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REVIEW ARTICLE

Immunopathogenesis in HIV-associated pediatric tuberculosis

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Tuberculosis (TB) is an increasing global emergency in human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) patients, in which host immunity is dysregulated and compromised. However, the pathogenesis and efficacy of therapeutic strategies in HIV-associated TB in developing infants are essentially lacking. Bacillus Calmette-Guerin vaccine, an attenuated live strain of *Mycobacterium bovis*, is not adequately effective, which confers partial protection against *Mycobacterium tuberculosis* (*Mtb*) in infants when administered at birth. However, pediatric HIV infection is most devastating in the disease progression of TB. It remains challenging whether early antiretroviral therapy (ART) could maintain immune development and function, and restore *Mtb*-specific immune function in HIV-associated TB in children. A better understanding of the immunopathogenesis in HIV-associated pediatric *Mtb* infection is essential to provide more effective interventions, reducing the risk of morbidity and mortality in HIV-associated *Mtb* infection in infants.

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IMPACT:

- Children living with HIV are more likely prone to opportunistic infection, predisposing high risk of TB diseases.
- HIV and *Mtb* coinfection in infants may synergistically accelerate disease progression.
- Early ART may probably induce immune reconstitution inflammatory syndrome and TB pathology in HIV/*Mtb* coinfected infants.

INTRODUCTION

Mycobacterium tuberculosis (*Mtb*) remains a major global public health problem with more than one million deaths each year, and patients infected with *Mtb* develop latent tuberculosis infection (LTBI) or active tuberculosis (TB).[1–3] Human immunodeficiency virus (HIV) infection markedly increases susceptibility to TB, 20–30 times greater to develop active TB than those without HIV infection (https://www.who.int/hiv/topics/tb/about_tb/en/).[4] *Mtb* and HIV act in detrimental synergy, accelerating the decline of immunological functions and subsequent death if untreated. Given distinct immune systems, children infected with TB are more prone to develop active disease, occurring sooner and more frequently,[5–9] yet the immunopathogenesis and clinical outcomes in infants with HIV/Mtb coinfection are unknown.

HIV-ASSOCIATED *MTB* INFECTION IN INFANTS

HIV infection is a significant driving force of the global TB epidemic, especially in sub-Saharan Africa,[4] resulting in epidemiologic shifts in pediatric TB cases, with an increased incidence of TB among HIV-infected women and their infants.[10] HIV-infected infants (≤12 months of age) and young children have a high risk of TB disease, with an estimated incidence of culture-confirmed TB ~>24-fold higher among HIV+ than HIV− infants,[11] and a 20-fold increase in the incidence of LTBI in HIV-exposed uninfected (HEU) children compared to children unexposed to HIV.[12] Antiretroviral therapy (ART) during pregnancy prevents maternal HIV disease progression and significantly reduces rates of perinatal transmission,[13,14] yet there is a substantial risk of several adverse pregnancies and negative birth outcomes in "uninfected" infants.[14–20] Although the majority of infants now remain uninfected due to improved pre- and postnatal HIV care, there is a rapidly increasing population of HEU infants who still show persistent inflammation and many abnormalities of immune function and suffer from poor health outcomes, especially in infancy.[15,18,21–30] Indeed, there is a growing awareness that this large and expanding population of HEU infants may have compromised immune function,[15,18,22,23,29–41] which may influence subsequent immune responses to *Mtb*, increasing the risk of TB incidence.[42] These immunological differences indicate uniquely altered host–pathogen interactions in developing infant immune systems, which likely increase host vulnerability to *Mtb*. Notably, inducible bronchus-associated lymphoid tissue (iBALT), an organized structure for initiation of antibody responses, is essentially not present in infants, which may be implicated in the exacerbation of *Mtb* infection of infants.[43–45] HIV-associated chronic lung disease is increasingly more prevalent in children with lower CD4+ T cell counts and high viral loads. These children often show chronic cough, pneumonia (e.g., *Pneumocystis jirovecii* or/and lymphocytic interstitial pneumonia) and clinical respiratory symptoms (e.g., tachypnea, mild to severe distress and hypoxia, lymphoproliferative response, pulmonary immune reconstitution inflammatory syndrome/IRIS), which are caused by multifactor including recurrent bacterial (e.g., *Streptococcus pneumoniae*) or severe viral (*Cytomegalovirus* or/and Epstein–Barr virus) or fungal (e.g., *Candida albicans*) infection as long-term sequelae.[46–54] Although the live attenuated Bacillus Calmette-Guérin (BCG) vaccine is routinely administered to 80% of neonates globally and effectively prevents the most severe complications of TB, its efficacy wanes with age.[55,56] BCG vaccination is contraindicated in

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HIV-infected infants, and infants at risk for HIV due to the potential of inducing disseminated BCG disease,[11,57,58] which is consistent with simian immunodeficiency virus (SIV)-infected infant macaque studies vaccinated with attenuated *Mtb* or *Mycobacterium bovis* BCG.[59] Multifactor, including unique immunoregulation and ontogeny in infants and children, and HIV-associated immunodeficiency, may be implicated in the poor Mtb containment, as indicated by: (1) HIV-infected children with TB tend to have more extensive lung involvement;[60–62] (2) HIV-related immune suppression increases susceptibility to *Mtb* infection;[63] (3) HIV-infected children with a CD4 percentage of <15% had a fourfold higher TB incidence;[64] and (4) among HIV-infected children with TB, the mortality increases sixfold (41 vs. 7%).[65] Notably, initiation of ART in HIV-infected infants reduces mortality and opportunistic infection including TB, suggesting that early combination ART is necessary,[66] because primary isoniazid prophylaxis treatment alone does not improve TB-free survival among HIV-infected children.[67]

POTENTIALLY COMPROMISED IMMUNE RESPONSES IN PEDIATRIC HIV AND *MTB* COINFECTION

The lung is the primary mucosal portal of *Mtb* entry, thus both innate and adaptive immune responses in the mucosal system desperately play an essential role in immune control of *Mtb* infection.[68–72] Strikingly, converging evidence indicates that the neonatal immune system is highly compartmentalized: the mucosal immune system is more competent and develops faster than the systemic immune system. This different organ-specific maturation of the immune system between these two systemic and mucosal systems may directly affect the infection and transmission,[73,74] so mucosal immune responses against infections might be similar between infants and adults. In the context of HIV and/or *Mtb* infection, many immune cells, including T/B cells and innate lymphoid cells (macrophages, monocytes, natural killer cells, and myeloid-derived cells), are involved.

It is reported that CD4+ T-helper type 1 (Th1) cells and CD8+ T cells, which produce interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), and cytolytic granules, may be essential for effective immune controls to bacterial *Mtb*.[75–79] However, most people with active TB typically exhibit robust Th1 and IFN-γ responses,[80] contributing to immunopathology.[81] It is widely accepted that HIV infection results in massive depletion of mucosal lymphocyte cells in mucosal tissues, especially Th17 and Th22 and other innate lymphoid cells responsible for the regulation of mucosal integrity.[82–85] HIV/*Mtb* coinfection thus devastates multiple aspects of host immunosurveillance, as indicated by altered production of TNF-α, IFN-γ, interleukin-2 and interleukin-10,[86,87] and impaired differentiation and function of *Mtb*-specific CD4+ and CD8+ T cells.[88–92] Meanwhile, *Mtb*-specific antibody responses also play an essential role in bacterial containment upon pulmonary challenge with *Mtb*.[93–95] The ectopic lymphoid and iBALT in lung parenchyma adjacent to granulomas, which usually have normal to reactive B cell and germinal centers (GCs) containing follicular Th cells (Tfh),[96–98] are believed to defend against *Mtb* invasion.[93,99] Since Tfh cells are critical for cognate B cell help in generating humoral immune responses, Tfh cells, together with macrophage and other CD4+ T cells as major cellular HIV reservoir within these "sanctuary sites" of lymphoid tissues,[100–102] definitely display impaired immune function, leading to active TB and rapid disease progression. However, the events and outcomes in *Mtb* and HIV coinfection in infants remain elusive due to lack of iBALT.

Mtb-specific innate immunity, which shows long-lasting memory responses mediated by innate cells, persists in the host providing long-lived protection termed trained immunity.[72,103–106] These innate cells have the potential to undergo expansions and/or acquire epigenetic modifications that primed against *Mtb*, yet trained immunity in HIV-associated pediatric TB remains unknown. Of innate cells, macrophages are the predominant sentinel immune cells and the primary target cell for both HIV and *Mtb* infection. Macrophages are involved in recognition, phagocytosis and elimination of pathogens and debris, and producing cellular mediators to prime immune responses with different activation states (proinflammatory M1 and anti-inflammatory M2 phenotype). Two macrophage populations exist in the BAL and lung tissues: lung-resident alveolar macrophages (AMs) and interstitial macrophages (IMs).[107,108] AMs are a larger proportion of long-lived cells (75–80%) derived from embryonic precursors, which replenish their populations by in situ self-renewal, but not from the circulation.[109,110] The AMs support bacterial growth, albeit bacilli are distributed both AM and peripheral monocyte-derived IMs,[111] yet HIV-infected AMs are insensitive to ART.[112,113] Interestingly, peripheral AMs seem to be absent in infants at birth,[108,114] suggesting that AM precursors may exist in lung tissues of newborn and gradually expand with age. Conversely, IMs exhibit a higher turnover rate, similar to peripheral monocytes, and implement the important immune function. Infant AMs have less capacity to restrict *Mtb* replication and unresponsive to *Pneumocystis murina* infection,[115–118] yet the role of neonatal IMs is unknown. Further, SIV/*Mtb* coinfection in infants increases the turnover of monocytes, in which massive numbers of macrophages in the lung are infected and eventually depleted, which may contribute to active pediatric TB disease.[119] These findings support the concept that pulmonary macrophages, especially AM in the lung and BAL, are unique in HIV-associated pediatric TB, compared with those in adults.

PATHOLOGICAL CHANGES IN HIV-ASSOCIATED PEDIATRIC TB

Highly pathogenic mycobacterial infections breach mucosal barriers in the lung parenchyma and cause inflammation, granuloma formation, cavitation, and scarring, leading to the loss of pulmonary function. Granuloma formation is triggered by the macrophages and then develops with multinucleated giant cells and an intracytoplasmic frothy appearance. In active TB, granulomas are a hallmark of the local response against *Mtb* in the lung, which form an immunological barrier to limit bacterial dissemination and growth.[120,121] Granuloma is surrounded by a ring, which comprises macrophages, dendritic cells, and aggregated lymphocytes. Inside the granuloma, neutrophil granulocytes (myeloperoxidase-expressing cells) are predominantly distributed (Fig. 1a, b), accompanied by hypoxia and a high concentration of nitric oxide (NO).[122–124] In some infant macaques with typically active *Mtb*, less organized coalescing granulomas are observed, exhibiting distinct macrophage layers, more significant infiltration of T cells into it, and clustered B cells along the peripheral margin of the granuloma (Fig. 1c, d), in concert with constituted indoleamine 2, 3-dioxygenase (IDO)-expressing cells in the layer (Fig. 1e, f). Note IDO catalyzes the rate-limiting step in the kynurenine production, which suppresses innate and adaptive immunity,[125–129] probably explaining why host immunity fails to fully kill bacilli. Granulomas can form in any tissue, but predominantly in the lungs and lymph nodes. Lymph nodes are the primary site for the development of adaptive immune responses. It is reported that initiation of the adaptive immune response to *Mtb* depends on antigen production in the local lymph node, not the lungs.[130] There simply is no bronchus-associated mucosal tissues in infant, as these develop in response to antigen exposures after birth. Thus, the onset of the adaptive immune response to *Mtb* is delayed compared with intestinal infections, likely due to lack of iBALT.[131,132] Even though lymph nodes are present at birth, lymphoid follicle organization and GC formation and T cell recruitment do not occur until several weeks after birth in normal infants.[133] In contrast, GC Tfh cell development in

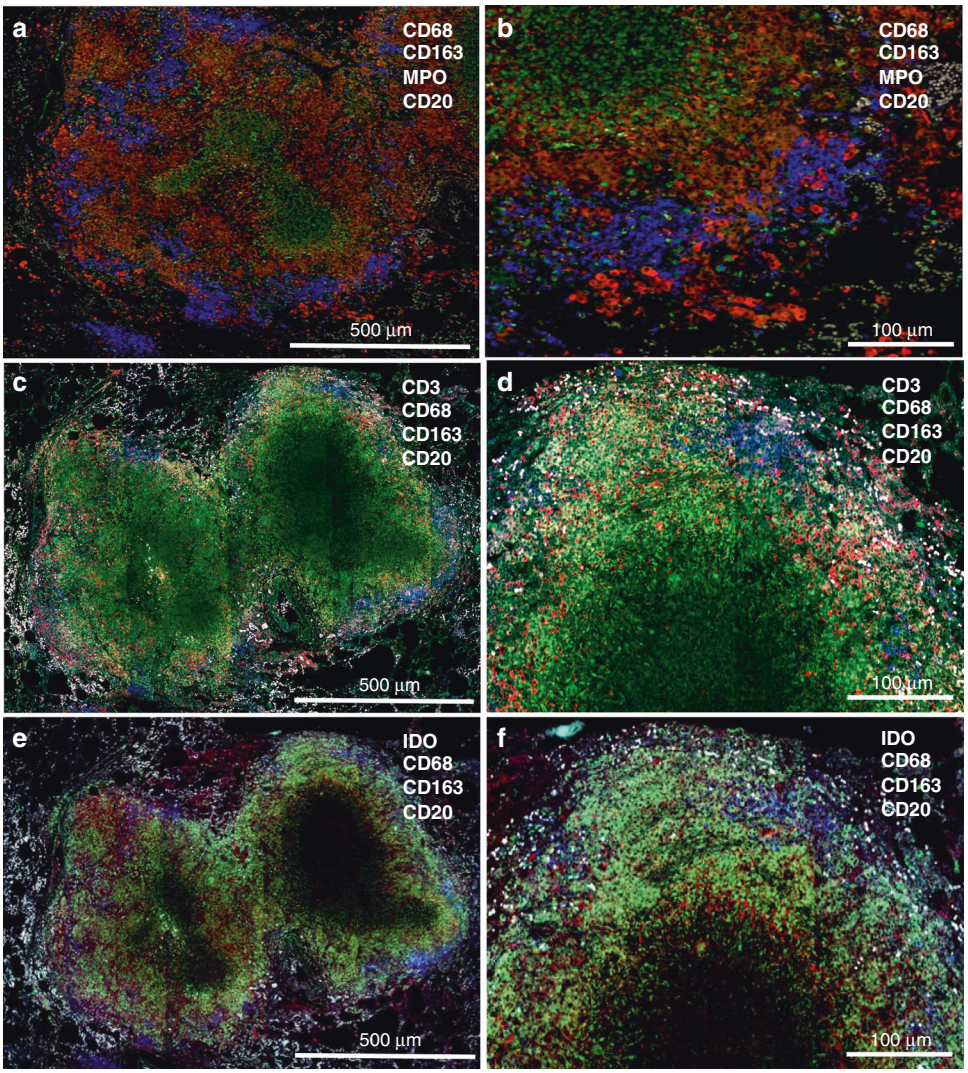

Fig. 1 Pulmonary granulomas in infant macaques with tuberculosis. a, **b** Granulomas, comprising of macrophage layers (red) and clusters of CD20+ B cells (blue), are organized well with a central area of caseous necrosis (MPO-expressing neutrophils). **c**–**f** Less organized coalescing granulomas, surrounded by a layer of macrophages (green) and IDO-expressing cells (red, **e**, **f**) with infiltration of CD3+ T cells (red, **c**, **d**). Clustered 20+ B cells (blue) distributed along the layer. MPO myeloperoxidase, IDO indoleamine-pyrrole 2,3-dioxygenase.

SIV-infected infants is markedly impaired throughout infection, accompanied by impaired follicular development and defective B cell proliferation and differentiation. Lymph nodes are thus the most common site of extrapulmonary TB (EPTB) infection in HIV-infected children,[134,135] and endothelial cells in lymph nodes have been shown to be potential niches for *Mtb* that allows persistent infection.[136] Higher rates of EPTB are observed in HIV-infected infants and adults,[134,137,138] suggesting inadequate immunological control of HIV/*Mtb* coinfected patients. Impaired immune development and function in pediatric lymph nodes might get worse in HIV-associated pediatric TB.

HIV infection may alter host immunity and affects the integrity of the *Mtb* granuloma structure, and is more likely to reactivate latent *Mtb* infection into active TB, thus exacerbating the disease.[89,139,140] In support of this concept, HIV-infected patients without ART have >20-fold higher risk of developing active TB disease than those without HIV infection.[141] In contrast, very early ART initiation has a tremendous impact on reducing the risk of TB disease in HIV-infected patients (~67%).[141,142] Although ART in HIV/*Mtb* coinfected patients reduces HIV-associated opportunistic infections and increased *Mtb*-specific T cell responses. However, this treatment may not ameliorate TB pathology and may even accelerate TB progression due to the possible immune reconstitution inflammatory syndrome, especially in patients with lower CD4 T cell counts, high viral loads or EPTB.[143–146] TB-IRIS is an adverse consequence of the restoration of local pathogen-specific immune responses in HIV-infected patients during the initial ART (~18% HIV/TB coinfection),[147] resulting in abnormal cytokine responses and cell migration to the inflammatory sites,[148–151] yet paradoxical TB-IRS initiating ART in children is observed.[152–154] Taken together, HIV and *Mtb* coinfection in infants may have synergistic detrimental effects on immunologic functions, resulting in conditions favoring replication of both pathogens and accelerating disease progression and increasing morbidity and mortality in HIV-associated pediatric TB. Understanding the mechanisms behind the susceptibility of infants with HIV to TB and immunopathogenesis is critical for preventing and treating HIV/*Mtb* coinfection.

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ADDITIONAL INFORMATION

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