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結核合併エイズ患者の免疫病理

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Immunopathology in AIDS/TB

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Abstract

Human immunodeficiency virus（HIV）weakens immune responses against mycobacterium tuberculosis（MTB）, and HIV infection is the most potent risk factor for developing TB. People living with HIV have 19 times increased risk of developing TB and makeup 17% of all TB deaths worldwide. HIV-1 infection is increasingly considered a chronic inflammatory disease that leads to immunodeficiency. The translocation of microbial products from the gastrointestinal lumen into the bloodstream following massive T cell depletion in gastrointestinal-associated lymphoid tissue. Furthermore, immunosuppression seen after mycobacterial stimulation in patients with active TB is associated with naturally occurring regulatory T cells. The treatment of AIDS/TB is challenging, and their sputum is often negative for acid-fast bacteria. All varieties of extrapulmonary TB（ExTB）have been described in AIDS/TB. A paradoxical worsening of signs and symptoms of AIDS/TB patients may occur when the patients are treated effectively for their TB and have commenced ART.

In HIV/AIDS, a compromised immune system with lower CD4 T cell counts might waive the clinical symptoms and inflammatory responses, which suggests lymphocyte redistribution as an immunopathology leading to lymphopenia in COVID-19. These analyses in AIDS/TB are helpful for the pathological study of COVID-19 patients.

Keywords：AIDS, Tuberculosis, COVID-19

Introduction

Tuberculosis（TB）is caused by the bacillus *Mycobacterium tuberculosis*（MTB）, which is spread when people sick with TB expel bacteria into the air. About a quarter of the global population is estimated to have been infected with MTB. Without treatment, the death rate from TB deaths is high. The reported number of people newly diagnosed with TB are gradually decreasing. From a peak of 7.1 million in 2019, this fell to 5.8 million in 2020（−18%）, back to the level last seen in 2012. In 2021, there was a partial recovery to 6.4 million（the level of 2016−2017）（*1*）. This decline is caused by SARS-CoV-2 transmission and the swift implementation of public health measures to try and contain its spread provides an uncomfortable mirror to the slow pace of *M. tuberculosis* transmission research and improved global tuberculosis control（*2*, *3*）. But the current situation is far from the target value（Fig 1）.

In a majority of individuals who inhale M. tuberculosis bacilli, the infection is eliminated by innate immune responses or subsequently contained by poorly understood host defenses, and infection remains latent. People with latent TB infection（LTBI）are typically considered to be asymptomatic and not infectious to others. However, people classified as having LTBI may harbor viable MTB that can reactivate later, causing active TB disease. Studies suggest that 5 to 15% of individuals recently infected with MTB progress rapidly（within 2 years）to active disease（*4*）.

Human immunodeficiency virus（HIV）weakens immune responses against MTB and HIV infection is the most potent risk factor for developing TB（*5*, *6*）, resulting in TB associated with acquired immune deficiency syndrome（AIDS, AIDS/TB）. According to the reports of the natural history of HIV infection in india, the most common acquired immune deficiency syndrome-defining illnesses were

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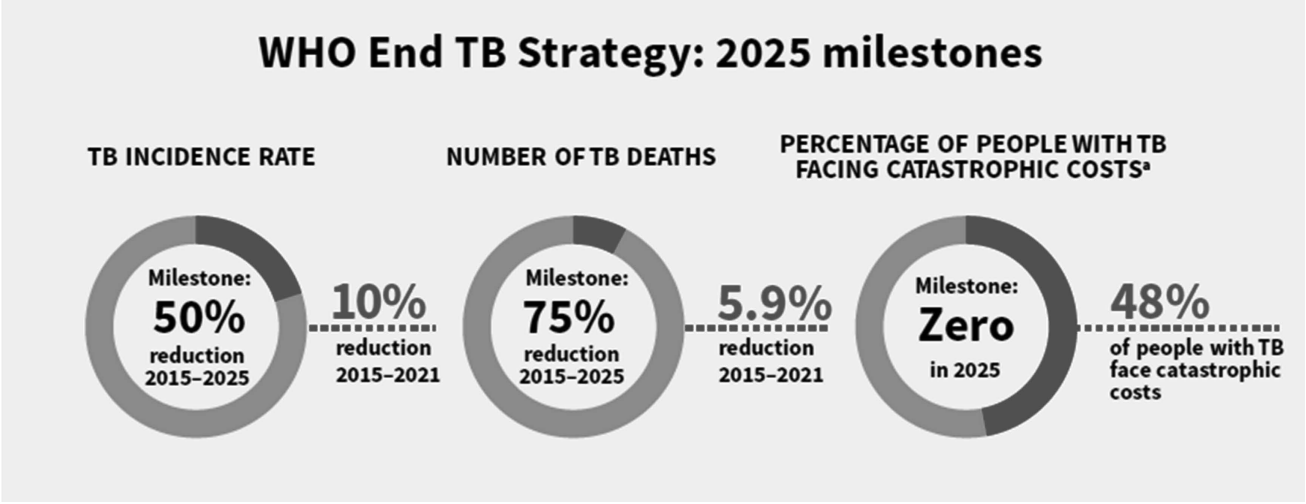

Figure 1. WHO end TB strategy 2025 milestones. (Ref 1)

pulmonary tuberculosis (49%; median duration of survival, 45 months) (*7*). People living with HIV have a 19 times increased risk of developing TB, and make up 17% of all TB deaths worldwide. HIV-1 co-infection is the single greatest risk factor for developing active TB. TB infection leads to increased HIV replication and HIV contributes to TB progression due to HIV mediated immune suppression (*8*). Importantly, in comparison to the general population, the risk of active TB remains higher in patients infected with HIV-1 even after becoming established on effective ART (*9*). In Thailand, the probability of incident TB was 0.7%, 1.7%, 3.3% and 4.3%, at 1, 2, 5 and 7 years after ART initiation, respectively. Low CD4 count, BMI < 18 kg/m^2, and substance use in the previous six months were significantly associated with incident TB. In Pune, 1904 patients with a median duration of follow up on ART of 57 (IQR = 32.0, 84.0) months were included. Of these, 182 developed incident TB (22% definitive TB, 38% recurrent cases). TB incidence at 6–12 months, 13–24 months, 25–60 months and > 60 months of ART was 24.32, 5.46, 2.54 and 0.75 cases per 100 person years respectively. Current time updated CD4 count < 500 cells/mm^3 ($p < 0.0001$), virologic failure on ART (adjusted Hazard Ratio (aHR): 3.05 (95% CI: 2.094, 4.454), $p < 0.0001$) and receipt of ART without IPT (aHR: 8.24 (95% CI, 3.358, 20.204), $p < 0.0001$) were associated with higher risk of incident TB (*10*). HIV-infected adults on ART exhibited lower plasma HIV viral load and higher blood CD4(+) T cell count than ART-naive adults. Total influenza-specific alveolar Th1 CD4(+) T cell responses were intact in all individuals receiving ART. In contrast, irrespective

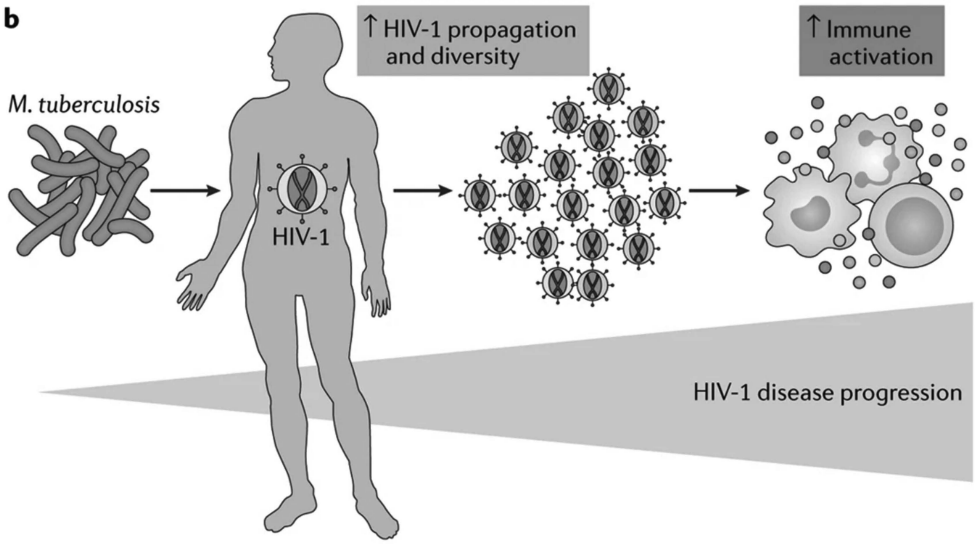

Figure 2. HIV-1 and MTB infection increases HIV-1 disease progression. (Ref 8)

of duration, broncho alveolar lymphocytes and blood mycobacteria-specific polyfunctional CD4(+) T cell responses were impaired in adults on ART (*11*).

Clinical manifestation of AIDS/TB

The complex interaction between MTB and HIV causes immune activation in AIDS/TB patients (Fig 2) (*12*). HIV-induced immunosuppression modifies the clinical presentation of AIDS/TB (*13*). Individuals who are infected with HIV-1 and have CD4(+) T cell counts in the normal range present with classic symptoms of pulmonary TB, but the disease that is restricted to the lung apices is less frequent. In contrast, pleural effusions and lymph node disease are more likely. In advanced AIDS the patients show atypical signs and symptoms and more frequent extrapulmonary dissemination (*14*).

Point-of-care screening assays have been developed to identify those patients with extra pulmonary TB (EPTB) that might be otherwise missed. The urine lateral flow assay for LAM has become an attractive option to diagnose disseminated TB in people with HIV due to their ease of incorporation into HIV clinics for rapid screening (*15*).

Chronic immune activation in AIDS/TB

HIV-1 infection is increasingly considered a chronic inflammatory disease that leads to immunodeficiency. Several mechanisms are thought to lead to the chronic immune activation that is associated with HIV-1 infection (Fig. 3) (*16*). Chief among these is the translocation of microbial products from the gastrointestinal lumen into the bloodstream following massive T cell depletion in gastrointestinal-associated lymphoid tissue (GALT) during primary HIV-1 infection (*17*). This depletion is thought to be caused by lytic infection of GALT T helper17 cells (TH 17 cells), which are particularly permissive to retroviral infection (*18*). Another T cell population that becomes depleted in HIV-1 infection are mucosal associated invariant T (MAIT) cells. These are CD8+ innate lymphoid cells that recognize bacterial metabolites of vitamin B that are presented by a non-polymorphic major histocompatibility complex-like molecule, MR1 (*19*). MAIT cells are activated by *M. tuberculosis* and are enriched at the site of TB disease (*20*). Therefore, their depletion in HIV-1 infection may attenuate a component of host immune responses to *M. tuberculosis*. MAIT cells are not infected by HIV-1. Their depletion is thought to be caused indirectly by immune activation. In this context, the failure of ART to restore the T cell repertoire, including MAIT cells may also be an important factor in the persistently elevated risk of TB.

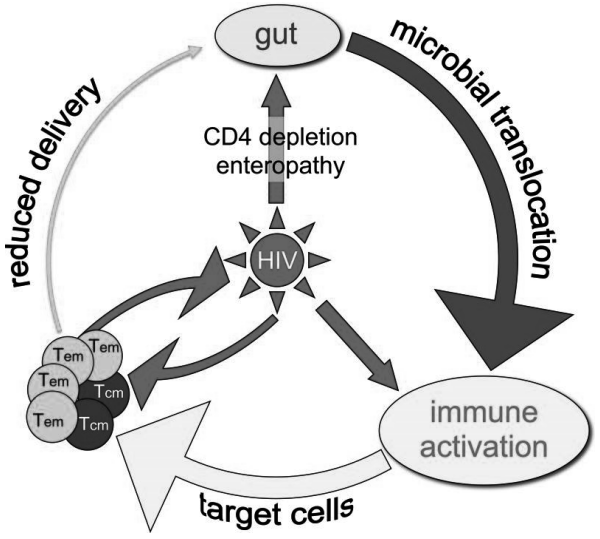

Figure 3. Immune activation in AIDS/TB. (Ref 16)

BCG was found to increase effector and regulatory T cell phenotypes as defined by CD4(+)CD25(lo) and CD4(+)CD25(hi) T cells, respectively. Together, these results suggest that immunosuppression seen after mycobacterial stimulation in patients with active TB is associated with naturally occurring regulatory T cells (*21*).

Therapy against AIDS/TB

The treatment of AIDS/TB is also more challenging, and their sputum is often negative for acid-fast bacteria (*22*). All varieties of EPTB have been described in AIDS/TB (bone marrow infiltration and bone, hepatic, splenic, cerebral, vertebral, meningeal, spinal and kidney involvements). Isolated extrapulmonary localisations are described in 53–63% of TB cases in HIV-infected patients (*22*). A positive culture of MTB confirms the diagnosis. Acid-fast bacilli in sputum smears are positive in 30–60% of AIDS-related TB cases (compared to 57% in HIV-seronegative patients) (*23*).

The standard 6-month regimen results in prompt sterilization of sputum and low rates of treatment failure, similar to those obtained in HIV-negative persons (*24*). However, studies have documented higher rates of relapse in AIDS/TB patients who received anti-TB therapy for 6 months, as compared with 9–12 months (*25*). In a Kenyan cohort, drug intolerance has been recorded in 26% of AIS/TB patients taking a four-drug anti-tuberculous regimen, often occurring early after the initiation of therapy (before the second month). The most frequent drug intolerance is observed with rifampicin (10%), followed by isoniazid (3–6%) and, more rarely, ethambutol and pyrazinamide (*26*). The risk of drug-resistant TB is

higher among HIV-infected persons than in HIV-seronegative patients. HIV-infected patients with TB who were born in the USA, and who had not been treated previously for TB, were infected by bacterial isolates with an incidence of isoniazid resistance of 11.3% and rifampicin resistance of 8.9%. These figures are nearly double those seen in the HIV-negative population (*27*).

A paradoxical worsening of signs and symptoms of AIDS/TB patients may occur when the patients are treated effectively for their TB and have commenced ART. These paradoxical reactions consist of a hectic fever, the occurrence or enlargement of lymphadenopathies, worsening of chest infiltrates, and increased pre-existing TB lesions (cutaneous and peritoneal) (*28*). Paradoxical reactions, called immune reconstitution inflammatory syndrome (IRIS), were related to the initiation of combination ART (mean 15 ± 11 days afterward) than to the initiation of anti-TB treatment (mean 109 ± 72 days afterwards). Experience of TB-IRIS was found to be associated with long-term remodeling of the CD4 T cell memory compartment towards an effector memory-dominated phenotype (*29*).

Survival function for the TB treatment outcomes and factors predicting the probability of survival were tested and described. Adjusted Cox regression model death hazard showed association with missing ART treatment (HR: 1.699, 95%CI 1.164, 2.481, p = 0.006) and having CD4 count < 499 (HR 2.398, 95%CI 1.191, 4.830, p < 0.014). TB treatment outcomes, ART treatment, and the CD4 count of HIV/TB coinfected population substantially influence their life duration (*30*).

Prevention

ART is strongly associated with a reduction in the incidence of tuberculosis across all CD4 count strata. Earlier initiation of ART may be a key component of global and national strategies to control the HIV-associated tuberculosis syndemic (*6*). Both ART to treat HIV and restore immune function, and isoniazid preventive therapy to treat *M. tuberculosis* infection, independently decrease the risk of progressing from *M. tuberculosis* infection to TB disease (*31*). *Mycobacterium tuberculosis*/simian immunodeficiency virus-coinfected (*M. tuberculosis*/SIV-coinfected) macaques to model *M. tuberculosis*/HIV coinfection and study the impact of ART on TB reactivation due to HIV infection. Although ART significantly reduced viral loads and increased CD4(+) T cell counts in blood and bronchoalveolar lavage (BAL) samples, it did not reduce the relative risk of SIV-induced TB reactivation in ART-treated macaques in the early phase of treatment (*32*).

COVID-19 infection on AIDS/TB patients

Overall, it was estimated that COVID-19 has an impact on life expectancy by 0.12 years during the study period. Even though mortality due to COVID-19 was high, factors such as lockdown, vaccination, and accidents also had an influence on mortality. Thus, there is a need to assess the impact of COVID-19 on life expectancy in the future (*33*). Compared to the reported mortality rate (nearly 4%–10%) and severity rate (up to 20%–40%) among COVID-19 patients in hospitals, a benign duration with 0% severity and mortality rates was shown by 21 HIV/AIDS patients. In HIV/AIDS, a compromised immune system with lower CD4 T cell counts might waive the clinical symptoms and inflammatory responses, which suggests lymphocyte redistribution as an immunopathology leading to lymphopenia in COVID-19 (*34*). Another study showed that HIV-1 and TB coinfection skewed the SARS-CoV-2 T cell response. HIV-1-mediated CD4(+) T cell depletion associated with suboptimal T cell and humoral immune responses to SARS-CoV-2, and a decrease in the polyfunctional capacity of SARS-CoV-2-specific CD4(+) T cells was observed in COVID-19 patients with active TB. It was also found that COVID-19 patients displayed reduced frequency of *MTB*-specific CD4(+) T cells, with possible implications for TB disease progression (*35*).

和訳要約

ヒト免疫不全ウイルス（HIV）は結核に対する免疫能を弱めてHIV感染が結核を発症する最大の因子である。HIV感染者は健常人に比べ、19倍も結核を発症しやすく、すべての結核死の17％を占める。HIV感染症は免疫活性化による慢性感染症で最終的に免疫不全を導く。特に腸管リンパ球の欠損により腸内細菌成分が血中に侵入することが慢性炎症の原因と思われる。さらに結核感染においては制御T細胞も増加して、免疫低下も観察される。エイズ結核の治療はエイズ結核患者の喀痰検査が陰性であるために、困難がつきまとう。すべてのタイプの肺外結核がみられる。また結核治療を進めている途中にエイズの治療を開始すると免疫再構築症候群が生ずることもある。エイズにSARS-CoV2が感染すると特にCD4細胞が少ない症例では炎症反応が乏しいという所見もあり、これはリンパ球が免疫病理学的に作用していることを示唆している。ここに示したエイズ結核の解析はCOVID-19感染者の病態解析にも参考となりうる。

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