Mycobacterium tuberculosis and human immunodeficiency virus type 1 interaction: Pathogenesis and disease modulation in dual infection

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Chapter 1
General Introduction
The advent of human immunodeficiency virus (HIV) infection and disease over three decades ago was associated with an exponential increase in the incidence and prevalence of various chronic infectious diseases. One of the most devastating has been active tuberculosis. In sub-Saharan Africa with the high rates of Mycobacterium tuberculosis (MTB) infection, the impact of HIV was quickly observed with the severely debilitating “wasting syndrome” or “slim disease”. What remained unclear for a long time was the impact of MTB infection and disease on HIV-1 progression; the overarching subject of this thesis.

The following chapter gives an overview of the epidemiology of HIV-1/MTB interaction, with a brief outline on the interaction between HIV-1 and TB presentation. Next, we outline some immune responses in TB and HIV-1 that may be relevant in the dual mechanisms of disease, with particular emphasis on mononuclear cell responses, and chemokine and chemokine receptor mechanisms. Lastly the clinical presentation of HIV-1 and active TB is presented with emphasis on the deleterious effect of these two diseases in patients.

1.1 EPIDEMIOLOGY OF MYCOBACTERIUM TUBERCULOSIS AND HIV-1

Tuberculosis (TB), the commonest mycobacteriosis in man, is caused by the Mycobacterium tuberculosis (MTB) bacillus. Active TB is a common cause of morbidity and mortality worldwide, and in developing countries in particular, and contributes to over 30% of HIV-related deaths (1, 2). One third of the world population has been infected with MTB, of whom about 10-12 million develop active TB each year (3).

The advent of HIV disease was associated with a marked increase in notification rates of active TB, with MTB infection as the commonest co-infection in HIV-1 infected people (4) (5). The World Health organization (WHO) estimates that there are about 12 million people dually infected with MTB and HIV-1 worldwide, with over 70% living in sub-Saharan Africa (6). The WHO projects that by the year 2020, there will be about 20 million people with dual HIV/MTB infection, most in sub-Saharan Africa where the prevalence of HIV infection among TB patients is as high as 50% (7) (8) (Figure 1).
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![Figure 1: Estimated HIV prevalence in incident TB cases (WHO)](image)

1.2 EFFECT OF HIV INFECTION ON MTB INFECTION AND DISEASE

There has been a dramatic increase in the incidence of TB in sub-Saharan Africa, most of it attributable to the HIV pandemic with about 15-75% of TB patients in Africa being HIV infected (9). Since the mid 1990’s, TB case numbers have increased 300-400% in high HIV prevalent countries (10) (6). In Uganda, a sudden increase in the notification of active TB in the late 1980’s related to the increasing HIV infection rates was noted, with over 40% of patients with active TB also HIV infected (11). Between 1985 and 1989, a doubling in the admissions to adult tuberculosis wards in Kampala, Uganda, was observed, probably due to a combination of the rising HIV rates as well as declining health care infrastructure at the time (12). In 1995, Aisu reported a rate of active tuberculosis of 6% among persons with HIV-1 infection (13). In fact the original description of “slim disease” in Uganda may have referred to dual HIV/TB disease (14).

In Uganda, about 7.3% of the population is HIV infected while over 60% are infected with MTB (WHO, Global Tuberculosis Control: Surveillance, Planning, Financing. 2009) (15), (12), (16). Active TB is often a consequence of reactivation of latent infection, but may follow acute infection in about 5% of the cases presenting with active TB, especially among children. HIV contributes to the reactivation of latent MTB infection and progression to active TB by impairing the cell mediated immunity (CMI) associated with a decline in CD4 T cell numbers.

In a cohort of tuberculin test positive intravenous drug users, active TB developed in 4% of 217 HIV infected, with none among 303 HIV uninfected subjects (17). Overall, risk of activation of
TB among those latently infected is over 20 times higher in HIV-1 infected, compared to non-HIV-1 infected persons (18, 19).

In the pre-HIV era, TB was mainly a disease of men, especially alcoholics, and those of low socio-economic status. With the advent of HIV, TB is now seen equally in both men and women, and across the socio-economic divide.

The mechanism of increased prevalence of active TB in HIV infection is not clearly understood. It has been shown that atypical pulmonary TB (PTB) and extrapulmonary TB are seen among patients with very low CD4 T cell counts. However even at high CD4 T cell counts PTB is common and presents with the typical pattern of apical lung cavitating disease. It is possible that HIV through immune activation may exhaust the non-specific and MTB-specific T cell immune responses and decrease the functionality of the MTB granuloma, promoting MTB escape from the granuloma and increasing the risk of dissemination (20-24). Thus the mechanism of active TB seems to be multifactorial partly due to low CD4 T cells, but also probably related to mononuclear cell dysfunction.

In pleural disease, levels of CD4 T cells are higher in pleural fluid compared to blood of patients with HIV and TB pleurisy (25). Also cells from patients with active PTB with and without HIV infection show increased cytokine related mononuclear cell apoptosis (26). Studies have shown in-vivo CD4 T cell depletion and in-vitro increased spontaneous CD4 T cell apoptosis and defects in IFN-g responses among patients with HIV-1 infection and active PTB (27). Thus it is possible that in active TB, CD4 cells traffic to sites of active disease, which in combination with increased apoptosis contributes to the decline of circulating CD4 T cell counts, increasing the risk of HIV progression (figure 2).

1.3 THE EFFECT OF MTB ON HIV-1 REPLICATION
Tuberculosis has also been shown to adversely affect the course of HIV infection. Active TB in HIV infected people leads to an increase in viral replication and load with a 5-160 fold increase in plasma HIV RNA (28), and is associated with progression of HIV disease, and increased susceptibility to opportunistic infections (29). Mortality is higher in HIV-active TB patients, compared to those with HIV infection alone, at comparable CD4 T cell counts (29,30).

Various studies have shown increased HIV load in the circulation and in pleural fluid of patients with HIV-1 and TB (31). TB is also associated with increased heterogeneity and diversity of HIV-1 quasispecies (32, 33). However, how TB affects HIV disease is not well understood. We hypothesize two possible mechanisms are hypothesized for enhanced HIV load during TB and MTB infection:

a) Transcriptional activation of the virus in latently or newly HIV infected cells;

b) Enhanced infectivity of the target cells through dysregulation of chemokines and chemokine receptors.

MTB infection of macrophages leads to increased expression and production of Tumour Necrosis Factor alpha (TNF-alpha) (34,35), which through activation of its TNF-alpha receptor...
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![Figure 2: CD4 T cell trafficking in active tuberculosis](image)

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potentiates Nuclear Factor-kappa B (NF-kB)-induced transcription of nuclear HIV provirus in dually infected cells (36-46) (figure 3). In-vitro studies have shown that monocytes from TB patients are more receptive to HIV-1 infection than monocytes from healthy controls (47).

**Figure 3. Mechanism of increased viral load in active tuberculosis**

The mechanism of enhanced HIV replication is believed to be through antigen specific activation of memory T cells (48- 50). This cellular activation and increase in HIV viremia is also seen in HIV infected persons after influenza and tetanus toxoid vaccines (51, 52).

In TB this is due to antigen dependent CD4+ T cell activation (28), and is inhibited by CD8+ T cells in presence of IL-2 (53 -57). Further, in vitro studies showed that HIV replication was more intense in CD8-depleted PBMC of PPD reactive persons, but not in cells of those who were PPD negative (58, 59). Active MTB infection expands and activates T cells, which in turn provides HIV a new source of target cells for HIV-1 growth and cytopathicity, thus exacerbating the level of immune suppression (60). Thus, each pathogen potentiates the pathogenicity of the other.
1.4 IMMUNE HOST RESPONSES IN HIV AND MTB CO-INFECTION

The control of TB depends on a robust cell-mediated immune (CMI) response against the organism, and impairment of this CMI, as in HIV-1 infection, predisposes to active mycobacterial diseases (61, 62).

The host immune responses in dual HIV/MTB infection is complex, variable and multi-factorial, involving the innate, cell-mediated (both monocyte and T lymphocyte) and possibly humoral arms of the immune system.

1.4.1 Immune responses to HIV infection

HIV-1 is primarily an infection of CD4 positive cells (63- 65), with CD4 T-cells, monocytes, macrophages, dendritic cells, and microglial cells of the central nervous system being the main targets (66-68). Host cell CD4 molecules bind viral envelope glycoprotein, gp120, followed by CD4 conformational changes (69) in the presence of chemokine co-receptors (70- 72).

HIV infection of CD4 T cells leads to depletion of these cells through syncytial formation and increased apoptosis. The CD4 T cells are important in the immune response to MTB. HIV also infects macrophages where it remains quiescent as a provirus within the human host chromosomes. Activation of HIV infected cells with RNA transcription and translation leads to increased HIV replication and load. Thus both HIV and MTB infect macrophages and can co-replicate in the same cells contributing to the dual pathogenesis.

As CD4 T cell numbers and function decline in HIV disease, the immune response to MTB is compromised, leading to the activation of latent MTB infection.

1.4.2 Role of monocytes/macrophages in MTB infection

The macrophage is a major cell in the host microbial interplay in both MTB and HIV infection. MTB infects macrophages, through the process of phagocytosis where the bacilli replicate and persist by evading the intracellular killing mechanism. These macrophages together with CD3 lymphocytes elicit formation of granulomas which are a major response to infection promoting containment of the bacillus. Macrophage apoptosis, an innate host response, contributes towards the control of MTB infection and decreases the possible spread of the infection and disease.

Macrophages also produce inducible nitric oxide synthetase (iNOS) as well as nitric oxide (NO) radicles which mediate intracellular killing of MTB. However to survive the acidic milieu of the...
macrophage phagocytic vacuoles and its hydrolytic enzymes, the MTB bacilli has evolved mechanisms of survival and multiplication within the macrophage. This may in part be due to MTB production of lipoarabinomannan (73), a cell wall-associated glycolipid that inactivates the macrophage effector killing by blocking of the cytotoxic oxygen-free radicals and by blocking of interferon gamma genes (74). LAM may also inhibit macrophage activation and its cytocidal activity thus contributing to the persistence of mycobacteria within the macrophages (74). MTB has thus developed a system of survival with the ability of the organisms remaining dormant for decades within the macrophages (75).

It is possible that the peripheral blood monocytes from patients with active TB are more susceptible to HIV-1 infection in vitro than monocytes from healthy subjects (76). Also, MTB and its protein and non-protein components/moieties increase HIV-1 replication in cells latently or acutely infected with the virus (77, 79).

1.4.3 The role of MTB induced cytokines in HIV-1 replication

MTB specific CD4 T cell-induced immune responses play a major role in the host response to the bacilli. Upon infection of the macrophage, secretion of cytokines including IL-12 is turned on. This in turn activates the CD4 T cells leading to activation of IL-2 secretion, an autocrine cytokine which increases CD4 T cell differentiation and activation. These CD4 T cells on activation differentiate to Th1 subsets which produce IFN-gamma and TNF-alpha, as well as cytosolic hydrolytic enzymes (perforin and granzyme) which in concert work towards activation of the MTB-infected macrophage and subsequent killing of MTB (27) (figure 4).

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**Figure 4.** Mononuclear cell response to MTB infection
Active infection with MTB in humans leads to enhanced expression and release of mononuclear phagocyte pro-inflammatory cytokines like IL-1 beta, TNF alpha, and IL-6 (80) (81), which may enhance the replication of HIV-1 (82). MTB also releases lipoarabinomannan (73), which by triggering cytokine release from macrophages increases production of HIV from normal human lymphocytes (83) (84). MTB infection of cells triggers signal transduction cascades including Nuclear Factor-kappa B (NF-kB). This transcriptional factor leads to HIV replication in monocytes by binding to the enhancer region of the HIV-1 long terminal repeat (LTR) sequence, in an activated cell (85) (46). Two studies by Zhang and Shattock et al (86) (87) showed that in monocytic cells transfected with HIV LTR chloramphenicol acetyltransferase constructs (HIV-LTR-CAT), phagocytosis of MTB enhances HIV-1 transcription by as much as 20-fold (87) (86). This enhancement was dependent on activation of NF-kB, and its binding site on HIV-LTR, and was independent of TNF-alpha secretion (87). Further in vitro studies showed that blood monocytes from patients with tuberculosis have enhanced susceptibility to HIV-1 infection (76) and activation of these monocytes might potentially activate or enhance HIV replication in these cells.

1.5 CHEMOKINES AND CHEMOKINE RECEPTORS IN MTB AND HIV-1

1.5.1 Beta-chemokines

The beta-chemokines which are chemo-attractant for monocytes to sites of infection and chronic inflammation may play a role in modulating HIV infection of cells. Naturally, these chemokines are critical in the chemotaxis of mononuclear cells to the sites of infection, particularly in chronic tissue infections. Here, beta chemokines are released from epithelial cells, which in turn promote extravasation and chemotaxis of mononuclear cells to the infection site by attaching to the CCR5 cell surface receptors. (Figure 5). However, HIV has used this same system to potentiate infection of mononuclear cells. The chemokines (intercrines) are low molecular weight chemotactic proteins subclassified in humans into C, CC, CXC and CXXXC groups, depending on the number of amino acids between the conserved cysteines of the molecule. These molecules are macrophage chemotactic factors, attracting mononuclear cells to sites of infection and inflammation.
The CC beta-chemokines, which have the first two of the four adjacent cysteines conserved, include Macrophage Inflammatory Protein-1-alpha (MIP-1-alpha) and beta (MIP-1-beta), and Regulated Upon Activation Normal T-cell Expressed and Secreted (RANTES) induce migration of blood monocytes and T lymphocytes which express CD4 surface receptors (88). Studies suggest that MIP-1-beta acts mainly on CD8+ T cells, MIP-1-alpha on CD4+ cells and RANTES on both (89). Others have suggested that only MIP-1-beta but not MIP-1-alpha or RANTES, shows activity on T cells (90), yet results of other studies suggest that MIP-1-alpha is chemotactic for all CD4+ and CD8+ T lymphocytes, and B lymphocytes (91).

MCP-1, another chemokine, is chemotactic for both monocytes and lymphocytes, and is produced by a variety of cells including fibroblasts and mesothelial cells (92). In TB, MCP-1 producing cells include both macrophages of granulomas and endothelial cells (24).

Beta-chemokines are chemo-attractant for monocytes and lymphocytes by providing directional cues for the movement of leukocytes to sites of infection/inflammation. Selectins facilitate the movement of leukocytes along the surface of endothelial cells, and integrins lead to their extravasation between the vascular endothelial cells to the site of infection (93). Chemokines are thought to provide the signals that convert the low-affinity selectin-mediated interaction into the high-affinity integrin-mediated interaction with endothelial surfaces and extravasation of inflammatory cells (94).
1.5.2 Chemokines and HIV

Most of the recently infected HIV strains exhibit tropism for macrophages (M tropic) while the variants found in late HIV infection have mainly tropism for T lymphocytes (T tropic). CC chemokines secreted by CD8+ cells (95) and monocyte/macrophages (96) suppress M-tropic but not T-tropic HIV-1 replication in CD4+ T cells and PBMC (97) (72). However, CC chemokines per se do not suppress HIV in monocytes and macrophages, but probably in concert with as yet not fully characterized CD8+ T cell derived soluble factor(s) (98).

The antiviral effect seen by the CC chemokines RANTES, MIP-1-alpha and MIP-1-beta has not been reported with other chemokines like Monocyte Chemo-attractant Protein-1 (MCP-1) or MCP-3 (99, 100), and is probably mediated through blockage or downregulation of CCR5 (97) (101). MIP-1-alpha, RANTES and MCP-1 are released by blood macrophages and alveolar macrophages stimulated with MTB (96), while others have shown that MCP-1 but not MIP-1-beta was produced from a human alveolar epithelial cell line infected with MTB (24). The mechanism by which chemokines inhibit HIV-1 entry is complex. It may be through binding of chemokine ligands to their receptors, with resultant receptor blockade, desensitization, sequestration or internalization, phosphorylation, and/or change in receptor affinity state due to G protein uncoupling (102).

Activation of CCR5 and other beta-chemokine receptors on T cells by CC chemokines induces a rapid and transient rise in cytosolic free calcium, which initiates the process of chemotaxis (104, 105). It has been shown that the increase in chemokine secretion in lung diseases results in the selective recruitment of mononuclear leukocytes to the site of infection (106). This chemotactic activity has been demonstrated from supernatants of MTB-infected cells in vitro, and can partially be inhibited by neutralizing antibodies to beta-chemokines (96).
1.5.3 Role of chemokine receptors in HIV-MTB co infection

Successful infection of mononuclear cells by HIV-1 requires the interplay between HIV envelope glycoprotein (gp) 120, CD4 T cell receptor and the chemokine receptors which act as cofactors (107, 108). Chemokine receptors are seven transmembrane (7tm) cellular proteins, predominately expressed on the surface of monocytes/macrophages and primary T cells as well as dendritic cells (DC).

HIV infects target cells by binding its viral gp120 onto the cell surface CD4 molecule (109) and the CCR5 chemokine receptor. CD4 is highly expressed on specific CD3-positive lymphocytes, with low expression on macrophages and DC. These chemokine receptors have emerged as major determinants of viral tropism (70-72). Clinical isolates of HIV-1 differ in their ability to infect CD4 positive cells; HIV-1 strains capable of infecting primary CD4 + T cells and macrophages are M-tropic whereas those which predominately infect laboratory-adapted CD4+ T cell lines and primary CD4 + T cells are T tropic (72). Certain HIV-1 isolates are dual tropic, and are capable of infecting both macrophages and T cell lines (71).

The CXCR4 chemokine receptor when co-expressed with CD4 receptors, renders T lymphocytes permissive to HIV-1, and env mediated syncytial formation of blood mononuclear cells (108), (110). The CXCR4 binds gp120 from T-tropic isolates, but is not a co-receptor for M-tropic viral envelopes (110) (111). It appears that T-tropic viruses play a smaller role in early HIV disease and sexual viral transmission, and are usually not recovered in HIV-1 positive persons until late in the course of HIV infection (112). Generally, CXCR4 using viral isolates are syncytial inducing (SI), and are associated with a rapid decline in CD4+ cells and progression to AIDS (113).

The CCR5 co-receptor potentiates non syncytial inducing (NSI) HIV-1 virus fusion and entry of M tropic viruses into monocyte/macrophage target cells (114), (101). The mechanism by which CCR5 interacts with CD4 and gp120 is unclear, but could be by utilization of the hypervariable third region (V3 loop) of gp120 protein (72). Either a ternary complex of gp120-CD4-CCR5 is formed, or there is sequential interaction of gp120 with CD4, then with CCR5. The amino
terminus of CCR5, with one or more additional domains, plays an important role in its cofactor function for HIV-1 entry into cells.

The gene for CCR5 is generally quiescent, with minimal expression on purified CD4 positive cells (115). CCR5 is expressed on activated CD4+ and CD8+ human peripheral blood mononuclear cells (PBMC) (116). Interestingly, CCR5 expression is high on Th1 cells, but is virtually absent on Th2 lymphocytes (117). On fresh monocytes, CCR5 expression is low, but increases when cells are cultured, and differentiate from monocytes to macrophages (118). In-vitro studies have investigated the activation and up-regulation of CCR5 on mononuclear cells. Stimulation with phytohemagglutinin (PHA) or interleukin-2 (IL-2) lead to a significant increase in CCR5 mRNA levels, and surface binding of MIP-1-alpha (119). Macrophage and granulocyte-macrophage colony-stimulating factors increase surface expression of CCR5, whereas the Th2 cytokines, IL-4 and IL-13, prevent the induction of CCR5 (120). Although IL-10 a Th2 anti-inflammatory cytokine inhibits HIV-1 replication in macrophages, it does not suppress surface CCR5, but up-regulates its expression in human monocytes by prolonging its mRNA half-life (120) (121). Intracellular cyclic adenosine monophosphate (91) rapidly down-regulates CCR5 gene expression with consequent loss of CCR5 expression and function in monocytes/macrophages, and a marked decrease of HIV-1 entry into these cells (122). Other than its role as a co-receptor for HIV-1, CCR5 is important in recruitment of mononuclear cells to sites of inflammation and infection.

1.6 CLINICAL PRESENTATION OF HIV/TB CO-INFECTION
HIV-1 infected patients are at higher risk of both developing primary TB after MTB exposure (123, 124), and of reactivating latent MTB infection (125). As compared to uninfected subjects, the risk of developing TB is 170 times higher in AIDS patients, and 113 times in HIV infected people (126). Dually infected people with both HIV-1 and active TB have a shorter survival than those with HIV-1 alone (29).

At the Mulago hospital medical wards (Kampala, Uganda), tuberculosis has been one of the commonest causes of admission over the years (figure 6, Mulago hospital records).
In an autopsy study at Mulago hospital (medical ward deaths) in 2009, in 53 complete autopsies (66% of HIV-positive persons), disseminated TB was the main cause of death in 20 (37%) patients. (131).

Figure 6. TB presentation among patients admitted on the Mulago hospital (hospital records)

Extra-pulmonary tuberculosis is common among patients with HIV infection especially at the very low CD4 T cell counts. This is seen at different sites in the body, including the serosal membranes, abdomen, spine etc (figure 7).

Extrapulmonary TB Common in HIV

Figure 7: Extra-pulmonary tuberculosis in HIV-1 infection.
HIV is associated with increased risk of TB reactivation and with high rates of smear-negative pulmonary tuberculosis, pleural, systemic and other forms of extra-pulmonary tuberculosis (127) (128) (129). Conversely, active MTB infection contributes to increased HIV-1 replication and load in dually infected patients, with increase in levels of plasma viremia in HIV infected people in the acute phase of MTB disease, compared to prior to the onset of TB, or after successful anti-TB treatment (28) (130).

In much of sub-Saharan Africa, active tuberculosis is the commonest cause of mortality among adult medical ward patients, contributing to over 30% of deaths in a postmortem study (132). Patients with HIV infection with low CD4 T cell counts below 50 cells/microliter and a Body Mass Index (BMI) below 18 are at high risk of active TB (133). Among patients with HIV infection presenting with fever of uncertain origin or septicemia among adults on medical wards, over 20% showed mycobacteriosis on blood culture (134 - 136).

The association of HIV and MTB is bidirectional, each infection potentiating the other. This leads to severe clinical manifestation, with accelerated morbidity and mortality among HIV infected persons who get active MTB disease (figure 8).

The overall objective of this thesis was to determine regulation of selected chemokines and cytokines in active mycobacterial tuberculosis disease in HIV-1 infected subjects, and impact their perturbation on HIV-1 disease progression. Specific objectives were:
1. To define factors that may affect viral activity among HIV-1-infected adults with active TB. Here we assessed plasma viral load in HIV-1 infected patients with PTB, and asymptomatic HIV-1 infected controls, stratified by CD4 T cell counts. We also evaluated the status of HIV-1 gene expression in peripheral blood mononuclear cells (PBMC) and serum from HIV/TB and CD4-matched healthy HIV-infected controls. Finally, we looked at how treatment of pulmonary TB affected HIV-1 activity in HIV-1/TB-co-infected subjects with CD4 cell counts of >100 cells/μL in vitro. Chapters 2, 3.

2. To determine the expression and regulation of Th1 cytokines, beta-chemokines, and the chemokine CCR5 receptor in patients with active pulmonary tuberculosis with and without HIV-1 infection. To this regard, we determined the expression and regulation of MIP-1-alpha and RANTES beta-chemokines and their CCR5 receptor in patients with active pulmonary TB with without HIV-1 infection. We also compared the production of IFN-gamma and TNF-alpha by peripheral blood mononuclear cells from HIV-1-infected and -uninfected patients with newly diagnosed PTB for the relationship of the cytokine profiles with the clinical presentation of tuberculosis. Chapters 4, 5.

3. To assess the impact of dysregulations in chemokines and Th1 cytokines in HIV-1 activation during MTB infection. We examined the role of TNF-alpha cytokine and MCP-1 chemokine interaction in vitro on MTB-induced HIV-1 transcriptional activation in mononuclear cells from HIV-1/TB subjects with pleural TB. Chapter 6.

4. To assess the effect of the beta-chemokine RANTES analogue in vitro, anti-TB treatment, and safety and effect of oral prednisolone as an immunoadjuvant therapy in vivo on HIV load and cytokine expression in HIV-associated TB. Here we assessed the regulation of chemokines and expression of CCR5 during MTB infection on HIV-1 load in cells from HIV-1/TB patients. Chapter 7, 8.
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