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Role of blood cells in HIV-TB Co infection epidemiology diagnosis and management

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Abstract
HIV/AIDS pandemic has caused a resurgence of TB, resulting in increased morbidity and mortality worldwide. HIV and Mycobacterium tuberculosis have a synergistic interaction; each accentuates progression of the other. Clinical presentation of TB in early HIV infection resembles that observed in immune competent persons. In late HIV infection, however, TB is often atypical in presentation, frequently causing extrapulmonary disease. These factors coupled with low sputum smear-positivity, often result in a delayed diagnosis. HIV-infected patients respond well to the standard 6-month antituberculosis treatment regimens, although mortality is high. Antituberculosis treatment is complicated by frequent drug-interactions with highly active antiretroviral therapy (HAART) and adverse drug reactions are more common among HIV-infected patients. Guidelines for the management of patients co-infected with HIV and TB are still evolving. Timely institution of antituberculosis treatment using the directly observed treatment, short-course (DOTS) strategy and HAART markedly improves the outcome of HIV-infected patients with TB.

Keywords: *Rhododendron arboreum*, *R. campanulatum*, Jack bean urease, leaf extract, inhibition

Introduction

Human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), since the time of its initial description more than two decades ago, has relentlessly spread all around the globe showing no sign of abatement. In 2004, there were 4.9 million new infections and 3.1 million deaths due to HIV/AIDS1, largely in the sub-Saharan Africa and South-East Asia. Unfortunately, these are the parts of the world where tuberculosis (TB) has been flourishing unhindered since ages, forming a deadly synergy. Advent of the HIV/AIDS pandemic has led to a dramatic increase in the number of TB cases worldwide. Globally, 9 per cent of all new TB cases (31% in Africa) in adults were attributable to HIV/ AIDS, as were 12 per cent of the 1.8 million deaths from TB, in the year 2002. As a result of HIV/AIDS, incidence rates of TB in certain countries have gone up by >6 per cent per year2, crippling the already overburdened health care resources. Considering the fact that about a third of the world's population is infected with Mycobacterium tuberculosis, more than a half of which lives in countries ravaged by HIV/AIDS, the gravity of the situation becomes evident3-5. TB is a leading cause of morbidity and mortality in patients with HIV/AIDS6,7. HIV and TB are also intricately linked to malnutrition, unemployment, alcoholism, drug abuse, poverty and homelessness. The direct and indirect costs of illness due to TB and HIV are enormous, estimated to be more than 30 per cent of the annual household income in developing countries and have a catastrophic impact on the economy in the developing world 8. Thus, co-infection with HIV and TB (HIV-TB) is not only a medical malady, but a social and an economic disaster and is aptly described as the "cursed duet".

Epidemiology of HIV-TB

According to the recent estimates by the WHO and Joint United Nations Programme on HIV/AIDS (UNAIDS), nearly 39.4 million people were living with HIV/AIDS, worldwide; more than a half of them in sub-Saharan Africa and nearly about a fifth in South and South-East Asia1. In India, the overall prevalence of HIV infection is less than 1 per cent and India continues to be in the category of low prevalence countries 9. However, this blurs the actual picture of the epidemic in a vast, populous country like India. As per estimates, about 5.1 million people were infected with HIV in the year 2003, in India (Fig.1) 9. Prevalence of TB in patients with HIV infection In contrast to western countries, where Pneumocystis jiroveci pneumonia was the commonest AIDS-defining illness10, in developing countries TB is the most common life-threatening opportunistic infection (OI) in patients with HIV/AIDS with about 25 to 65 per cent patients with HIV/AIDS having tuberculosis of any organ3,11-14. By the end of 2000, about 11.5 million people were co-infected with HIV and M. tuberculosis, globally; 70 per cent of co-infected people were in sub-Saharan Africa, 20 per cent in South-East Asia and 4 per cent in Latin America and the Caribbean (Table I)2,6. TB accounts for about 13 per cent of all HIV-related deaths worldwide2,6. Of the 5.1 million HIV-infected people in India, about half of them are co-infected with M. tuberculosis; approximately 200,000 of these coinfected persons will develop active TB each year in association with HIV infection15. HIV seroprevalence in Patients with TB In sub-Saharan Africa, HIV seroprevalence rates among patients with TB are high, ranging from 24 to 67 percent 2. In Asia, the rate of HIV infection among TB patients has been lower. Studies from India have reported HIV-seropositivity rates ranging from 0.4 to 20.1 per cent16-26. In certain cities such as Chennai and Mumbai, a higher prevalence has been observed. There has been a steady increase in HIV seroprevalence rates over the years17,18,20. In Pune, the HIV seroprevalence rate was observed to have steadily increased from 3.2 per cent in 1991 to 20.1 per cent in 1996, among patients with pulmonary TB (PTB)18. HIV seroprevalence rate at a tertiary care referral hospital at New Delhi was reported to

have increased from 0.4 per cent (1994-1999) to 9.4 per cent (2000-2002)16,20. The occurrence of localised epidemics and/or selection bias could be the cause of this large regional variation in reported rates of HIV seropositivity among patients with TB. HIV-TB: A

Table 1: Number of adults (15-49) co-infected with HIV-TB in WHO regions end 20023

WHO Region	Number of co-infected with HIV-TB (millions)	% of global total
Africa	8979	80
Americas	568	5
Europe	136	1
South-East Asia	2278	2
Eastern	428	21
Western pacific	453	4
Total	12706	113

Table 2: Clinical presentation of TB in HIV -infected patients

characteristic	Late HIV infection	Early HIV infection
pulmonary	56:56	83:40
Intrathoracic lymphadenopathy	Common	Rare
Lower lobe involvement	Common	Rare
cavitation	Common	Rare

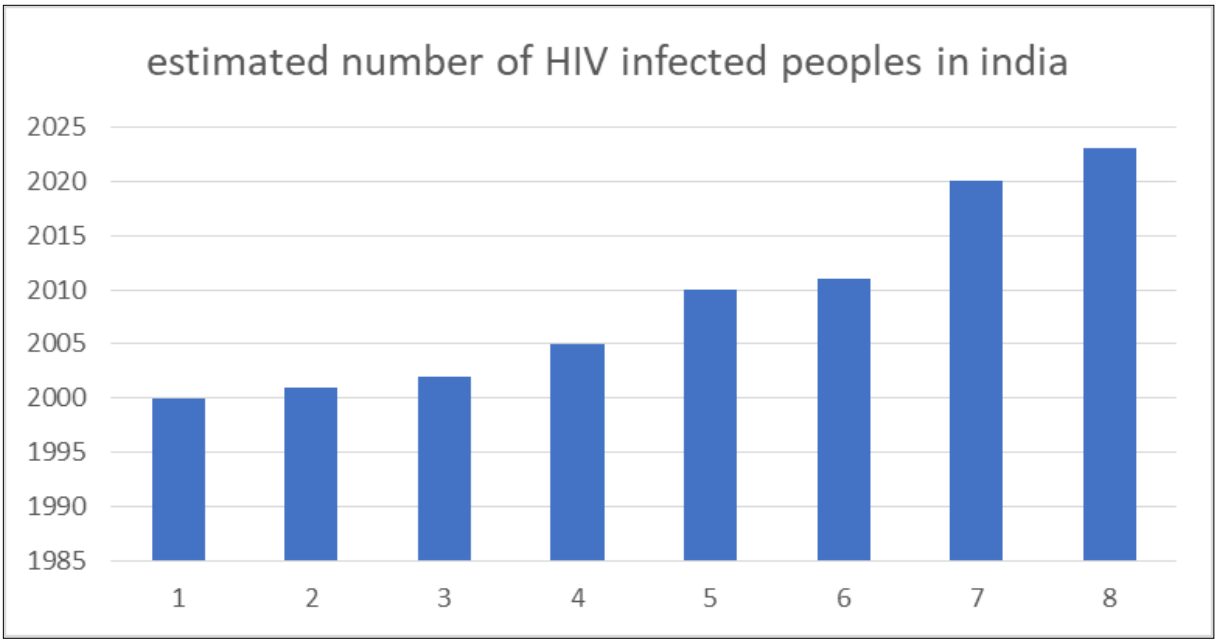

Fig 1: Estimated number of HIV-infected people in India (1980-2023).

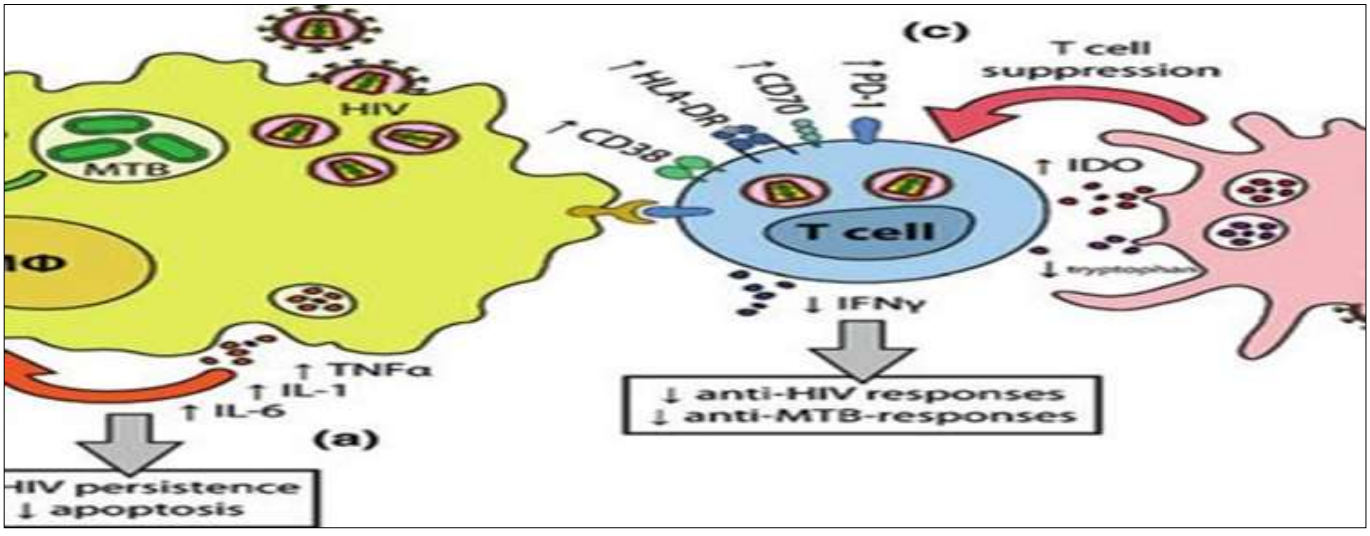

Fig 2: Natural history of Mycobacterium tuberculosis infection in immune competent and HIV-infected individuals

Bidirectional Interaction

HIV infection is the strongest of all known risk factors for the development of TB. HIV-infected persons are at markedly increased risk for progressive disease following primary TB infection27-29, as well as reactivation of latent tuberculosis infection (LTBI). HIV infection also increases the risk of subsequent episodes of TB from exogenous reinfection30-32 (Fig.2). The estimated annual risk of reactivation among those co-infected with HIV and TB is about 5 to 8 per cent with a cumulative lifetime risk of 30 per cent or more compared to a cumulative lifetime risk of 5 to 10 per cent in HIV-negative adult patients.2,33 Th1 type immune response characterised by adequate cell-mediated immunity is the crucial host.

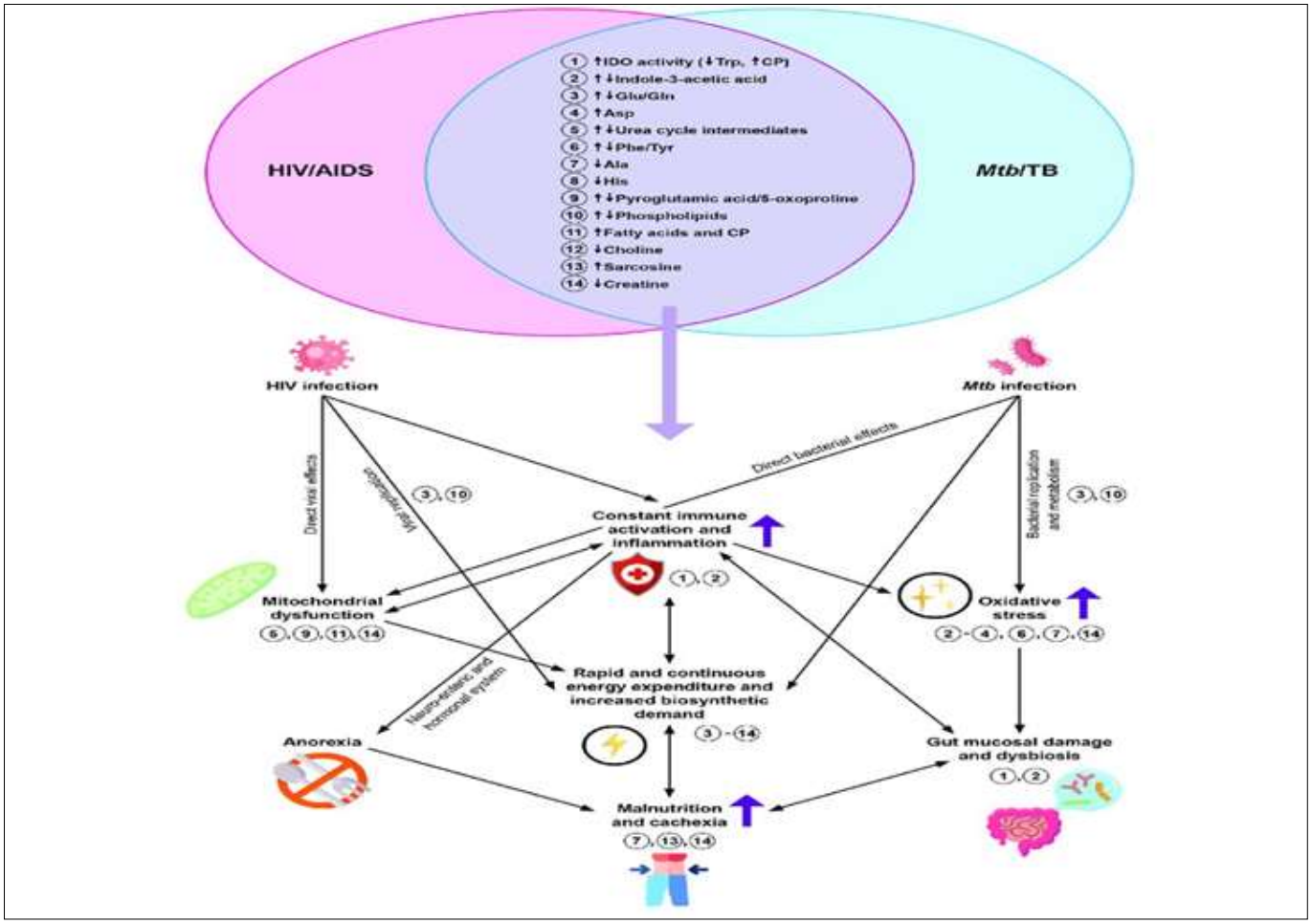

Fig 3: Effect of TB on HIV Infection

Defence against M. tuberculosis 34. HIV infection primarily affects those components of host immune response responsible for cell-mediated immunity. Thus in HIV infected individuals with LTBI, the fine balance between M. tuberculosis and the host immunity gets tiltled in favour of the former, resulting in reactivation35. Moreover, the infection is poorly contained following reactivation, resulting in widespread dissemination causing extrapulmonary disease. This is corroborated by experimental findings that when peripheral blood lymphocytes of patients with HIV-TB are exposed to M. tuberculosis *In vitro*, they produce decreased amounts of Th1 type cytokines, as compared with HIV-negative patients with TB36,37. The interaction between HIV and TB in persons co-infected with them is bidirectional and synergistic. The course of HIV infection is accelerated subsequent to the development of TB and the inverse relationship between HIV viraemia and CD4+ count gets shifted to the right38. Compared with CD4+ count-matched HIV-infected controls without TB, the relative risk of death and development of other OIs is higher in HIV-TB co-infected patients 39. Accelerated HIV progression is partly attributable to the increased systemic immune activation in patients with HIV-TB40. Further, increased HIV replication has been demonstrated locally, at sites of disease affected by TB such as affected lung and pleural fluid, in patients with HIV-TB41,42. Moreover, the genetic diversity of the locally replicating HIV viral population is higher than the circulating population and the local immune activation also favours the development of latent HIV infection of macrophages and dendritic cells, thereby potentially enhancing dissemination of HIV38,42,43. Thus in HIV-infected persons with active TB, the sites of active TB infection act as epifoci of HIV replication and evolution independent of systemic HIV disease activity. 38 The proximate molecular mechanisms of increased HIV replication in patients with HIV-TB are increasingly being understood; increased levels of proinflammatory cytokines such as tumour necrosis factor-α (TNF-α) and chemokines such as monocyte chemotactic protein 1 (MCP1) result in transcriptional activation of HIV genes through activation of nuclear factor-κB (NF-κB) and mitogen-activated protein (MAP) kinase pathways38 (Fig.3).

HIV/AIDS and Drug-resistant TB

In early 1990s, several institutional outbreaks of multidrug-resistant (MDR) TB among HIV-infected patients drew attention to the problem44-48. However, HIV infection per se does not appear to be a predisposing factor for the development of MDR-TB. Recent studies have found that drug-resistant TB including MDR-TB is no more common among people infected with HIV49,50. Inspite of this, several factors such as (i) increased susceptibility to TB, (ii) increased opportunity to acquire TB due to overcrowding, exposure to patients with MDR-TB due to increased hospital visits, and (iii) malabsorption of antituberculosis drugs resulting in suboptimal therapeutic blood levels inspite of strict adherence to treatment regimen, potentially increase the chances of MDR-TB in persons with HIV/AIDS, if not adequately addressed51. Acquired rifamycin monoresistance has also been described in HIV-TB patients treated with rifapentine52.

Clinical, radiographic and Pathologic Findings

Unlike other opportunistic infections which occur at CD4+ counts below 200/mm3, active TB occurs throughout the course of HIV disease27. Clinical presentation of TB in HIV-infected individuals depends on the level of immunosuppression resulting from HIV infection. In patients with relatively intact immune function (CD4+ count > 200/mm3), pulmonary TB (PTB) is more frequently seen than extrapulmonary TB (EPTB)53,54 (Table II). In these patients, chest radiographic findings include upper lobe infiltrates and cavitation, similar to those in HIV negative individuals with PTB55. Sputum smears are often positive for acid-fast bacilli (AFB) in these patients. As immunosuppression progresses, EPTB becomes increasingly common**.** In contrast to HIV-negative patients with EPTB, the disease is often disseminated involving two or more non-contiguous organs concomitantly, in patients with HIV/AIDS11

Diagnosis HIV

Testing in patients with TB Even though it is recommended that all patients with active TB should be tested for HIV infection73, compliance with this recommendation is poor even in developed nations74,75. Selective HIV testing of TB patients is considered unwise because physicians often fail to identify the risk factors for HIV transmission. Even when patients are questioned for risk factors, it has been observed that, up to 5 per cent of patients with TB, without any of the risk factors, had HIV infection76. Though HIV is a major risk factor for the development of TB, HIV testing is not a component of the Revised National Tuberculosis Control Programme (RNTCP) in India. The lack of co-ordination between the voluntary counselling and testing centres (VCTCs) and the directly observed treatment short-course (DOTS) centres in India, is a cause of concern and calls for increasing the collaboration between the RNTCP and the National AIDS Control Organization (NACO)77. Diagnosis of TB in HIV/AIDS Diagnosis of TB in HIV-infected patients is often difficult due to several reasons (i) frequently negative sputum smears, (ii) atypical radiographic findings. (iii) higher prevalence of EPTB especially at inaccessible sites, and (iv) resemblance to other opportunistic pulmonary infections. However, the diagnostic approach to suspected TB in a HIV infected individual is similar to that in immune competent patients56, except that invasive diagnostic procedures are more often required to establish the diagnosis. Universal precautions need to be followed meticulously. CT scan and magnetic resonance imaging (MRI) have facilitated the detection and characterisation of occult foci of EPTB. Attempts should be directed towards arriving at a bacteriological diagnosis, since multiple pathogens often coexist78, and it is not possible to distinguish from atypical mycobacterial infections based on clinical and radiological findings alone. Peripheral blood cultures need to be performed to detect mycobacteraemia. Automated and semi-automated liquid culture systems considerably reduce the delay in obtaining culture results79. Several molecular diagnostic techniques based on detection of M. tuberculosis specific DNA or ribosomal RNA sequences by polymerase chain reaction (PCR) have been developed in the recent past79. However, the appropriate use of these tests in the diagnosis of active TB, especially in patients with HIV/AIDS needs to be defined27. Messenger RNA (mRNA) based PCR techniques may be useful in assessing the response to treatment80 and detection of mutations in the rpoB gene might be useful for rapid drug susceptibility testing79.

Treatment of HIV-TB CO-Infection

Availability of highly active antiretroviral therapy (HAART) has significantly improved the outcome of HIV/AIDS, in terms of prevention of OIs as well as mortality81. Specifically, benefit in terms of prevention of TB has been demonstrated in South Africa82 and outcome of patients with HIV-TB co-infection has improved over the years, attributable to improvements in antiretroviral and antituberculosis treatment83. Thus understandably, both antituberculosis treatment and HAART are indispensable in the management of patients with HIV-TB. However, substantial pharmacokinetic interactions occur between the rifamycin component of antituberculosis treatment and antiretroviral drugs especially, protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs)84. Moreover, short-course antituberculosis regimens used in immune competent patients are not so well studied in the setting of HIV co-infection85. The key therapeutic principles underlying the treatment of HIV-TB are, (i) treatment of TB always takes precedence over the treatment of HIV infection, (ii) in patients who are already on HAART, the same has to be continued with appropriate modifications both in HAART and antituberculosis treatment, and (iii) in patients who are not receiving HAART, the need and timing of initiation of HAART have to be decided after assessing the short-term risk of disease progression and death, based on CD4+ count and type of TB, on an individualised basis86-89. There is no evidence regarding the appropriate time for initiating HAART in patients with HIV-TB87. A retrospective study found that in severely immunosuppressed patients with HIV-TB, early initiation of HAART was associated with reduced mortality and disease progression90. British HIV Association (BHIVA) recommends that if CD4+ counts are >200/mm3, HAART can be started after completion of antituberculosis treatment, if indicated; if CD4+ counts are 100-200/mm3, HAART can be started after 2 months of TB treatment and when CD4+ counts.

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