1. INTRODUCTION

Human immunodeficiency virus (HIV) can lead to acquired immunodeficiency syndrome (AIDS). There are two types of HIV, HIV-1 and HIV-2. Both HIV lentiviruses destroy specific type of WBC cells, called CD4+ T cells, which are crucial in helping the body to fight diseases.

At the end of 2011 World Health Organization (WHO) reported 34 million [31.4 million – 35.9 million] people living with HIV globally and 1.7 million [1.5 million – 1.9 million] deaths from AIDS related causes. Almost 5 million people are living with HIV in South, South-East and East Asia. In 2011, people living with HIV accounted for 1.1 million (13%) of the estimated 8.7 million people who developed TB worldwide.1 People with HIV have a 20–30 times higher lifetime risk of developing active tuberculosis (TB), compared to people without HIV.2 In 2010, people living with HIV accounted for about 13% of all new TB cases worldwide, and about 360,000 people died from HIV-related TB.3 As per 2012 WHO report, in India, HIV reactive patients on antiretroviral therapy (ART) have a high prevalence of TB (51-75%).1

The percentage of screening acid fast bacilli (AFB) smear-negative, newly notified TB cases using culture and/or molecular-based test is less than 1% as per WHO TB report 2010.3 TB and HIV has a complex relationship that results in a synergistic increase in prevalence, morbidity and mortality. The occurrence of both infections is a great public health problem. TB is second only to HIV/AIDS as the greatest killer worldwide due to a single infectious agent. TB is the most common opportunistic disease and is a leading killer of people living with HIV causing one
quarter of all deaths. TB and HIV both fuel each other. HIV is the main risk factor for progression from latent TB infection to active disease and increases the risk of recurrent TB due to decreased immunity. It is substantiated by the fact that an HIV positive person has 50-60% lifetime risk of developing TB disease than compared to HIV negative person who has a risk of just 10%. Thus with an increase in the number of TB in people living with HIV/AIDS (PLWHA) there might be an increase in the risk of transmission of TB in the general community. This leads to hot spots of TB transmission and worsening of the TB scenario.\textsuperscript{4,5,6}

The rapid growth of the HIV epidemic and the emergence of drug resistant TB has highlighted the major deficiencies in current diagnostic technologies both for pathogen detection and for diagnosis of drug resistance.\textsuperscript{7} The diagnostic sensitivity of direct smear microscopy is further reduced with HIV infection because of a lower bacillary burden in the lung.\textsuperscript{8,9,10} To improve diagnosis and accelerate the development of TB laboratory diagnostic services for the people with HIV, WHO released new guidelines for TB diagnosis in 2006 and 2007. The guidelines put forward that, the mycobacterial sputum culture is to be performed in HIV-infected patients with a clinical suspicion of TB - who are sputum smear negative, and also to culture other specimens for diagnosing common types of extrapulmonary TB.\textsuperscript{11,12}

WHO’s Directly observed therapy – Short course (DOTS) recommends microscopic examination of sputum smears to identify and control infectious TB. But this technique can diagnose only 50–60% of TB patients, and it has a very limited sensitivity in patients with paucibacillary forms of pulmonary and extrapulmonary disease.\textsuperscript{13,14} HIV changes the presentation of smear negative pulmonary TB from a slowly progressive disease with a low bacterial load and reasonable prognosis, to one with reduced pulmonary cavity formation and sputum bacillary load.\textsuperscript{15} Culture of
clinical specimens are more sensitive than the smear microscopy, as only 10–100 viable organisms will result in a positive culture while a minimum of 5000–10,000 AFB per ml are required for detection by smear.\(^\text{16}\)

Mycobacteraemia is detected in many active TB and in HIV infected patients. Hence blood culture was suggested as a tool to assist the diagnosis of TB in HIV positive patients especially those with disseminated disease.\(^\text{17,18}\) Diagnosis of smear negative TB case is challenging, though BACTEC and other systems are providing the most rapid method for detection in resource limited settings. Culture being the gold standard is very sensitive; the clinical samples and blood collected from the patients with features suggestive of TB could be processed to obtain mycobacterial isolates. The isolates obtained from cultures can be used for mycobacterial species identification, drug susceptibility and molecular epidemiology.\(^\text{19,20,21}\) Christie JD and Callihan DR (1995) suggested that, ultimately the techniques used in the laboratory to diagnose mycobacterial diseases should be matched to the resources available to the laboratory, and the incidence of those diseases in the area served by the laboratory.\(^\text{22}\)

Mycobacterial drug resistance of TB is rapidly emerging worldwide.\(^\text{23}\) There are two ways that people get drug resistant TB; one is when TB treatment is inadequate (patients fail to adhere to proper treatment regimes, the wrong drugs prescribed, when the supply of drugs is not continuous or substandard drugs used for treatment), the other is from the direct transmission of drug resistant TB from one person to another.

WHO reported an alarming rise of not only multidrug resistant (MDR) TB but also extremely drug resistant (XDR) TB globally. In 2011, WHO estimated that there
were globally 310,000 cases of MDR-TB among those cases of pulmonary TB that were reported to them. It was also estimated that in total there were 630,000 cases of MDR-TB among the world’s 12 million prevalent cases of active TB. Almost 60% of MDR-TB cases are in India, China and the Russian Federation. It is estimated that about 9% of MDR-TB cases have XDR-TB. India stands one among 27 “high burden” MDR countries and has over 2 million new TB cases every year and TB kills nearly 1000 people every day. These high burden countries have at least 4,000 cases of MDR-TB each year and/or at least 10% of newly registered TB cases are MDR. WHO currently estimates that India has about 100,000 people with MDR-TB. A team from Mumbai in Jan 2012 reported twelve cases of the strain as totally drug resistant TB and suggested that it cannot be cured because of resistance to all the TB drugs tested.

The MDR-TB prevalence is important as it directly influences the active transmission of strains of MDR-TB. Epidemiological studies for the assessment of local rates and the detection of MDR-TB are important to optimize drug therapy and prevent the dissemination of resistant strains in the community. Although drug resistance in TB has been reported frequently during the last four decades, the available data from India is localized, inaccurate or incomplete. In this background, the study was carried out at JSS Medical College and Hospital, being one of the biggest tertiary care centers in Mysore, Karnataka, India, to diagnose the smear negative TB and analyse the drug resistance pattern of *M. tuberculosis* isolates in HIV reactive patients.

Opportunistic infections were the principal cause of morbidity and mortality in the HIV population, and it still continues to be due to the following reasons:
(1) Many patients are unaware of their HIV infection and seek medical care only when an OI becomes the initial indicator of their disease;

(2) Certain patients are aware of their HIV infection, but do not take ART because of psychosocial or economic factors; and

(3) Certain patients are prescribed ART, but fail to attain adequate virologic and immunologic response because of factors related to adherence, pharmacokinetics, or unexplained biological factors.  

Though OI have been reduced globally by highly active ART, the situation remains same in most developing countries, including India, where patients can hardly afford ART treatment. WHO predicts India to be one of the biggest repositories of HIV/AIDS patients in the coming decades. National AIDS Control Organization (NACO) data revealed that TB is the commonest infection in AIDS patients, followed by candidiasis.  

*Candida* as a part of the normal microflora of healthy individuals - is an opportunist and quickly transforms into a highly pathogenic form with significant mortality and morbidity under appropriate conditions. Candidiasis occurs in 3 forms in persons with HIV infection: oropharyngeal, esophageal, and vulvovaginal disease. Oral candidiasis (OC) is the most common opportunistic infection seen in all continents. Its prevalence in HIV infection has been well documented in developed countries. It is the most common manifestation observed in HIV reactive patients reflecting a declining immune system and can predict the development of AIDS. Oral candidiasis affects 1/3rd of the seropositive and more than 90% of the patients with AIDS at some point during their progression to full-blown AIDS.
Saha et al. and Ali Abdul Lattif et al. in their studies indicated that 53 to 75% of the individuals are affected with OC.\textsuperscript{44,45}

Studies have shown that fluconazole resistant strains of oropharyngeal yeast-like cells exist in about 9.5% of HIV/AIDS patients. Enwuru CA et al. in 2008 and Martinez M et al. in 2002, highlighted the need for routine AST in HIV patients with cases of initial or repeat episodes of candidiasis.\textsuperscript{46,47} Treatment of oropharyngeal candidiasis, in patients with an immunocompromised system, is often more difficult, and relapses are common among them.\textsuperscript{48}