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A Brief Review on Pathophysiology and Treatment of HIV and TB Co-Infection

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ABSTRACT

The incidence of tuberculosis (TB) is currently increasing in HIV-infected patients living in Africa and Asia, where TB endemicity is high, reflecting the susceptibility of this group of patients to mycobacteria belonging to the TB group. HIV and tuberculosis (TB) are so closely connected that their relationship is often described as a co-epidemic. In the last 15 years the number of new TB cases has more than doubled in countries where the number of HIV infections is also high. If a person has HIV and TB co-infection it means that they have both HIV infection and either latent TB or active TB disease. When someone has both HIV and TB, each disease speeds up the progress of the other. In addition to HIV infection speeding up the progression from latent to active TB, TB bacteria also accelerate the progress of HIV infection.

INTRODUCTION

The incidence of tuberculosis (TB) is currently increasing in HIV-infected patients living in Africa and Asia, where TB endemicity is high, reflecting the susceptibility of this group of patients to mycobacteria belonging to the TB group. In this population, extension of multiple resistances to anti-tuberculous drugs is also a matter of anxiety. HIV-induced immunosuppression modifies the clinical presentation of TB, resulting in atypical signs and symptoms, and more frequent extra pulmonary dissemination. The treatment of TB is also more difficult to manage in HIV-infected patients, particularly with regard to pharmacological interactions secondary to inhibition or induction of cytochrome P450 enzymes by protease inhibitors with Rifampicin or rifabutin, respectively. Finally, immune restoration induced by highly active anti-retroviral therapy (HAART) in developed countries may be responsible for a paradoxical worsening of TB manifestations.

THE LINK BETWEEN TUBERCULOSIS AND HIV

HIV and tuberculosis (TB) are so closely connected that their relationship is often described as a co-epidemic. In the last 15 years the number of new TB cases has more than doubled in countries where the number of HIV infections is also high.

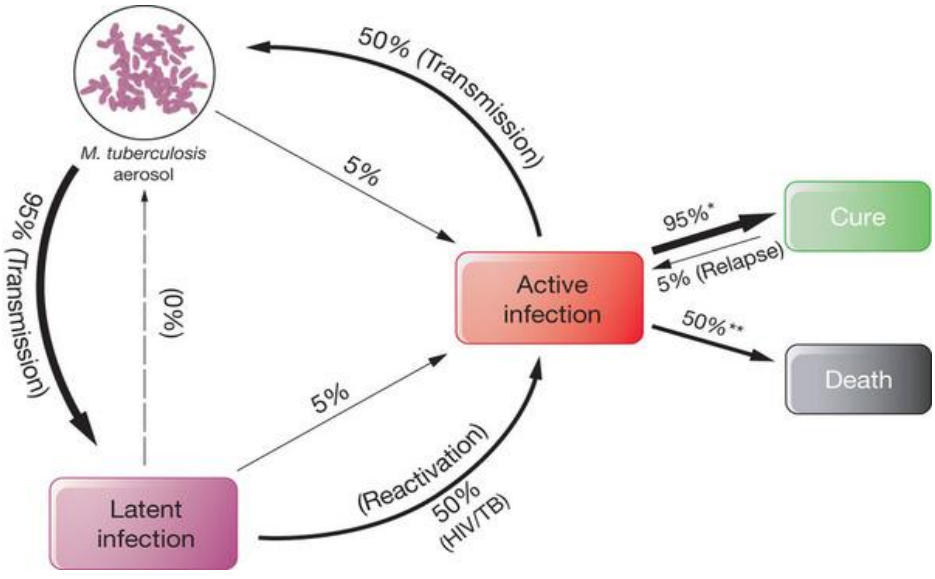

Fig. No. -1[22]

"We cannot win the battle against AIDS if we do not also fight TB. TB is too often a death sentence for people with AIDS. It does not have to be this way. We have known how to cure TB for more than 50 years. What we have lacked is the will and the resources to quickly diagnose people with TB and get them the treatment they need." - Nelson Mandela July 15, 2004 [(1)].

TB AND HIV COINFECTION

If a person has HIV and TB co-infection it means that they have both HIV infection and either latent TB or active TB disease. When someone has both HIV and TB, each disease speeds up the progress of the other. In addition to HIV infection speeding up the progression from latent to active TB, TB bacteria also accelerate the progress of HIV infection [(2)]. HIV infection and infection with TB bacteria are though completely different infections. If you have HIV infection you will not get infected with TB bacteria unless you are in contact with someone who also is infected with TB bacteria. Although if you live in a country with a high prevalence of TB this may have happened without you realize it. Similarly if you have TB you will not get infected with HIV unless you carry out an activity with someone who already has HIV infection, which results in you getting the virus HIV from them. TB also occurs earlier in the course of HIV infection than many other opportunistic infections. The risk of death in co-infected individuals is also twice that of HIV infected individuals without TB, even when CD4 cell count and antiretroviral therapy are taken into account [(3)]. It is estimated that one third of the 40 million people living with HIV/AIDS worldwide are co-infected with TB [(4)].

Winstone Zulu 1964-2011

Winstone Zulu

One of the first people to speak out openly about the problems of TB and HIV co-infection was the Zambian Winstone Zulu. Winstone was a prominent global advocate on TB and HIV.

Winstone was the first person in Zambia to speak openly about being HIV positive. Also, although he himself survived TB he watched four of his brothers' die from TB due to lack of access to anti TB drugs. He was moved to turn his personal loss into ceaseless advocacy for worldwide awareness for the fight against TB and TB-HIV co-infection [(5)].

PATHOPHISIOLOGY

TB results from infection by a pathogen belonging to the *M. tuberculosis* complex, primarily *M. tuberculosis* (Koch's bacillus), and rarely *Mycobacterium bovis* or *Mycobacterium africanum*. After penetration into the respiratory tract, these bacilli infect macrophages, while CD4+ T-lymphocytes and Tγδ-lymphocytes produce interferon gamma (IFN-γ), interleukin-2, tumour necrosis factor alpha (TNFα), and macrophage colony-stimulating factor, which activate macrophages and cytotoxic cells to inhibit their intracellular growth. TB appears when the immune response inducing granuloma is insufficient to limit the growth of mycobacteria. IFN-γ plays a pivotal role at this stage. Indeed, people harbouring genetic defects that result in reduced production of either IFN-γ or its cellular receptors develop severe and fatal TB [(6)].

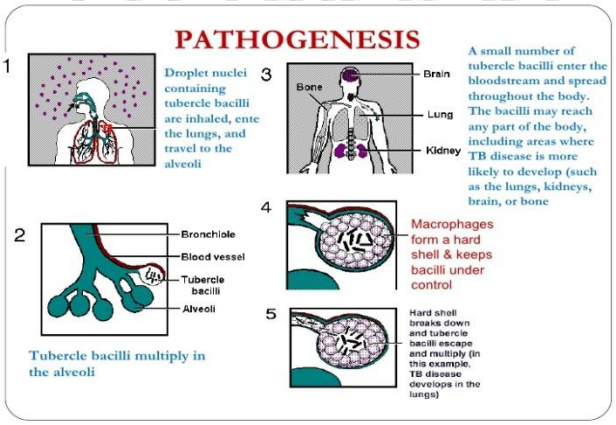

Fig. No. – 2[(23)]

During HIV infection, IFN-γ production is decreased dramatically in parallel with the reduction of CD4+ T-lymphocytes, which leads finally to a markedly increased risk of developing reactivation or reinfection by *M. tuberculosis* in these patients [(7)].

Conversely, TB may also influence HIV evolution. Proinflammatory cytokine production by tuberculous granulomas (in particular TNFα) has been associated with increased HIV viraemia, which might accelerate the course towards severe immunosuppression [(8).]

The risk of death in HIV-infected patients with TB is twice that in HIV-infected patients without TB with matched CD4 cell counts, with most deaths caused by progressive HIV infection, rather than TB [(9)].

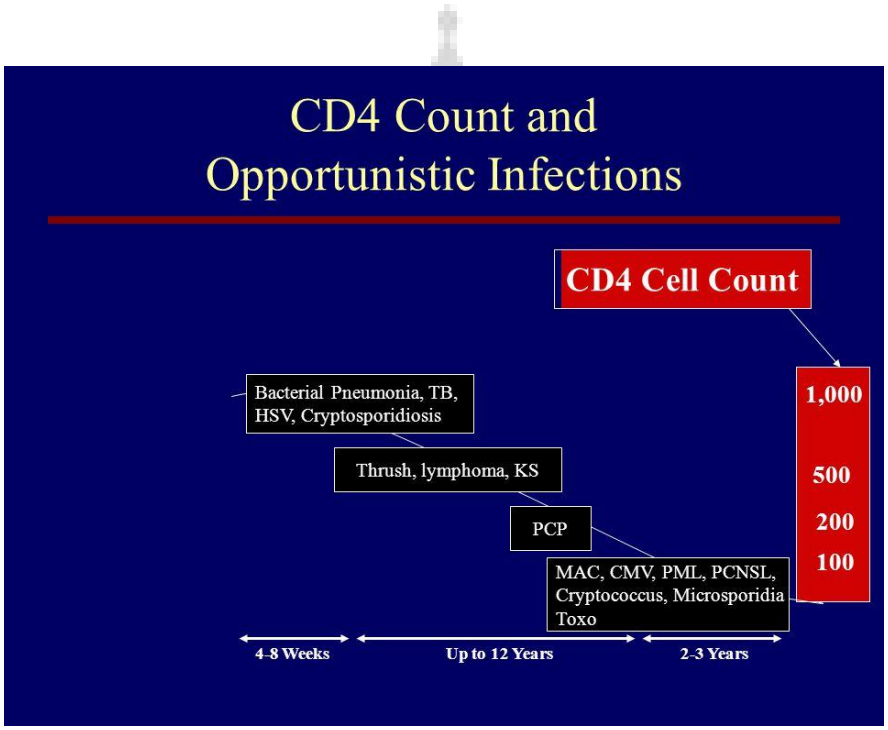

Fig. No. – 3[(24)]

TREATMENT FOR TB AND HIV CO-INFECTION

INITIATING TREATMENT FOR EITHER TB AND HIV

The decision to initiate treatment for either HIV or TB when there is co-infection, should take into account a number of factors including:

- Has the person got symptoms of, and is ill with either TB, or some other HIV related opportunistic infection?
- Is the person already having treatment for either TB or HIV infection?
- What drugs are available for the treatment of HIV infection, and indeed TB, if the person is not already receiving treatment?
- If there is a need for both HIV and TB treatment, are there experienced health care workers and/or guidelines available to provide the necessary expertise on this?

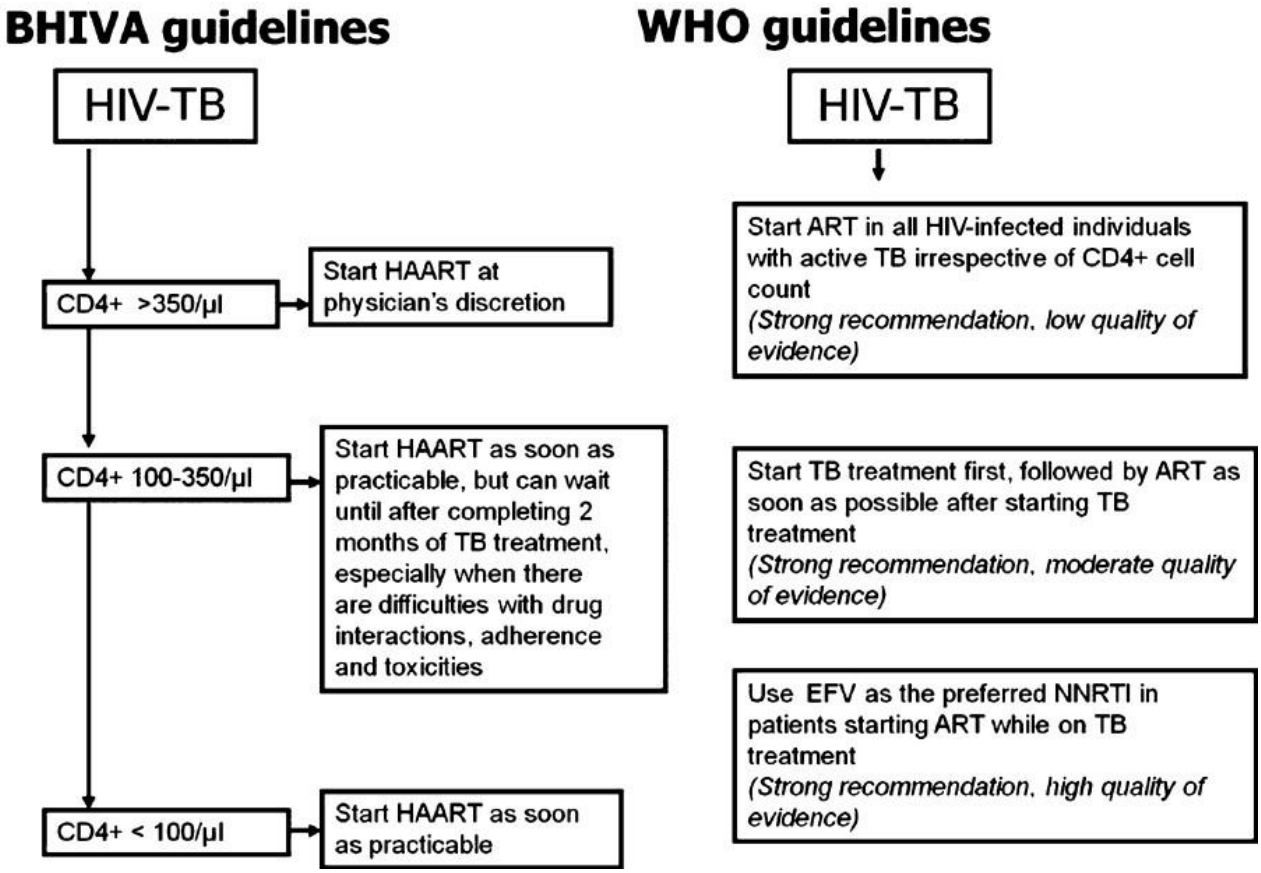

Fig. No.- 4[25]

DIFFICULTIES IN PROVIDING ANTI TB DRUG THERAPY AND ANTIRETROVIRAL THERAPY TOGETHER

The provision of HIV antiretroviral therapy and anti TB drug treatment at the same time involves a number of potential difficulties including [10];

- Cumulative drug toxicities

- Drug - drug interactions
- A high pill burden
- The Immune Reconstitution Inflammatory Syndrome (IRIS)

IMMUNE RECONSTITUTIONAL INFLAMMATORY SYNDROME (IRIS)

IRIS refers to a phenomenon experienced by people with HIV who have recently started antiretroviral therapy. The partial recovery of the immune system can result in an exaggerated inflammatory response against any concurrent opportunistic infection. Tuberculosis Immune Reconstitution Inflammatory Syndrome (TB-IRIS) refers specifically to IRIS that occurs when a patient has active *Mycobacterium tuberculosis* infection. TB-IRIS is estimated to occur in 11% to 45% of patients co-infected with TB and HIV [(11)].

Sometimes TB is clinically "silent" and undiagnosed before the starting of HIV antiretroviral treatment, and this is known as the "unmasking" form of TB-IRIS. By contrast the "paradoxical" form of TB-IRIS is when a person has previously been diagnosed with TB and they start HIV antiretroviral therapy when already on TB treatment. The symptoms of unmasking TB-IRIS is that a few weeks after starting antiretroviral therapy, the patient will have an inflammatory and/or accelerated presentation of TB. The symptoms of paradoxical TB-IRIS are that there will be recurrent, new or worsening TB symptoms, signs and/or radiological findings. Typically there will be a fever 1 - 4 weeks after the start of antiretroviral therapy [(12)].

TB TREATMENT IN HIV PATIENTS

Each of the major anti-tuberculous drugs varies in its capacity to kill *M. tuberculosis* and prevent the emergence of drug resistance. Isoniazid is the most potent bactericidal drug, killing > 90% of bacilli within 7 days by acting on metabolically active bacilli. It is also quite effective in preventing the emergence of drug resistance. Rifampicin is also a bactericidal drug with a potent sterilizing effect and the ability to prevent emergence of drug resistance. Pyrazinamide, although bactericidal, is used mainly for its sterilizing effect, and is effective for killing bacilli sequestered by macrophages in an acidic environment. Ethambutol and Streptomycin are less potent, and Ethambutol is probably only bactericidal at high concentrations. The latter two drugs are less effective in preventing emergence of resistance to Rifampicin and Isoniazid. A fourth drug (ethambutol, streptomycin or, potentially, amikacin) can play a role in HIV-infected patients who

present with an increased risk of drug resistance. Such drugs might be included in the initial phase of anti-TB therapy [13].

Rifapentine has been approved recently as part of a combination regimen for pulmonary TB when given weekly with Isoniazid in the continuation phase (after 2 months of four-drug treatment with Isoniazid, Rifampicin, Pyrazinamide and Streptomycin) [14].

The potential advantages over Rifampicin are once-weekly dosage in the continuation phase, and a better adverse reactions profile. However, it is not recommended for use in HIV-infected patients because of the high rate of relapse with rifamycin-resistant organisms [15].

In HIV-infected patients with TB, the priority is to treat TB because of public health issues, especially in smear-positive cases, before the initiation of HAART in anti-retroviral-naive patients. 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. In various studies, relapse rates were 3–5% after a follow-up of 18–22 months. However, two studies have documented higher rates of relapse in HIV patients who received anti-TB therapy for 6 months, as compared with 9–12 months. However, the latter studies are limited and their results remain a matter of debate. The most recent guidelines of the Centres for Disease Control recommend that HIV-infected patients with drug-susceptible TB be treated with Rifampicin, Isoniazid, ethambutol and Pyrazinamide for 6 months, a similar regimen to that used currently in HIV-negative patients (Table 1). Therefore, if the clinical or bacteriological response is slow, treatment for pulmonary TB should be continued for a total of 9 months, or for 4 months after culture becomes negative. Moreover, when patients are not observed while taking therapy, or when they are severely immunosuppressed, treatment might be for a total of 9 months. For extra-thoracic or disseminated TB, treatment should be given for 9–12 months. Therapy for at least 12 months is recommended for patients who have miliary, meningeal or skeletal TB. Such recommendations mean that, if possible, bacterial eradication should be assessed systematically in HIV-infected patients.

Table 1. Anti-TB regimens recommended for HIV-infected patients (adapted from- [16])		
Drug resistance	**Patients without HIV infection**	**Patients with HIV infection**
I, Isoniazid; R, Rifampicin; P, Pyrazinamide; E, ethambutol; S, streptomycin. [a] Ethambutol may be omitted only if rates of Isoniazid resistance in the community are known to be <4%. [b] Therapy for a total of 12 months is recommended for patients who have miliary or skeletal tuberculosis, with or without HIV infection.		
None	IRPE for 2 months, IR for 4 months	IRPE for 2 months, IR for 4–7 months *or* IPE plus rifabutin for 2 months, I + rifabutin for 4–7 months
Isoniazid	RPE for 6 months	RPE for 6–9 months *or* rifabutin + PE for 6–9 months
Rifampicin	IPE for 18–24 months	IPE for 18–24 months *or* IPSE for 2 months, IPS for 7–10 months

TB drug regimens with rifabutin instead of Rifampicin appear to offer the best alternative for the treatment of active TB among patients taking or requiring anti-retroviral therapy that includes protease inhibitors (PIs) or NNRTIs. Standard anti-TB therapy could be administered more simply with a triple nucleoside reverse-transcriptase inhibitor (NRTI) combination, with anti-retroviral therapy being changed if necessary after anti-TB therapy. To reduce the risk of sub-therapeutic levels of PIs, an alternative is to treat TB with regimens that do not include Rifampicin. These regimens have demonstrated efficacy only in HIV-negative patients, and their utility is limited by toxicity, increased duration (18 months) and non-adherence to therapy.

The major obstacle to control TB is probably non-compliance. If non-compliance is anticipated or suspected, fully supervised intermittent, directly administered ambulatory therapy should be initiated. Drug dosages can help to ensure compliance, in association with measurement of uricaemia in Pyrazinamide-treated patients and the observation of the orange colour of urine resulting from Rifampicin treatment [17].

STARTING BOTH HIV ANTIRETROVIRAL AND ANTI TB THERAPY

For adults with both TB and HIV infection, who need to receive both antiretroviral and TB drugs, WHO guidelines recommend starting HIV antiretroviral between 2 and 8 weeks after

starting TB treatment for those individuals who have a CD4 count of less than 200 mm^3. For people with both TB and HIV, it is not now considered necessary to delay the initiation of antiretroviral therapy until TB treatment has been completed [(18)].

The STOP TB Partnership's Global Plan to STOP TB now has as a target, that by 2015, all HIV positive TB patients should be receiving antiretroviral treatment [(19).]

GLOBAL POLICY ON HIV AND TB SERVICES [(20)]

Although complete integration of HIV and TB services may be difficult, it is clear that a greater awareness of the problem of TB for people with HIV, and closer collaboration between services has already resulted in significant benefits. In 2012, World health Organization (WHO) claimed that 900,000 lives had already been saved over six years by protecting people living with HIV from TB.

In 2011, some 3.2 million people living with HIV were screened for TB, and 2.46 million TB patients were tested for HIV.

THE WHO HIV/TB POLICY INCLUDES [(21)]

The provision of antiretroviral therapy for all HIV positive TB patients, regardless of their CD4 count.

Provision of co-trimoxazole to provide TB patients with HIV with protection against lung and other infections.

In addition, it is recommended that there should be surveillance of HIV and TB amongst health care workers, and that health care workers who are HIV positive, should be moved from areas with high TB exposure.

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