune control of *Mycobacterium tuberculosis*.

## Recent findings

Depletion of effector memory CD4 T cells from the air–tissue interphase, their dysfunctional regeneration and the preferential depletion of *MTB*-specific CD4 T cells from circulation and from the air–tissue interphase might be key factors for the increased susceptibility to develop active TB after HIV infection.

## Summary

Early initiation of antiretroviral therapy or the development of an efficacious HIV vaccine would be the best options to reduce morbidity and mortality associated with the HIV/TB syndemic.

## Keywords

CD4 T cell, HIV, tuberculosis

## INTRODUCTION

Originating from multiple zoonotic transmissions of simian immunodeficiency virus (SIV) to humans in west and central Africa, HIV-1 started to spread in the early 1990s into larger populations. The most successful branch of HIV, group M was transmitted from the chimpanzee *Pan troglodytes troglodytes* in which it is endemic [1]. Initially, the spread of HIV-1 group M was geographically confined to western–central Africa, but international migration and travel enabled a successful spread across the world in the second half of the 20th century. Since its discovery, as the causative agent of the AIDS in 1983 [2,3], HIV prevalence rates have increased steadily on a global scale to 33 million infected patients – 0.8% of the adult population – in 2009 [4]. The most dramatic increase in HIV prevalence rates was observed in sub-Saharan African countries and an estimated 68% of globally HIV-infected people live in sub-Saharan Africa. Particularly, South African countries are at the ‘epicenter’ of the HIV epidemic, with adult prevalence rates of up to 25% population [4].

Globally, active tuberculosis (TB) remains among the leading causes of death from an

infectious agent. In 2010, the estimated global TB incidence rate was 128 cases per 100 000 population, which equates to 8.8 million (range, 8.5–9.2 million) incident TB cases [5]. Since the 1990s, the worldwide TB incidences have developed quite divergently. Whereas in most parts of the world TB incidence rates remained stable or declined, African incidence rates increased by almost 30%. This increase was most pronounced in Southern Africa, especially South Africa where the incidence nearly quadrupled to 981 cases per 100 000 population (95% uncertainty interval 806–1170). HIV/TB coinfection numbers (Fig. 1; red line) indicate that in these countries a large proportion of the TB incidence is related to

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## KEY POINTS

- *Mycobacterium tuberculosis* (*MTB*) specific CD4 Th1-cell responses are critical for immune control of tuberculosis in the murine *MTB* infection model.
- Effector memory CD4 T cells within the primary site of *MTB* infection – the air–tissue interphase of the lung – are a major target for depletion after AIDS virus infection.
- The extent of CD4 T-cell depletion from the air–tissue interphase during acute simian immunodeficiency virus infection is associated with early disease reactivation in macaques with latent *MTB* infection.
- *MTB*-specific CD4 T cells are preferentially depleted from circulation and from the air–tissue interphase in TB asymptomatic patients after HIV infection.
- Depletion of CD4 T cells, particularly effector memory CD4 T cells and *MTB*-specific CD4 T cells within the air–tissue interphase, might be a key factor in the impaired control of *MTB* infection after HIV infection.

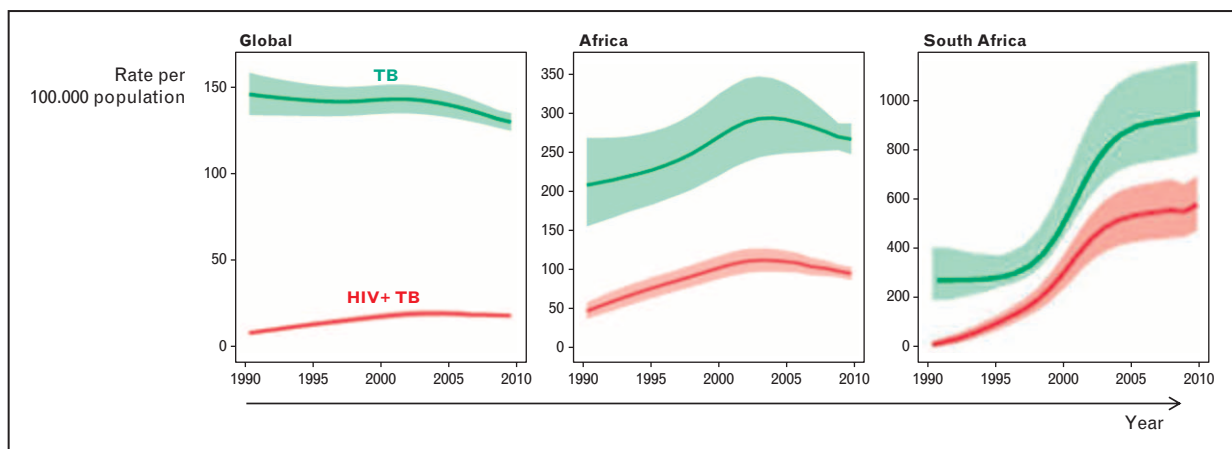
immunodeficiency caused by HIV infection. In South Africa, approximately 60% of TB incident cases are HIV infected and in total the African region accounts for 82% of TB cases among people living with HIV [5]. The dramatic mortality of this co-epidemic in Southern Africa is highlighted by a recent postmortem study of young inpatients (18–45 years) of a hospital in KwaZulu-Natal that found that 94% were HIV<sup>+</sup> and 69% of them had active TB or were currently on TB treatment at the time of death [6].

The HIV-related factors that contribute to the increased prevalence of active TB in HIV high-endemic areas are obvious. An impaired immune system will change the acquisition rate of infection following exposure. Similarly will the loss of immune control influence the rate of recurrence of subclinically infected individuals. The proportional contribution of these factors is unclear and subject of an ongoing debate [7]. There are data from cohorts that indicate a two-fold to three-fold increase of active TB disease within the first year after HIV seroconversion and that is not a direct function of the depletion of the blood CD4 cells [8,9]. In a macaque model for HIV-induced TB reactivation, eight of eight macaques, who were latently infected with *MTB*, reactivated within less than a year after infection with a high dose of SIV [10<sup>\*\*\*</sup>].

Here, we discuss how the depletion of memory CD4 T cells and *MTB*-specific CD4 T cells after HIV infection could contribute to loss of *MTB* immune control.

## IMMUNITY TO MYCOBACTERIUM TUBERCULOSIS INFECTION

Infection with *MTB* is caused by aerosolic transmission and primarily targets the respiratory system. Immune correlates of protection are best defined in the murine model. Although not reflecting all aspects of human TB pathogenesis, it serves as a good animal model to elucidate fundamental questions of host–pathogen interaction and immunity [11,12]; upon inhalation, *MTB* is phagocytosed by alveolar macrophages and myeloid dendritic cells (mDCs) [13]. *MTB* is adapted to survive and replicate intracellularly within the macrophage phagosome.



**FIGURE 1.** Estimated tuberculosis incidence rates, 1990–2010. Global and African trends in estimated tuberculosis (TB) incidence rates (green) and estimated incidence rates of HIV-positive TB (red). Shaded areas represent uncertainty bands. Figure was adapted and modified from the WHO Report 2011 Global tuberculosis control.

*MTB*-infected myloid dendritic cells, which actively sample the mucosal environment, migrate to the draining, lymph nodes to support initiation of the *MTB*-specific adaptive immune responses [13,14]; a delay in priming the adaptive immune response is thought to be critical in establishing bacterial persistence [14,15]. Initial priming of the adaptive immune response triggers expansion and phenotypic and functional maturation of *MTB*-specific T cells, which recirculate and home to the primary site of infection, in which they activate infected macrophages through the secretion of interferon gamma (IFN- $\gamma$ ) and tumor necrosis factor alpha (TNF  $\alpha$ ) [16<sup>22</sup>,17]. These Th1 cytokines are important mediators for arresting intraendosomal *MTB* growth, for microbial killing and, perhaps most importantly, for granuloma formation and maturation [12,18]. In addition, IFN- $\gamma$ /TNF-independent T-cell-mediated effector mechanisms also contribute to the control of *MTB* [16<sup>22</sup>,19]. The TB granuloma is the hallmark of the *MTB*-specific immune response and locally restricts mycobacterial spread both in humans and in mice [12,20]. Murine studies using advanced dynamic imaging methodology have shown a surprisingly mobile CD4 T-cell population during early granuloma formation and only low frequencies of IFN- $\gamma$  secreting mycobacteria-specific CD4 T cells (5–8%) at a given time point [16<sup>22</sup>,21]. Indeed, during these early stages of granuloma formation, the T cells surrounding the mycobacteria are somehow reminiscent of riot police kettling tactics to contain street protests.

*MTB*-specific CD4 T-cell responses play a central role in the control of aerosolic *MTB* infection [15,17,22,23]; Antibody-mediated depletion of CD4 T cells but not CD8 T cells, slightly reminiscent of HIV pathogenesis, drastically reduces control of *MTB* growth and survival upon challenge of mice [24]. Perhaps most conclusive, adoptive transfer of transgenic *MTB*-specific CD4 Th 1 cells potently restricts *MTB* growth in the lungs of recipient mice in a dose-dependent manner [17]. Thus, although CD4 T-cell independent mechanisms are likely to contribute to microbial immunity, CD4 T cells are key in the control of murine *MTB* infection.

Protective immunity against human TB remains poorly characterized. Human genetic mutations in IL-12p40 or IFN- $\gamma$  receptor genes [25] or treatment with TNF antagonists [26] are associated with a greater risk of TB disease progression, consistent with a central role of 'TH1 cytokines' for efficient control of *MTB* infection also in humans. Nonhuman primate experiments not only support an important role for CD4 T cells [10<sup>22</sup>,27] but also suggest a more prominent role

for CD8 T cells, which include nonclassical CD8 T cells found in humans, but not in mice [28]. Thus, impaired control of *MTB* infection after HIV infection still provides the best evidence for an important role of CD4 T cells in human anti-*MTB* immunity.

### **AIDS VIRUS-INDUCED DEPLETION OF CD4 T CELLS FROM THE AIR-TISSUE INTERPHASE IN THE LUNG**

Loss of CD4 T cells during HIV disease progression is brought on by persistent viral replication. Interfering with viral replication by highly active antiretroviral therapy (HAART) initiation reconstitutes CD4 T-cell counts, largely restores pathogen-specific CD4 T-cell responses and substantially decreases the risk of developing active TB [29–31]. CCR5-tropic virus variants are responsible for most transmission events and typically prevail until late phase of infection [32]. During natural HIV infection, CXCR4 tropism evolves only relatively late in infection after CD4 T-cell numbers have dropped substantially [33] and is associated with infection and depletion of naive CD4 T cells [34]. Thus, early loss of *MTB* immune control should usually be linked to CCR5 tropism and selective targeting CCR5<sup>+</sup> CD4 T cells; CCR5 expression is characteristic of effector memory CD4 T cells isolated from mucosal tissues including the lung [35–37] and can be induced by antigenic stimulation and activation of CD4 T cells *in vitro* [38], but is largely absent from naive CD4 T cells. CCR5-tropic viruses preferentially infect and replicate in activated memory CD4 T cells that express the chemokine receptor CCR5 and these cells are preferentially depleted after AIDS virus infection [35]. Pathogenesis of CCR5-tropic virus infection has been intensively studied after experimental infection of simian rhesus macaques with SIVs – a good model for human HIV infection. Both, acute and chronic SIV and HIV infection results in extensive depletion of effector memory CD4 T cells from mucosal effector sites, [39–42] including the tissue-air interphase of the lung [36,43]. Hence, effector memory CD4 T cells at the primary site of aerosolic *MTB* infection, are also a primary target for depletion after infection with CCR5 tropic viruses and the timing of their depletion after SIV infection is associated with reactivation of *MTB* infection in macaques [10<sup>22</sup>]. Influx of newly generated CD4 T effector memory cells can partially replenish CD4 T cells in the air-tissue interphase, despite their reduced life span during SIV infection [36,43,44]. Increased cellular turn over and maturation of central memory into effector memory CD4 T cells are responsible for continuous renewal of this

effector memory T-cell population and probably simultaneously promote AIDS virus replication in transitional CD4 T cells [45,46], resulting in a net loss of effector memory CD4 T-cell output from secondary lymphoid organs. Progressive loss of the capacity for renewal of this effector memory CD4 T-cell pool is thought to be central to the pathogenesis AIDS virus infection [43]. Substantial and progressive depletion of CD4 T cell within tissue–air interphase is also characteristic of chronic HIV-infected humans [47<sup>••</sup>,48<sup>••</sup>,49<sup>•</sup>]. Human tissue–air interphase CD4 T cells are effector memory T cells as characterized by a CD45RA<sup>+</sup>CCR7<sup>-</sup>CD27<sup>-</sup> phenotype [47<sup>••</sup>,48<sup>••</sup>]. Blocking virus replication by HAART initiation reverses CD4 T-cell depletion within tissue–air interphase [49<sup>•</sup>] and reduces the risk of developing active TB by at least 70% [29]. Together, these data demonstrate that the site of primary *MTB* infection is particularly vulnerable to AIDS virus-induced immune defects.

The timing of effector memory CD4 T-cell depletion from the air–tissue interphase after SIV infection is associated with reactivation of *MTB* infection [10<sup>••</sup>], suggesting that HIV infection can reduce efficacy of the protective properties of an existing granuloma [50<sup>•</sup>]. This finding is supported by histological studies that found differences in the cellular composition, architecture and function of *MTB* granulomas associated with HIV infection, such as fewer mononuclear cells, fewer CD4 T cell [51,52], perturbations in TNF expression and larger areas of necrosis [51,53]. A more recent study found no such morphological alterations in granulomas during pleural TB during earlier HIV disease stages [53]. Interestingly, granulocyte involvement appears to be increased granulomas from HIV<sup>+</sup> patients, resembling a pattern also observed in *MTB*-infected CD4 knockout mice [11,23,51]. In summary, relatively little information is known about HIV interference with the *MTB* granuloma. The pathogenic mechanisms of AIDS virus-induced granuloma dysfunction need further clarification.

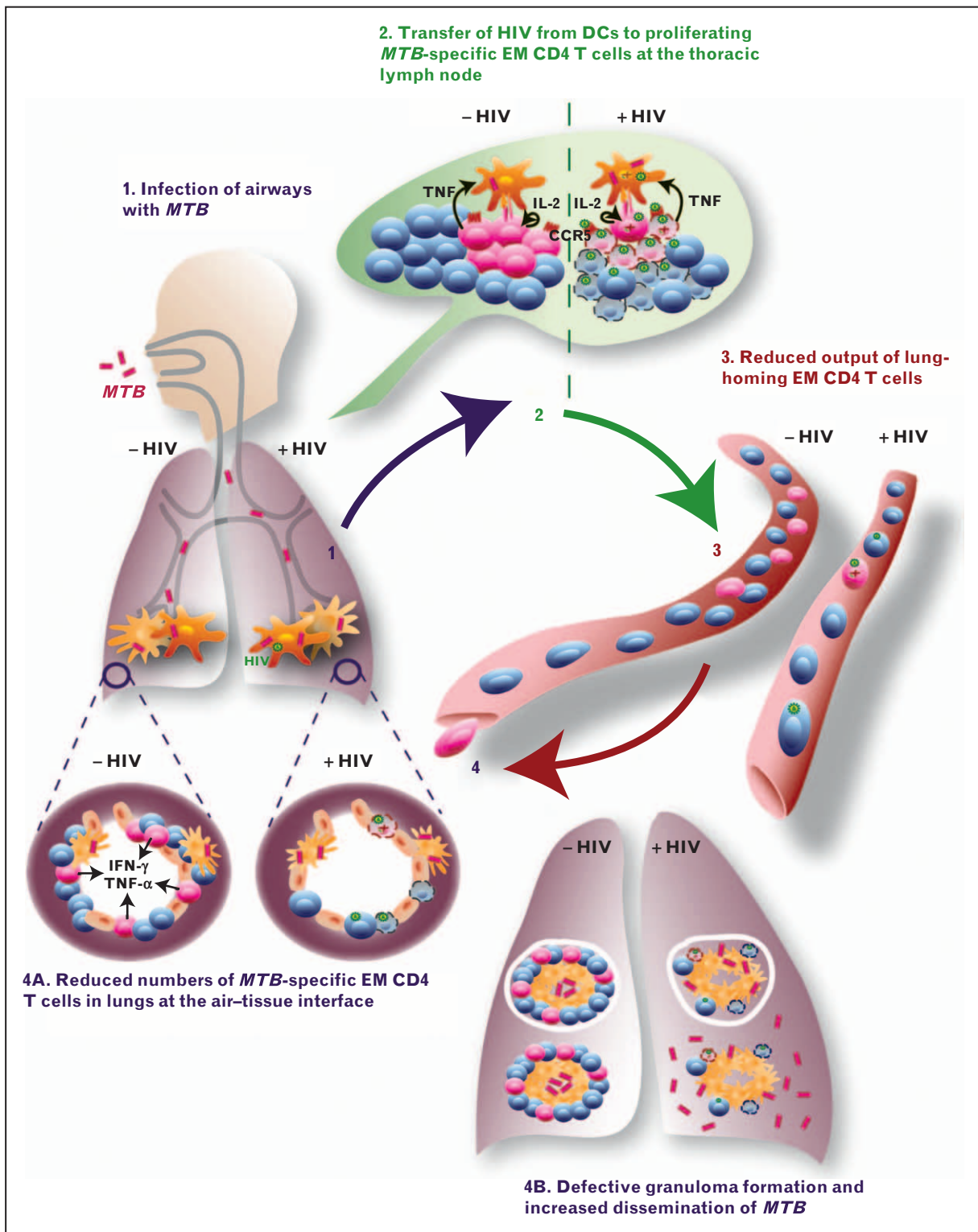
### **DYNAMICS OF MYCOBACTERIUM TUBERCULOSIS-SPECIFIC CD4 TH1-CELL RESPONSES AFTER HIV INFECTION**

The timing of disease caused by opportunistic infections is not strictly related to the extent of CD4 T-cell depletion for a given pathogen. HIV-associated changes in the quantity or quality of opportunistic pathogen-specific CD4 T-cell responses could potentially contribute to increased susceptibility to a given pathogen [54]. For example, clinical complications caused by cytomegalovirus (CMV) closely correlates with depletion of CMV-specific CD4 T-cell responses

[55–57]. Similarly, in SIV/bacillus Calmette-Guérin coinfecting rhesus macaques reactivation of tuberculosis-like disease coincides with waning mycobacterial-specific T-cell proliferative responses [27]. Several studies, including our own, have recently shown that *MTB*-specific CD4 T-cell responses are preferentially depleted after HIV infection from circulation and also from the tissue–air interphase [47<sup>••</sup>,48<sup>••</sup>,58<sup>•</sup>] suggesting that *MTB*-specific immunity is particularly vulnerable to HIV-induced defects. These data support the hypothesis that a reduction in the generation of lung homing *MTB*-specific effector memory CD4 Th1 cells after HIV infection is a key factor in the increase risk for development of active TB (Fig. 2).

The reasons for differential depletion of different pathogen-specific CD4 T cells after HIV infection are probably multifactorial. Phenotypic and functional properties of *MTB*-specific CD4 T cells, such as surface expression of CCR5 [59], a low capacity to secrete ‘protective’ CCR5 ligand MIP-1 $\beta$  and large capacity for interleukin (IL) 2-dependent T-cell proliferation promote cellular HIV infection *in vitro* and *in vivo* [58<sup>•</sup>,59–61]. And indeed, *MTB*-specific CD4 T cells have significantly higher cell-associated viral loads *in vivo* as compared with total memory CD4 T cells during active TB [58<sup>•</sup>]. Activated mycobacteria-specific CD4 T-cell responses strongly promote HIV replication both *in vitro* [60] and *in vivo* [62,63]. These data support a model in which a combination of proinflammatory cytokines and cell-contact dependent costimulatory interactions maximize transcription of the HIV genome and production of virions in HIV-infected antigen-presenting cells, which transmit to responding CCR5<sup>+</sup>, proliferating *MTB*-specific CD4 T cells [64,65] Refer to Fig. 4/2. Such a scenario would depend on ongoing *MTB*-specific stimulation of CD4 T cells during latency. A continuous crosstalk between the host immune system and the persisting pathogens [66] would support such a model.

However, the level of antigenic stimulation during *MTB* latency is unclear and probably varies between individuals. Loss of *MTB*-specific CD4 T-cell response rather argues against strong antigenic stimulation after HIV infection, because, somehow counterintuitive, *MTB*-specific CD4 T cells can often be detected in HIV-positive patients with active TB, most probable due to antigen-driven CD4 T-cell expansion counteracting (or concealing) depletion. Persistent or expanding *MTB* responses after HIV and SIV infection have indeed rather been associated with subsequent progression [59,67,68]. As a consequence, it is difficult to dissect the effects of AIDS virus-associated CD4 T-cell depletion in the presence of strong antigen-driven cellular CD4 T-cell



**FIGURE 2.** Proposed mechanism of how HIV-induced CD4 T-cell depletion impairs immune control of *MTB* infection. 1, Infection of airways with *MTB* (red rods); the bacilli are taken up by alveolar macrophages (pale orange) and dendritic cells (DCs, dark orange). *MTB*-infected DCs then migrate to the thoracic lymph nodes to trigger the adaptive *MTB*-specific CD4 T-cell response. Some *MTB*-infected DCs are coinfecting with HIV. 2, Within the lymph node, HIV is efficiently transferred from DCs to *MTB*-specific CD4 T cells that respond to cognate antigen. DC-T-cell interaction maximizes HIV virion production in antigen-presenting cells and simultaneously increases CCR5 expression by activated *MTB*-specific CD4 T cells (pink). IL-2-dependent cell cycling promotes complete reverse transcription of the viral RNA genome and as a consequence productive

expansion during reactivating TB. In the majority of 'latently' infected humans, T-cell stimulation apparently is insufficient to maintain *MTB*-specific CD4 T-cell responses after HIV infection, implying that other protective mechanisms, such as 'hermetically sealed granulomas' or other immune cell subsets [28] might contain *MTB* replication. Alternatively, the presence of *MTB*-specific T-cell memory might not necessarily equate with reactivatable disease [29,69,70]. Epidemiological studies are divided: some studies argue rather for *novo* exposure as compared with reactivation as a frequent cause of HIV-associated active TB in high-burden settings of sub-Saharan Africa [7], whereas a recent study shows a five-fold increased TB incidence of HIV<sup>+</sup>/interferon gamma release assay positive (IGRA<sup>+</sup>) patients (5%) compared with HIV<sup>+</sup>/IGRA<sup>-</sup> patients (<1%), supporting latent *MTB* reactivation as an important cause for active TB in HIV patients [71]. Thus, both mechanisms are likely to play a role. However, it is tempting to speculate that recent exposure and early granuloma formation and maturation is more likely to be affected by HIV interference, as compared with old, mature, 'fibrotic and calcified' lesions, which might restrict bacterial dissemination more independent of T-cell effector function.

## CONCLUSION

In conclusion, AIDS virus infection interferes with the generation of effector memory CD4 T cell that migrate to the primary site of *MTB* infection – the lung – and dramatically increases risk of developing active TB. Moreover, *MTB*-specific CD4 T-cell responses are selectively depleted both, in circulation and at the air–tissue interphase of the lung, and probably further aggravating the failure of the immune system to efficiently control *MTB* after HIV infection. Other 'more global' immune defects brought on by persistent viral replication, such as persistent immune activation or dysfunction and depletion of antigen-presenting cells, are also likely to promote TB disease progression in HIV-infected

individuals. Hence, at this point in time, early initiation of antiretroviral therapy or the development of an efficacious HIV vaccine would be the best options to reduce morbidity and mortality associated with this co-epidemic.

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## Conflicts of interest

We have no conflicts of interest to report.

## REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 287–289).

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**FIGURE 2.** (Continued) HIV infection of *MTB*-specific CD4 T cells. Non cycling CD4 T cells (blue) in close vicinity/contact to productively infected cells also die as a result of abortive HIV infection. 3, HIV infection reduces the output of lung homing effector memory and particularly *MTB*-specific CD4 T cells. 4, *MTB*-specific EM CD4 T cells home to the lung, the primary site of *MTB* infection. HIV reduces the overall number of lung homing *MTB*-specific EM CD4 TH1 cells and shortens cell survival of EM CD4 T cells. As a consequence, T-cell-mediated granuloma formation, maturation and thus the control of *MTB* infection is impaired leading to an increased risk to develop active TB upon new *MTB* infection. 4A, HIV reduces the overall number of lung homing *MTB*-specific EM CD4 TH1 cells and shortens cell survival of EM CD4 T cells. As a consequence, T-cell-mediated granuloma formation, maturation and thus the control of *MTB* infection is impaired leading to an increased risk to develop active TB upon new *MTB* infection. 4B, In HIV-infected humans with latent *MTB* infection, reduced delivery of *MTB*-specific CD4 TH1 cells decreases functionality of the *MTB* granuloma and promotes escape of *MTB* from the granuloma and increases the risk of systemic dissemination of *MTB* infection. It can be speculated that more mature, fibrotic granulomas might contain *MTB* infection more independently from CD4 T-cell depletion.

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