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Immunopathogenesis in HIV-associated pediatric tuberculosis

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Abstract

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 tuberculosis in developing infants are essentially lacking. Bacillus *Calmette-Guerin* (BCG) 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 tuberculosis. It remains challenging whether early antiretroviral therapy (ART) could maintain immune development and function, and restore *Mtb*-specific immune function in HIV-associated tuberculosis 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.

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 (TB) infection or active tuberculosis (1–3). HIV infection markedly increases susceptibility to TB, 20–30 times greater to develop active tuberculosis 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 tuberculosis 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

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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 approximately >24-fold higher amongst HIV+ than HIV negative infants (11), and a 20-fold increase in the incidence of latent TB infection (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 post-natal HIV care, there is a rapidly increasing population of HIV-exposed uninfected (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*, PCP; or/and lymphocytic interstitial pneumonia, LIP) 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,* CMV; 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 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 SIV-infected infant macaque studies vaccinated with attenuated *Mtb* or *M. 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 four-fold higher TB incidence (64); and 4) among HIV-infected children with TB, the mortality increases six-fold (41% vs. 7%) (65). Notably, initiation of antiretroviral therapy (ART) in HIV-infected infants reduces mortality and opportunistic infection including TB, suggesting that early cART is necessary (66), because primary isoniazid prophylaxis treatment alone does not improve tuberculosis-free survival among HIV-infected children (67).

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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+ Th1 cells and CD8+ T cells, which produce IFN-γ, 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 lymphocytes 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, IL-2 and IL-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 (GC) containing follicular T helper 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 tuberculosis 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).

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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 AM precursors may exist in lung tissues of newborn and gradually expand in with age. Conversely, IMs exhibit a higher turnover rate, similar to peripheral monocytes, and implement the important immune function. Infant AMs are 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 tuberculosis, compared with those in adults.

Pathological changes of HIV-associated pediatric tuberculosis

Highly pathogenic mycobacterial infections breach mucosal barriers in the lung parenchyma and cause inflammation, granuloma formation, cavitation, and scarring leading to loss of pulmonary function. Granuloma formation is triggered by the macrophages and then develops with multi-nucleated 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 (Figs. 1A and 1B), accompanying 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 (Figs. 1C and 1D), in concert with constituted indoleamine 2, 3 dioxygenase (IDO)-expressing cells in the layer (Figs. 1E and 1F). 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 germinal center (GC) formation and T cells recruitment do not occur until several weeks after birth in normal infants (133). In contrast, GC Tfh cell development in 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-

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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 tuberculosis, thus exacerbating the disease (89, 139, 140). In support of this concept, HIV-infected patients without antiretroviral therapy 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 antiretroviral therapy 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 (IRIS), 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 tuberculosis. 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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References

1. Manabe YC, Bishai WR 2000 Latent Mycobacterium tuberculosis-persistence, patience, and winning by waiting. Nat Med 6:1327–1329. [PubMed: 11100115]
2. Zumla A, Chakaya J, Centis R, D’Ambrosio L, Mwaba P, Bates M, Kapata N, Nyirenda T, Chanda D, Mfinanga S, Hoelscher M, Maeurer M, Migliori GB 2015 Tuberculosis treatment and management--an update on treatment regimens, trials, new drugs, and adjunct therapies. Lancet Respir Med 3:220–234. [PubMed: 25773212]
3. Salgame P, Geadas C, Collins L, Jones-Lopez E, Ellner JJ 2015 Latent tuberculosis infection--Revisiting and revising concepts. Tuberculosis (Edinb) 95:373–384. [PubMed: 26038289]
4. Corbett EL, Watt CJ, Walker N, Maher D, Williams BG, Raviglione MC, Dye C 2003 The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. Arch Intern Med 163:1009–1021. [PubMed: 12742798]
5. Esposito S, Tagliabue C, Bosis S 2013 Tuberculosis in children. Mediterr J Hematol Infect Dis 5:e2013064. [PubMed: 24363879]
6. Blusse van Oud-Alblas HJ, van Vliet ME, Kimpen JL, de Villiers GS, Schaaf HS, Donald PR 2002 Human immunodeficiency virus infection in children hospitalised with tuberculosis. Ann Trop Paediatr 22:115–123. [PubMed: 12070946]
7. Newton SM, Brent AJ, Anderson S, Whittaker E, Kampmann B 2008 Paediatric tuberculosis. Lancet Infect Dis 8:498–510. [PubMed: 18652996]

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8. Roya-Pabon CL, Perez-Velez CM 2016 Tuberculosis exposure, infection and disease in children: a systematic diagnostic approach. Pneumonia (Nathan) 8:23. [PubMed: 28702302]
9. Kay A, Garcia-Prats AJ, Mandalakas AM 2018 HIV-associated pediatric tuberculosis: prevention, diagnosis and treatment. Curr Opin HIV AIDS 13:501–506. [PubMed: 30286040]
10. Marais BJ, Gie RP, Schaaf HS, Hesseling AC, Obihara CC, Starke JJ, Enarson DA, Donald PR, Beyers N 2004 The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era. Int J Tuberc Lung Dis 8:392–402. [PubMed: 15141729]
11. Hesseling AC, Cotton MF, Jennings T, Whitelaw A, Johnson LF, Eley B, Roux P, Godfrey-Faussett P, Schaaf HS 2009 High incidence of tuberculosis among HIV-infected infants: evidence from a South African population-based study highlights the need for improved tuberculosis control strategies. Clin Infect Dis 48:108–114. [PubMed: 19049436]
12. Marquez C, Chamie G, Achan J, Luetkemeyer AF, Kyohere M, Okiring J, Dorsey G, Kamya MR, Charlebois ED, Havlir DV 2016 Tuberculosis Infection in Early Childhood and the Association with HIV-exposure in HIV-uninfected Children in Rural Uganda. Pediatr Infect Dis J 35:524–529. [PubMed: 26771662]
13. Tuomala RE, Shapiro DE, Mofenson LM, Bryson Y, Culnane M, Hughes MD, O'Sullivan MJ, Scott G, Stek AM, Wara D, Bulterys M 2002 Antiretroviral therapy during pregnancy and the risk of an adverse outcome. N Engl J Med 346:1863–1870. [PubMed: 12063370]
14. Bailey H, Zash R, Rasi V, Thorne C 2018 HIV treatment in pregnancy. Lancet HIV 5:e457–e467. [PubMed: 29958853]
15. Afran L, Garcia Knight M, Nduati E, Urban BC, Heyderman RS, Rowland-Jones SL 2014 HIV-exposed uninfected children: a growing population with a vulnerable immune system? Clin Exp Immunol 176:11–22. [PubMed: 24325737]
16. Evans C, Humphrey JH, Ntozini R, Prendergast AJ 2016 HIV-Exposed Uninfected Infants in Zimbabwe: Insights into Health Outcomes in the Pre-Antiretroviral Therapy Era. Front Immunol 7:190. [PubMed: 27375613]
17. Fowler MG, Qin M, Fiscus SA, Currier JS, Flynn PM, Chipato T, McIntyre J, Gnanashanmugam D, Siberry GK, Coletti AS, Taha TE, Klingman KL, Martinson FE, Owor M, Violari A, Moodley D, Theron GB, Bhosale R, Bobat R, Chi BH, Strehlau R, Mlay P, Loftis AJ, Browning R, Fenton T, Purdue L, Basar M, Shapiro DE, Mofenson LM, Team IBFPS 2016 Benefits and Risks of Antiretroviral Therapy for Perinatal HIV Prevention. N Engl J Med 375:1726–1737. [PubMed: 27806243]
18. Schoeman JC, Moutloatse GP, Harms AC, Vreeken RJ, Scherpbier HJ, Van Leeuwen L, Kuijpers TW, Reinecke CJ, Berger R, Hankemeier T, Bunders MJ 2017 Fetal Metabolic Stress Disrupts Immune Homeostasis and Induces Proinflammatory Responses in Human Immunodeficiency Virus Type 1- and Combination Antiretroviral Therapy-Exposed Infants. J Infect Dis 216:436–446. [PubMed: 28633455]
19. Caniglia EC, Zash R, Jacobson DL, Diseko M, Mayondi G, Lockman S, Chen JY, Mmalane M, Makhema J, Hernan MA, Shapiro RL 2018 Emulating a target trial of antiretroviral therapy regimens started before conception and risk of adverse birth outcomes. AIDS 32:113–120. [PubMed: 29112066]
20. Malaba TR, Phillips T, Le Roux S, Brittain K, Zerbe A, Petro G, Ronan A, McIntyre JA, Abrams EJ, Myer L 2017 Antiretroviral therapy use during pregnancy and adverse birth outcomes in South African women. Int J Epidemiol 46:1678–1689. [PubMed: 29040569]
21. Brennan AT, Bonawitz R, Gill CJ, Thea DM, Kleinman M, Useem J, Garrison L, Ceccarelli R, Udokwu C, Long L, Fox MP 2016 A meta-analysis assessing all-cause mortality in HIV-exposed uninfected compared with HIV-unexposed uninfected infants and children. AIDS 30:2351–2360. [PubMed: 27456985]
22. Miyamoto M, Gouvea A, Ono E, Succi RCM, Pahwa S, Moraes-Pinto MI 2017 Immune development in HIV-exposed uninfected children born to HIV-infected women. Rev Inst Med Trop Sao Paulo 59:e30. [PubMed: 28591258]
23. Clerici M, Saresella M, Colombo F, Fossati S, Sala N, Bricalli D, Villa ML, Ferrante P, Dally L, Vigano A 2000 T-lymphocyte maturation abnormalities in uninfected newborns and children with vertical exposure to HIV. Blood 96:3866–3871. [PubMed: 11090071]

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24. Weinberg A, Lindsey J, Bosch R, Persaud D, Sato P, Ogwu A, Asmelash A, Bwakura-Dangarambezi M, Chi BH, Canniff J, Lockman S, Gaseitsiwe S, Moyo S, Smith CE, Moraka NO, Levin MJ, Tshipidi Study T 2017 B and T Cell Phenotypic Profiles of African HIV-Infected and HIV-Exposed Uninfected Infants: Associations with Antibody Responses to the Pentavalent Rotavirus Vaccine. Front Immunol 8:2002. [PubMed: 29403482]

25. Bender JM, Li F, Martelly S, Byrt E, Rouzier V, Leo M, Tobin N, Pannaraj PS, Adisetiyo H, Rollie A, Santiskulvong C, Wang S, Autran C, Bode L, Fitzgerald D, Kuhn L, Aldrovandi GM 2016 Maternal HIV infection influences the microbiome of HIV-uninfected infants. Sci Transl Med 8:349ra100.

26. Roider JM, Muenchhoff M, Goulder PJ 2016 Immune activation and paediatric HIV-1 disease outcome. Curr Opin HIV AIDS 11:146–155. [PubMed: 26679413]

27. Kasahara TM, Hygino J, Blanco B, Xavier L, Araujo-Lima CF, Guillermo LV, Bittencourt VC, Guimaraes V, Andrade AF, Bento CA 2013 The impact of maternal antiretroviral therapy on cytokine profile in the uninfected neonates. Hum Immunol 74:1051–1056. [PubMed: 23792057]

28. Ruck C, Reikie BA, Marchant A, Kollmann TR, Kakkar F 2016 Linking Susceptibility to Infectious Diseases to Immune System Abnormalities among HIV-Exposed Uninfected Infants. Front Immunol 7:310. [PubMed: 27594857]

29. Kidzeru EB, Hesseling AC, Passmore JA, Myer L, Gamieldien H, Tchakoute CT, Gray CM, Sodora DL, Jaspan HB 2014 In-utero exposure to maternal HIV infection alters T-cell immune responses to vaccination in HIV-uninfected infants. AIDS 28:1421–1430. [PubMed: 24785950]

30. Kakkar F, Lamarre V, Ducruet T, Boucher M, Valois S, Soudeyns H, Lapointe N 2014 Impact of maternal HIV-1 viremia on lymphocyte subsets among HIV-exposed uninfected infants: protective mechanism or immunodeficiency. BMC Infect Dis 14:236. [PubMed: 24885498]

31. Yeo KT, Embury P, Anderson T, Mungai P, Malhotra I, King C, Kazura J, Dent A 2019 HIV, Cytomegalovirus, and Malaria Infections during Pregnancy Lead to Inflammation and Shifts in Memory B Cell Subsets in Kenyan Neonates. J Immunol 202:1465–1478. [PubMed: 30674575]

32. Dirajlal-Fargo S, Mussi-Pinhata MM, Weinberg A, Yu Q, Cohen R, Harris DR, Bowman E, Gabriel J, Kulkarni M, Funderburg N, Chakhtoura N, McComsey GA, Protocol NL 2019 HIV-exposed-uninfected infants have increased inflammation and monocyte activation. AIDS 33:845–853. [PubMed: 30649056]

33. Prestes-Carneiro LE 2013 Antiretroviral therapy, pregnancy, and birth defects: a discussion on the updated data. HIV AIDS (Auckl) 5:181–189. [PubMed: 23943659]

34. Baker CA, Swainson L, Lin DL, Wong S, Hartigan-O'Connor DJ, Lifson JD, Tarantal AF, McCune JM 2015 Exposure to SIV in utero results in reduced viral loads and altered responsiveness to postnatal challenge. Sci Transl Med 7:300ra125.

35. Miyamoto M, Pessoa SD, Ono E, Machado DM, Salomao R, Succi RC, Pahwa S, de Moraes-Pinto MI 2010 Low CD4+ T-cell levels and B-cell apoptosis in vertically HIV-exposed noninfected children and adolescents. J Trop Pediatr 56:427–432. [PubMed: 20388660]

36. Evans C, Jones CE, Prendergast AJ 2016 HIV-exposed, uninfected infants: new global challenges in the era of paediatric HIV elimination. Lancet Infect Dis 16:e92–e107. [PubMed: 27049574]

37. Bunders MJ, van Hamme JL, Jansen MH, Boer K, Kootstra NA, Kuijpers TW 2014 Fetal exposure to HIV-1 alters chemokine receptor expression by CD4+T cells and increases susceptibility to HIV-1. Sci Rep 4:6690. [PubMed: 25341640]

38. Pfeifer C, Bunders MJ 2016 Maternal HIV infection alters the immune balance in the mother and fetus; implications for pregnancy outcome and infant health. Curr Opin HIV AIDS 11:138–145. [PubMed: 26679415]

39. Gaensbauer JT, Rakhola JT, Onyango-Makumbi C, Mubiru M, Westcott JE, Krebs NF, Asturias EJ, Fowler MG, McFarland E, Janoff EN 2014 Impaired haemophilus influenzae type b transplacental antibody transmission and declining antibody avidity through the first year of life represent potential vulnerabilities for HIV-exposed but -uninfected infants. Clin Vaccine Immunol 21:1661–1667. [PubMed: 25298109]

40. Abu-Raya B, Kollmann TR, Marchant A, MacGillivray DM 2016 The Immune System of HIV-Exposed Uninfected Infants. Front Immunol 7:383. [PubMed: 27733852]

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41. Chougnet C, Kovacs A, Baker R, Mueller BU, Luban NL, Liewehr DJ, Steinberg SM, Thomas EK, Shearer GM 2000 Influence of human immunodeficiency virus-infected maternal environment on development of infant interleukin-12 production. J Infect Dis 181:1590–1597. [PubMed: 10823758]
42. Weld ED, Dooley KE 2018 State-of-the-Art Review of HIV-TB Coinfection in Special Populations. Clin Pharmacol Ther 104:1098–1109. [PubMed: 30137652]
43. Gould SJ, Isaacson PG 1993 Bronchus-associated lymphoid tissue (BALT) in human fetal and infant lung. J Pathol 169:229–234. [PubMed: 8445488]
44. Pabst R, Tschernig T 2010 Bronchus-associated lymphoid tissue: an entry site for antigens for successful mucosal vaccinations? Am J Respir Cell Mol Biol 43:137–141. [PubMed: 20508066]
45. Marin ND, Dunlap MD, Kaushal D, Khader SA 2019 Friend or Foe: The Protective and Pathological Roles of Inducible Bronchus-Associated Lymphoid Tissue in Pulmonary Diseases. J Immunol 202:2519–2526. [PubMed: 31010841]
46. Graham SM 2003 Impact of HIV on childhood respiratory illness: differences between developing and developed countries. Pediatr Pulmonol 36:462–468. [PubMed: 14618636]
47. Graham SM 2003 HIV and respiratory infections in children. Curr Opin Pulm Med 9:215–220. [PubMed: 12682567]
48. Zar HJ 2008 Chronic lung disease in human immunodeficiency virus (HIV) infected children. Pediatr Pulmonol 43:1–10. [PubMed: 18041077]
49. Theron S, Andronikou S, George R, du Plessis J, Goussard P, Hayes M, Mapukata A, Gie R 2009 Non-infective pulmonary disease in HIV-positive children. Pediatr Radiol 39:555–564. [PubMed: 19300991]
50. Pitcher RD, Lombard C, Cotton MF, Beningfield SJ, Zar HJ 2014 Clinical and immunological correlates of chest X-ray abnormalities in HIV-infected South African children with limited access to antiretroviral therapy. Pediatr Pulmonol 49:581–588. [PubMed: 23970463]
51. Mestdagh H 1976 Morphological aspects and biomechanical properties of the vertebroaxial joint (C2-C3). Acta Morphol Neerl Scand 14:19–30. [PubMed: 1274679]
52. Zampoli M, Kilborn T, Eley B 2007 Tuberculosis during early antiretroviral-induced immune reconstitution in HIV-infected children. Int J Tuberc Lung Dis 11:417–423. [PubMed: 17394688]
53. Adhikari M, Jeena P, Bobat R, Archary M, Naidoo K, Coutsoudis A, Singh R, Nair N 2011 HIV-Associated Tuberculosis in the Newborn and Young Infant. Int J Pediatr 2011:354208. [PubMed: 21541068]
54. Rabie H, Goussard P 2016 Tuberculosis and pneumonia in HIV-infected children: an overview. Pneumonia (Nathan) 8:19. [PubMed: 28702298]
55. Trunz BB, Fine P, Dye C 2006 Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness. Lancet 367:1173–1180. [PubMed: 16616560]
56. Roy P, Vekemans J, Clark A, Sanderson C, Harris RC, White RG 2019 Potential effect of age of BCG vaccination on global paediatric tuberculosis mortality: a modelling study. Lancet Glob Health 7:e1655–e1663. [PubMed: 31708146]
57. Hesseling AC, Marais BJ, Gie RP, Schaaf HS, Fine PE, Godfrey-Faussett P, Beyers N 2007 The risk of disseminated Bacille Calmette-Guerin (BCG) disease in HIV-infected children. Vaccine 25:14–18. [PubMed: 16959383]
58. Hesseling AC, Cotton MF, Marais BJ, Gie RP, Schaaf HS, Beyers N, Fine PE, Abrams EJ, Godfrey-Faussett P, Kuhn L 2007 BCG and HIV reconsidered: moving the research agenda forward. Vaccine 25:6565–6568. [PubMed: 17659816]
59. Jensen K, Dela Pena-Ponce MG, Piatak M Jr., Shoemaker R, Oswald K, Jacobs WR Jr., Fennelly G, Lucero C, Mollan KR, Hudgens MG, Amedee A, Kozlowski PA, Estes JD, Lifson JD, Van Rompay KK, Larsen M, De Paris K 2017 Balancing Trained Immunity with Persistent Immune Activation and the Risk of Simian Immunodeficiency Virus Infection in Infant Macaques Vaccinated with Attenuated Mycobacterium tuberculosis or Mycobacterium bovis BCG Vaccine. Clin Vaccine Immunol 24.

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60. Schaaf HS, Marais BJ, Whitelaw A, Hesseling AC, Eley B, Hussey GD, Donald PR 2007 Culture-confirmed childhood tuberculosis in Cape Town, South Africa: a review of 596 cases. BMC Infect Dis 7:140. [PubMed: 18047651]
61. Marais BJ, Donald PR, Gie RP, Schaaf HS, Beyers N 2005 Diversity of disease in childhood pulmonary tuberculosis. Ann Trop Paediatr 25:79–86. [PubMed: 15949195]
62. Madhi SA, Huebner RE, Doedens L, Aduc T, Wesley D, Cooper PA 2000 HIV-1 co-infection in children hospitalised with tuberculosis in South Africa. Int J Tuberc Lung Dis 4:448–454. [PubMed: 10815739]
63. Bucher HC, Griffith LE, Guyatt GH, Sudre P, Naef M, Sendi P, Battegay M 1999 Isoniazid prophylaxis for tuberculosis in HIV infection: a meta-analysis of randomized controlled trials. AIDS 13:501–507. [PubMed: 10197379]
64. Mukadi YD, Wiktor SZ, Coulibaly IM, Coulibaly D, Mbengue A, Folquet AM, Ackah A, Sassan-Morokro M, Bonnard D, Maurice C, Nolan C, Kreiss JK, Greenberg AE 1997 Impact of HIV infection on the development, clinical presentation, and outcome of tuberculosis among children in Abidjan, Cote d'Ivoire. AIDS 11:1151–1158. [PubMed: 9233463]
65. Palme IB, Gudetta B, Bruchfeld J, Muhe L, Giesecke J 2002 Impact of human immunodeficiency virus 1 infection on clinical presentation, treatment outcome and survival in a cohort of Ethiopian children with tuberculosis. Pediatr Infect Dis J 21:1053–1061. [PubMed: 12442029]
66. Wiseman CA, Schaaf HS, Cotton MF, Gie RP, Jennings T, Whitelaw A, Roux P, Hesseling AC 2011 Bacteriologically confirmed tuberculosis in HIV-infected infants: disease spectrum and survival. Int J Tuberc Lung Dis 15:770–775. [PubMed: 21575297]
67. Madhi SA, Nachman S, Violari A, Kim S, Cotton MF, Bobat R, Jean-Philippe P, McSherry G, Mitchell C, Team PS 2011 Primary isoniazid prophylaxis against tuberculosis in HIV-exposed children. N Engl J Med 365:21–31. [PubMed: 21732834]
68. North RJ, Jung YJ 2004 Immunity to tuberculosis. Annu Rev Immunol 22:599–623. [PubMed: 15032590]
69. Podinovskaia M, Lee W, Caldwell S, Russell DG 2013 Infection of macrophages with Mycobacterium tuberculosis induces global modifications to phagosomal function. Cell Microbiol 15:843–859. [PubMed: 23253353]
70. Parandhaman DK, Narayanan S 2014 Cell death paradigms in the pathogenesis of Mycobacterium tuberculosis infection. Front Cell Infect Microbiol 4:31. [PubMed: 24634891]
71. Kallenius G, Pawlowski A, Brandtzaeg P, Svenson S 2007 Should a new tuberculosis vaccine be administered intranasally? Tuberculosis (Edinb) 87:257–266. [PubMed: 17321797]
72. Khader SA, Divangahi M, Hanekom W, Hill PC, Maeurer M, Makar KW, Mayer-Barber KD, Mhlanga MM, Nemes E, Schlesinger LS, van Crevel R, Vankayalapati R, Xavier RJ, Netea MG, Bill, Melinda Gates Foundation Collaboration for TBVDIIWG 2019 Targeting innate immunity for tuberculosis vaccination. J Clin Invest 129:3482–3491. [PubMed: 31478909]
73. Wang X, Rasmussen T, Pahar B, Poonia B, Alvarez X, Lackner AA, Veazey RS 2007 Massive infection and loss of CD4+ T cells occurs in the intestinal tract of neonatal rhesus macaques in acute SIV infection. Blood 109:1174–1181. [PubMed: 17047153]
74. Wang X, Xu H, Pahar B, Alvarez X, Green LC, Dufour J, Moroney-Rasmussen T, Lackner AA, Veazey RS 2010 Simian immunodeficiency virus selectively infects proliferating CD4+ T cells in neonatal rhesus macaques. Blood 116:4168–4174. [PubMed: 20716768]
75. Mogues T, Goodrich ME, Ryan L, LaCourse R, North RJ 2001 The relative importance of T cell subsets in immunity and immunopathology of airborne Mycobacterium tuberculosis infection in mice. J Exp Med 193:271–280. [PubMed: 11157048]
76. Lazarevic V, Flynn J 2002 CD8+ T cells in tuberculosis. Am J Respir Crit Care Med 166:1116–1121. [PubMed: 12379557]
77. Lin PL, Flynn JL 2015 CD8 T cells and Mycobacterium tuberculosis infection. Semin Immunopathol 37:239–249. [PubMed: 25917388]
78. Shen L, Frencher J, Huang D, Wang W, Yang E, Chen CY, Zhang Z, Wang R, Qaqish A, Larsen MH, Shen H, Porcelli SA, Jacobs WR Jr., Chen ZW 2019 Immunization of Vgamma2Vdelta2 T cells programs sustained effector memory responses that control tuberculosis in nonhuman primates. Proc Natl Acad Sci U S A 116:6371–6378. [PubMed: 30850538]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

79. Day CL, Abrahams DA, Lerumo L, Janse van Rensburg E, Stone L, O'Rie T, Pienaar B, de Kock M, Kaplan G, Mahomed H, Dheda K, Hanekom WA 2011 Functional capacity of Mycobacterium tuberculosis-specific T cell responses in humans is associated with mycobacterial load. J Immunol 187:2222–2232. [PubMed: 21775682]
80. Sester M, Sotgiu G, Lange C, Giehl C, Girardi E, Migliori GB, Bossink A, Dheda K, Diel R, Dominguez J, Lipman M, Nemeth J, Ravn P, Winkler S, Huitric E, Sandgren A, Manissero D 2011 Interferon-gamma release assays for the diagnosis of active tuberculosis: a systematic review and meta-analysis. Eur Respir J 37:100–111. [PubMed: 20847080]
81. Elkington PT, Friedland JS 2015 Permutations of time and place in tuberculosis. Lancet Infect Dis 15:1357–1360. [PubMed: 26321650]
82. Xu H, Wang X, Liu DX, Moroney-Rasmussen T, Lackner AA, Veazey RS 2012 IL-17-producing innate lymphoid cells are restricted to mucosal tissues and are depleted in SIV-infected macaques. Mucosal Immunol 5:658–669. [PubMed: 22669579]
83. Klatt NR, Estes JD, Sun X, Ortiz AM, Barber JS, Harris LD, Cervasi B, Yokomizo LK, Pan L, Vinton CL, Tabb B, Canary LA, Dang Q, Hirsch VM, Alter G, Belkaid Y, Lifson JD, Silvestri G, Milner JD, Paiardini M, Haddad EK, Brenchley JM 2012 Loss of mucosal CD103+ DCs and IL-17+ and IL-22+ lymphocytes is associated with mucosal damage in SIV infection. Mucosal Immunol 5:646–657. [PubMed: 22643849]
84. Xu H, Wang X, Veazey RS 2013 Mucosal immunology of HIV infection. Immunol Rev 254:10–33. [PubMed: 23772612]
85. Wang X, Xu H, Shen C, Alvarez X, Liu D, Pahar B, Ratterree MS, Doyle-Meyers LA, Lackner AA, Veazey RS 2015 Profound loss of intestinal Tregs in acutely SIV-infected neonatal macaques. J Leukoc Biol 97:391–400. [PubMed: 25492938]
86. Patel NR, Zhu J, Tachado SD, Zhang J, Wan Z, Saukkonen J, Koziel H 2007 HIV impairs TNF-alpha mediated macrophage apoptotic response to Mycobacterium tuberculosis. J Immunol 179:6973–6980. [PubMed: 17982088]
87. Patel NR, Swan K, Li X, Tachado SD, Koziel H 2009 Impaired M. tuberculosis-mediated apoptosis in alveolar macrophages from HIV+ persons: potential role of IL-10 and BCL-3. J Leukoc Biol 86:53–60. [PubMed: 19383626]
88. Geldmacher C, Ngwenyama N, Schuetz A, Petrovas C, Reither K, Heeregrave EJ, Casazza JP, Ambrozak DR, Louder M, Ampofo W, Pollakis G, Hill B, Sanga E, Saathoff E, Maboko L, Roederer M, Paxton WA, Hoelscher M, Koup RA 2010 Preferential infection and depletion of Mycobacterium tuberculosis-specific CD4 T cells after HIV-1 infection. J Exp Med 207:2869–2881. [PubMed: 21115690]
89. Day CL, Abrahams DA, Harris LD, van Rooyen M, Stone L, de Kock M, Hanekom WA 2017 HIV-1 Infection Is Associated with Depletion and Functional Impairment of Mycobacterium tuberculosis-Specific CD4 T Cells in Individuals with Latent Tuberculosis Infection. J Immunol 199:2069–2080. [PubMed: 28760884]
90. Suarez GV, Angerami MT, Vecchione MB, Laufer N, Turk G, Ruiz MJ, Mesch V, Fabre B, Maidana P, Ameri D, Cahn P, Sued O, Salomon H, Bottasso OA, Quiroga MF 2015 HIV-TB coinfection impairs CD8(+) T-cell differentiation and function while dehydroepiandrosterone improves cytotoxic antitubercular immune responses. Eur J Immunol 45:2529–2541. [PubMed: 26047476]
91. Chetty S, Govender P, Zupkosky J, Pillay M, Ghebremichael M, Moosa MY, Ndung'u T, Porichis F, Kasprowicz VO 2015 Co-infection with Mycobacterium tuberculosis impairs HIV-Specific CD8+ and CD4+ T cell functionality. PLoS One 10:e0118654. [PubMed: 25781898]
92. Kalokhe AS, Adekambi T, Ibegbu CC, Ray SM, Day CL, Rengarajan J 2015 Impaired degranulation and proliferative capacity of Mycobacterium tuberculosis-specific CD8+ T cells in HIV-infected individuals with latent tuberculosis. J Infect Dis 211:635–640. [PubMed: 25205634]
93. Phuah J, Wong EA, Gideon HP, Maiello P, Coleman MT, Hendricks MR, Ruden R, Cirrincione LR, Chan J, Lin PL, Flynn JL 2016 Effects of B Cell Depletion on Early Mycobacterium tuberculosis Infection in Cynomolgus Macaques. Infect Immun 84:1301–1311. [PubMed: 26883591]
94. Maglione PJ, Xu J, Chan J 2007 B cells moderate inflammatory progression and enhance bacterial containment upon pulmonary challenge with Mycobacterium tuberculosis. J Immunol 178:7222–7234. [PubMed: 17513771]

Author Manuscript

95. Lu LL, Chung AW, Rosebrock TR, Ghebremichael M, Yu WH, Grace PS, Schoen MK, Tafesse F, Martin C, Leung V, Mahan AE, Sips M, Kumar MP, Tedesco J, Robinson H, Tkachenko E, Draghi M, Freedberg KJ, Streeck H, Suscovich TJ, Lauffenburger DA, Restrepo BI, Day C, Fortune SM, Alter G 2016 A Functional Role for Antibodies in Tuberculosis. Cell 167:433–443 e414. [PubMed: 27667685]
96. Slight SR, Rangel-Moreno J, Gopal R, Lin Y, Fallert Junecko BA, Mehra S, Selman M, Becerril-Villanueva E, Baquera-Heredia J, Pavon L, Kaushal D, Reinhart TA, Randall TD, Khader SA 2013 CXCR5(+) T helper cells mediate protective immunity against tuberculosis. J Clin Invest 123:712–726. [PubMed: 23281399]
97. Ulrichs T, Kosmiadi GA, Trusov V, Jorg S, Pradl L, Titukhina M, Mishenko V, Gushina N, Kaufmann SH 2004 Human tuberculous granulomas induce peripheral lymphoid follicle-like structures to orchestrate local host defence in the lung. J Pathol 204:217–228. [PubMed: 15376257]
98. Tsai MC, Chakravarty S, Zhu G, Xu J, Tanaka K, Koch C, Tufariello J, Flynn J, Chan J 2006 Characterization of the tuberculous granuloma in murine and human lungs: cellular composition and relative tissue oxygen tension. Cell Microbiol 8:218–232. [PubMed: 16441433]
99. Phuah JY, Mattila JT, Lin PL, Flynn JL 2012 Activated B cells in the granulomas of nonhuman primates infected with Mycobacterium tuberculosis. Am J Pathol 181:508–514. [PubMed: 22721647]
100. Xu H, Wang X, Malam N, Aye PP, Alvarez X, Lackner AA, Veazey RS 2015 Persistent Simian Immunodeficiency Virus Infection Drives Differentiation, Aberrant Accumulation, and Latent Infection of Germinal Center Follicular T Helper Cells. J Virol 90:1578–1587. [PubMed: 26608323]
101. Cubas RA, Mudd JC, Savoye AL, Perreau M, van Grevenynghe J, Metcalf T, Connick E, Meditz A, Freeman GJ, Abesada-Terk G Jr., Jacobson JM, Brooks AD, Crotty S, Estes JD, Pantaleo G, Lederman MM, Haddad EK 2013 Inadequate T follicular cell help impairs B cell immunity during HIV infection. Nat Med 19:494–499. [PubMed: 23475201]
102. Mouquet H 2014 Antibody B cell responses in HIV-1 infection. Trends Immunol 35:549–561. [PubMed: 25240985]
103. Joosten SA, van Meijgaarden KE, Arend SM, Prins C, Oftung F, Korsvold GE, Kik SV, Arts RJ, van Crevel R, Netea MG, Ottenhoff TH 2018 Mycobacterial growth inhibition is associated with trained innate immunity. J Clin Invest 128:1837–1851. [PubMed: 29461976]
104. Netea MG, van Crevel R 2014 BCG-induced protection: effects on innate immune memory. Semin Immunol 26:512–517. [PubMed: 25444548]
105. Ferluga J, Yasmin H, Al-Ahdal MN, Bhakta S, Kishore U 2020 Natural and trained innate immunity against Mycobacterium tuberculosis. Immunobiology:151951. [PubMed: 32423788]
106. Koeken V, Verrall AJ, Netea MG, Hill PC, van Crevel R 2019 Trained innate immunity and resistance to Mycobacterium tuberculosis infection. Clin Microbiol Infect 25:1468–1472. [PubMed: 30807849]
107. Yu YR, Hotten DF, Malakhau Y, Volker E, Ghio AJ, Noble PW, Kraft M, Hollingsworth JW, Gunn MD, Tighe RM 2016 Flow Cytometric Analysis of Myeloid Cells in Human Blood, Bronchoalveolar Lavage, and Lung Tissues. Am J Respir Cell Mol Biol 54:13–24. [PubMed: 26267148]
108. Bharat A, Bhorade SM, Morales-Nebreda L, McQuattie-Pimentel AC, Soberanes S, Ridge K, DeCamp MM, Mestan KK, Perlman H, Budinger GR, Misharin AV 2016 Flow Cytometry Reveals Similarities Between Lung Macrophages in Humans and Mice. Am J Respir Cell Mol Biol 54:147–149. [PubMed: 26274047]
109. Hashimoto D, Chow A, Noizat C, Teo P, Beasley MB, Leboeuf M, Becker CD, See P, Price J, Lucas D, Greter M, Mortha A, Boyer SW, Forsberg EC, Tanaka M, van Rooijen N, Garcia-Sastre A, Stanley ER, Ginhoux F, Frenette PS, Merad M 2013 Tissue-resident macrophages self-maintain locally throughout adult life with minimal contribution from circulating monocytes. Immunity 38:792–804. [PubMed: 23601688]
110. Yona S, Kim KW, Wolf Y, Mildner A, Varol D, Breker M, Strauss-Ayali D, Viukov S, Guilliams M, Misharin A, Hume DA, Perlman H, Malissen B, Zelzer E, Jung S 2013 Fate mapping reveals

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

origins and dynamics of monocytes and tissue macrophages under homeostasis. Immunity 38:79–91. [PubMed: 23273845]

111. Cohen SB, Gern BH, Delahaye JL, Adams KN, Plumlee CR, Winkler JK, Sherman DR, Gerner MY, Urdahl KB 2018 Alveolar Macrophages Provide an Early Mycobacterium tuberculosis Niche and Initiate Dissemination. Cell Host Microbe 24:439–446 e434. [PubMed: 30146391]
112. Wong ME, Jaworowski A, Hearps AC 2019 The HIV Reservoir in Monocytes and Macrophages. Front Immunol 10:1435. [PubMed: 31297114]
113. Jambo KC, Banda DH, Kankwatira AM, Sukumar N, Allain TJ, Heyderman RS, Russell DG, Mwandumba HC 2014 Small alveolar macrophages are infected preferentially by HIV and exhibit impaired phagocytic function. Mucosal Immunol 7:1116–1126. [PubMed: 24472847]
114. Alenghat E, Esterly JR 1984 Alveolar macrophages in perinatal infants. Pediatrics 74:221–223. [PubMed: 6540435]
115. Schneberger D, Aharonson-Raz K, Singh B 2011 Monocyte and macrophage heterogeneity and Toll-like receptors in the lung. Cell Tissue Res 343:97–106. [PubMed: 20824285]
116. Tan SY, Krasnow MA 2016 Developmental origin of lung macrophage diversity. Development 143:1318–1327. [PubMed: 26952982]
117. Goenka A, Prise IE, Connolly E, Fernandez-Soto P, Morgan D, Cavet JS, Grainger JR, Nichani J, Arkwright PD, Hussell T 2020 Infant Alveolar Macrophages Are Unable to Effectively Contain Mycobacterium tuberculosis. Front Immunol 11:486. [PubMed: 32265931]
118. Kurkjian C, Hollifield M, Lines JL, Rogosky A, Empey KM, Qureshi M, Brown SA, Garvy BA 2012 Alveolar macrophages in neonatal mice are inherently unresponsive to Pneumocystis murina infection. Infect Immun 80:2835–2846. [PubMed: 22665378]
119. Kuroda MJ, Sugimoto C, Cai Y, Merino KM, Mehra S, Arainga M, Roy CJ, Midkiff CC, Alvarez X, Didier ES, Kaushal D 2018 High Turnover of Tissue Macrophages Contributes to Tuberculosis Reactivation in Simian Immunodeficiency Virus-Infected Rhesus Macaques. J Infect Dis.
120. Gideon HP, Phuah J, Myers AJ, Bryson BD, Rodgers MA, Coleman MT, Maiello P, Rutledge T, Marino S, Fortune SM, Kirschner DE, Lin PL, Flynn JL 2015 Variability in tuberculosis granuloma T cell responses exists, but a balance of pro- and anti-inflammatory cytokines is associated with sterilization. PLoS Pathog 11:e1004603. [PubMed: 25611466]
121. Ehlers S, Schaible UE 2012 The granuloma in tuberculosis: dynamics of a host-pathogen collusion. Front Immunol 3:411. [PubMed: 23308075]
122. Orme IM, Basaraba RJ 2014 The formation of the granuloma in tuberculosis infection. Semin Immunol 26:601–609. [PubMed: 25453231]
123. Remot A, Doz E, Winter N 2019 Neutrophils and Close Relatives in the Hypoxic Environment of the Tuberculous Granuloma: New Avenues for Host-Directed Therapies? Front Immunol 10:417. [PubMed: 30915076]
124. Qualls JE, Murray PJ 2016 Immunometabolism within the tuberculosis granuloma: amino acids, hypoxia, and cellular respiration. Semin Immunopathol 38:139–152. [PubMed: 26490974]
125. Mandi Y, Vecsei L 2012 The kynurenine system and immunoregulation. J Neural Transm (Vienna) 119:197–209. [PubMed: 21744051]
126. Curti A, Trabanelli S, Onofri C, Aluigi M, Salvestrini V, Ocadlikova D, Evangelisti C, Rutella S, De Cristofaro R, Ottaviani E, Baccarani M, Lemoli RM 2010 Indoleamine 2,3-dioxygenase-expressing leukemic dendritic cells impair a leukemia-specific immune response by inducing potent T regulatory cells. Haematologica 95:2022–2030. [PubMed: 20801903]
127. Schmidt SV, Schultze JL 2014 New Insights into IDO Biology in Bacterial and Viral Infections. Front Immunol 5:384. [PubMed: 25157255]
128. Dagenais-Lussier X, Aounallah M, Mehraj V, El-Far M, Tremblay C, Sekaly RP, Routy JP, van Grevenynghe J 2016 Kynurenine Reduces Memory CD4 T-Cell Survival by Interfering with Interleukin-2 Signaling Early during HIV-1 Infection. J Virol 90:7967–7979. [PubMed: 27356894]
129. Gaelings L, Soderholm S, Bugai A, Fu Y, Nandania J, Schepens B, Lorey MB, Tynell J, Vande Ginste L, Le Goffic R, Miller MS, Kuisma M, Marjomaki V, De Brabander J, Matikainen S, Nyman TA, Bamford DH, Saelens X, Julkunen I, Paavilainen H, Hukkanen V, Velagapudi V,

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Kainov DE 2017 Regulation of kynurenine biosynthesis during influenza virus infection. FEBS J 284:222–236. [PubMed: 27860276]

130. Wolf AJ, Desvignes L, Linas B, Banaiee N, Tamura T, Takatsu K, Ernst JD 2008 Initiation of the adaptive immune response to Mycobacterium tuberculosis depends on antigen production in the local lymph node, not the lungs. J Exp Med 205:105–115. [PubMed: 18158321]
131. Chackerian AA, Alt JM, Perera TV, Dascher CC, Behar SM 2002 Dissemination of Mycobacterium tuberculosis is influenced by host factors and precedes the initiation of T-cell immunity. Infect Immun 70:4501–4509. [PubMed: 12117962]
132. Behr MA, Waters WR 2014 Is tuberculosis a lymphatic disease with a pulmonary portal? Lancet Infect Dis 14:250–255. [PubMed: 24268591]
133. Xu H, Ziani W, Shao J, Doyle-Meyers LA, Russell-Lodrigue KE, Ratterree MS, Veazey RS, Wang X 2018 Impaired Development and Expansion of Germinal Center Follicular Th Cells in Simian Immunodeficiency Virus-Infected Neonatal Macaques. J Immunol 201:1994–2003. [PubMed: 30104244]
134. Kritsaneepaiboon S, Andres MM, Tatco VR, Lim CCQ, Concepcion NDP 2017 Extrapulmonary involvement in pediatric tuberculosis. Pediatr Radiol 47:1249–1259. [PubMed: 29052770]
135. Maltezou HC, Spyridis P, Kafetzis DA 2000 Extra-pulmonary tuberculosis in children. Arch Dis Child 83:342–346. [PubMed: 10999874]
136. Lerner TR, de Souza Carvalho-Wodarz C, Repnik U, Russell MR, Borel S, Diedrich CR, Rohde M, Wainwright H, Collinson LM, Wilkinson RJ, Griffiths G, Gutierrez MG 2016 Lymphatic endothelial cells are a replicative niche for Mycobacterium tuberculosis. J Clin Invest 126:1093–1108. [PubMed: 26901813]
137. Bhattacharya D, Danaviah S, Muema DM, Akilimali NA, Moodley P, Ndung'u T, Das G 2017 Cellular Architecture of Spinal Granulomas and the Immunological Response in Tuberculosis Patients Coinfected with HIV. Front Immunol 8:1120. [PubMed: 28955338]
138. Naing C, Mak JW, Maung M, Wong SF, Kassim AI 2013 Meta-analysis: the association between HIV infection and extrapulmonary tuberculosis. Lung 191:27–34. [PubMed: 23180033]
139. Getahun H, Gunneberg C, Granich R, Nunn P 2010 HIV infection-associated tuberculosis: the epidemiology and the response. Clin Infect Dis 50 Suppl 3:S201–207.
140. Du Bruyn E, Wilkinson RJ 2016 The Immune Interaction between HIV-1 Infection and Mycobacterium tuberculosis. Microbiol Spectr 4.
141. Lawn SD, Harries AD, Williams BG, Chaisson RE, Losina E, De Cock KM, Wood R 2011 Antiretroviral therapy and the control of HIV-associated tuberculosis. Will ART do it? Int J Tuberc Lung Dis 15:571–581. [PubMed: 21756508]
142. Lawn SD, Wood R, De Cock KM, Kranzer K, Lewis JJ, Churchyard GJ 2010 Antiretrovirals and isoniazid preventive therapy in the prevention of HIV-associated tuberculosis in settings with limited health-care resources. Lancet Infect Dis 10:489–498. [PubMed: 20610331]
143. Elliott JH, Vohith K, Saramony S, Savuth C, Dara C, Sarim C, Huffam S, Oelrichs R, Sophea P, Saphonn V, Kaldor J, Cooper DA, Chhi Vun M, French MA 2009 Immunopathogenesis and diagnosis of tuberculosis and tuberculosis-associated immune reconstitution inflammatory syndrome during early antiretroviral therapy. J Infect Dis 200:1736–1745. [PubMed: 19874177]
144. Meintjes G, Wilkinson KA, Rangaka MX, Skolimowska K, van Veen K, Abrahams M, Seldon R, Pepper DJ, Rebe K, Mouton P, van Cutsem G, Nicol MP, Maartens G, Wilkinson RJ 2008 Type 1 helper T cells and FoxP3-positive T cells in HIV-tuberculosis-associated immune reconstitution inflammatory syndrome. Am J Respir Crit Care Med 178:1083–1089. [PubMed: 18755923]
145. Namale PE, Abdullahi LH, Fine S, Kamkuemah M, Wilkinson RJ, Meintjes G 2015 Paradoxical TB-IRIS in HIV-infected adults: a systematic review and meta-analysis. Future Microbiol 10:1077–1099. [PubMed: 26059627]
146. Gkentzi D, Tebruegge M, Tudor-Williams G, Walters S, Lyall H, Sharland M, Doerholt K 2014 Incidence, spectrum and outcome of immune reconstitution syndrome in HIV-infected children after initiation of antiretroviral therapy. Pediatr Infect Dis J 33:953–958. [PubMed: 24618936]
147. Boulougoura A, Sereti I 2016 HIV infection and immune activation: the role of coinfections. Curr Opin HIV AIDS 11:191–200. [PubMed: 26720550]

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148. Vignesh R, Kumarasamy N, Lim A, Solomon S, Murugavel KG, Balakrishnan P, Solomon SS, Mayer KH, Swathirajan CR, Chandrasekaran E, Pradeep A, Poongulali S, Benson CA, French MA 2013 TB-IRIS after initiation of antiretroviral therapy is associated with expansion of preexistent Th1 responses against Mycobacterium tuberculosis antigens. J Acquir Immune Defic Syndr 64:241–248. [PubMed: 23774879]
149. Bourgarit A, Carcelain G, Martinez V, Lascoux C, Delcey V, Gicquel B, Vicaut E, Lagrange PH, Sereni D, Autran B 2006 Explosion of tuberculin-specific Th1-responses induces immune restoration syndrome in tuberculosis and HIV co-infected patients. AIDS 20:F1–7. [PubMed: 16511406]
150. Tadokera R, Meintjes G, Skolimowska KH, Wilkinson KA, Matthews K, Seldon R, Chegou NN, Maartens G, Rangaka MX, Rebe K, Walzl G, Wilkinson RJ 2011 Hypercytokinaemia accompanies HIV-tuberculosis immune reconstitution inflammatory syndrome. Eur Respir J 37:1248–1259. [PubMed: 20817712]
151. Lai RP, Meintjes G, Wilkinson KA, Graham CM, Marais S, Van der Plas H, Deffur A, Schutz C, Bloom C, Munagala I, Anguiano E, Goliath R, Maartens G, Banchereau J, Chaussabel D, O'Garra A, Wilkinson RJ 2015 HIV-tuberculosis-associated immune reconstitution inflammatory syndrome is characterized by Toll-like receptor and inflammasome signalling. Nat Commun 6:8451. [PubMed: 26399326]
152. Van Rie A, Sawry S, Link-Gelles R, Madhi S, Fairlie L, Verwey C, Mahomed N, Murdoch D, Moultrie H 2016 Paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome in children. Pediatr Pulmonol 51:157–164. [PubMed: 26073306]
153. Sulis G, Amadasi S, Odone A, Penazzato M, Matteelli A 2018 Antiretroviral Therapy in HIV-Infected Children With Tuberculosis: A Systematic Review. Pediatr Infect Dis J 37:e117–e125. [PubMed: 28902004]
154. Fry SH, Barnabas SL, Cotton MF 2019 Tuberculosis and HIV-An Update on the “Cursed Duet” in Children. Front Pediatr 7:159. [PubMed: 32211351]

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Impact:

Children living with HIV are more likely prone to opportunistic infection, predisposing high risk of tuberculosis (TB) diseases. HIV and *Mycobacterial tuberculosis* (*Mtb*) coinfection in infants may compromise immune development and function, thereby synergistically accelerating disease progression. Despite early antiretroviral therapy reduces the risk of TB infection in HIV+ children, yet this treatment may probably induce immune reconstitution inflammatory syndrome (IRIS) and TB pathology in HIV/*Mtb* coinfected infants. Here we summarized and reviewed current understanding with regard to pathogenesis and immune responses in the HIV-associated pediatric tuberculosis, which is informative for the consideration of interventions and further study.

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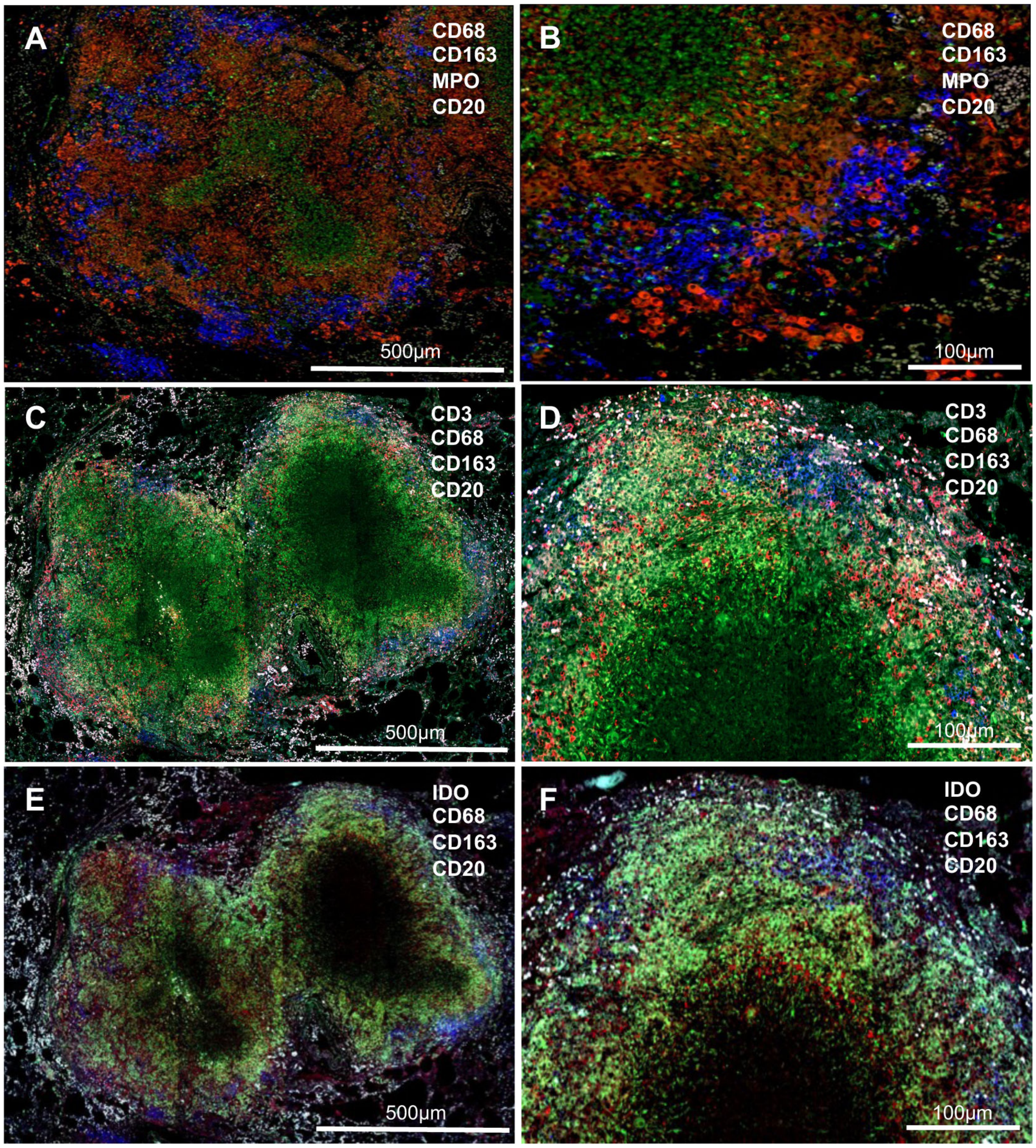

Figure 1. Pulmonary granulomas in infant macaques with tuberculosis.

(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.