The Human Immunodeficiency Virus (HIV-1) pandemic remains a major global public health challenge, with about 34 million (31.6 million-35.2 million) people living with HIV worldwide by the end of year 2011, up by 17% from 2001 (Joint United Nations Programme on HIV/AIDS). In 2010 alone, 2.7 million (2.4 million-2.9 million) people were newly infected with HIV (progress report 2011: Global HIV/AIDS response). The risk for active *Mycobacterium tuberculosis* (*M.tuberculosis*) is 20–37 times higher in people living with HIV than in the general population, depending on the prevalence of HIV in the population (Getahun et al., 2010). Recent data from World Health Organization (WHO) shows that, of the 8.5-9.2 million tuberculosis cases worldwide in 2010, those with HIV accounted for about 13% of all new tuberculosis cases (WHO, 2011b). On the other hand, one third living with HIV are co-infected with *M.tuberculosis* resulting in around 520,000 deaths from tuberculosis, equivalent to 26% of the estimated 2 million deaths from HIV and 29% of the 1.8 million deaths from tuberculosis in 2008 (WHO, 2010). Till date, there is no cure to the HIV disease and this 19 protein virus is still running loose.

HIV-1 infects mainly CD4 (cluster of differentiation 4) positive cells which include T-helper cells among lymphocytes and monocytes, macrophages and dendritic cells among myeloid cells (Rubbert et al., 1998; Lusso, 2006) bearing the CD4 molecule along with chemokine receptors CCR5 (C-C chemokine receptor type 5) and/or CxCR4 (C-X-C chemokine receptor 4) on their surface (Shacklett et al., 2003). CD4+ T helper cells play an important role in facilitating and enhancing the functions of other immune cells that protect the host from invading pathogens. The hallmark of HIV-1 infection is the gradual decline in the CD4 T-cell number, making the individual vulnerable to opportunistic infections like *M.tuberculosis*. With the onset of tuberculosis (TB), it notably accelerates the course of HIV-1 disease progression (Whalen et al., 1995). One possible reason is increased HIV-1 replication and expression of its co-receptors that would help in its spread (Whalen et al., 2000). The co-infection of HIV-1 and *M.tuberculosis* in a common host is well established, but little is known about synergistic mechanisms favoring the co-infection. These may be pathogen-related, host-related or both. Understanding the host related factors
underlying this synergistic interaction between HIV-1 and TB may provide valuable information on HIV pathogenesis.

Regulatory aspect of immunity is critical for the host to develop a properly balanced immunity in favor of the host so that disease is contained without much bystander damage of the host tissue by the exaggerated immune response. Regulatory balance shifting to excessive immune response potentially eradicates the pathogen, but at the cost of heightened host tissue destruction. On the other hand, tilting balance towards immune-suppression fails to contain the infection with minimal immune mediated host tissue damage. With HIV-1 infection, it is important to understand how this precise balance of the host immune response and its regulation is disturbed in the favor of M.tuberculosis infection. At present, the role of regulatory T-cells (Treg) in HIV infection has not been fully defined and remains debatable (Fazekas de St Groth and Landay, 2008; Brandt et al., 2011). Although some studies conclude that Treg suppresses the host adaptive antiviral immune response and is therefore considered harmful (Aandahl et al., 2004; Kinter et al., 2004; Weiss et al., 2004; Andersson et al., 2005; Boasso et al., 2006; Nilsson et al., 2006; Kinter et al., 2007b; Cao et al., 2009) others hold that Treg cells prevent chronic immune activation and are therefore considered beneficial (Oswald-Richter et al., 2004; Eggena et al., 2005; Tsunemi et al., 2005; Baker et al., 2007; Chase et al., 2007; Ndhlovu et al., 2008; Card et al., 2009). As the role of Treg remains inconclusive in HIV infection, in this study we have tried to elucidate, if there is any correlation between Treg and HIV-1 disease progression in therapy naïve individuals. Further, we have tried to understand how M.tuberculosis infection in HIV patients affects the Treg population and CCR5 and CxCR4 expression on CD4 T-cells.

HIV-1 is a lentivirus belonging to the Retroviridae family. It initiates infection via interaction of viral envelope glycoprotein gp120 with cell surface CD4, followed by association with a co-receptor that triggers the fusion of viral and host-cell membranes. The chemokine receptors, CCR5 and CXCR4 are predominant co-receptors utilized by HIV-1 in vivo. All HIV-1 strains are classified phenotypically as R5 (Macrophage tropic), X4 (T-cell tropic), or R5X4 (dual tropic i.e. both M-tropic and T-tropic) depending on whether they preferentially utilize CCR5, CXCR4, or
either, respectively (Berger et al., 1999). In early stage, HIV infection is dominated by CCR5 tropism (de Mendoza et al., 2007; Frange et al., 2009) and at the most only about 15% are dual/mixed tropic. But in later stage of disease, dual/mixed tropism or pure CxCR4 tropism reaches upto 60% when measured by the enhanced tropism assay (Wilkin et al., 2011), and is highest with CD4 count ≤ 200 cells/μl (Brumme et al., 2005; Hunt et al., 2006). However these results may vary with the prevalence of HIV-1 subtype in the region. Our study aims at cross-sectional analysis looking at the expression of two main co-receptors of HIV-1, CxCR4 and CCR5, on subpopulations of CD4 T-cells based on intensity of CD25 expression on their surface. CD25 is α-chain of the interleukin 2 (IL-2) receptor and is constitutively expressed by T-regulatory cells.

Normal functioning of viral infected host cells is altered by invading viral proteins leading towards the benefit of the virus (Evans et al., 2009). There have been constant efforts to understand these interactions between viral and cellular gene products that together determine the host’s susceptibility to infection and have led to significant new insights about HIV-1 disease (Samuel, 2006). This study focuses on alteration in the expression of some of such molecules and how they behave during HIV-1 disease progression and M.tuberculosis co-infection.

1.) Precursors and catabolic products of heme oxygenase (HO) system are capable of antimicrobial and antiviral activities. HO-1 induction or overexpression promotes a wide range of antiviral activities in HIV-1 (Devadas and Dhawan, 2006). On the other hand, HO-1 derived carbon monoxide can induce the dormancy survival regulon (DosR regulon) in Mycobacteria leading to its latency and survival of the organism inside the host granuloma (Kumar et al., 2008; Shiloh et al., 2008).

2.) Ras-related C3 botulinum toxin substrate 1 (Rac1) is specifically involved in regulating the conformation of CxCR4, which is the main co-receptor for HIV-1 in advanced stages of the disease, thereby controlling the efficiency of this receptor. The conformation adopted by CxCR4 after blocking Rac1, does not support HIV-1 binding and entry into the host cells (Zoughlami et al., 2012). Thus, Rac1 may play an important role in viral switch and later appearance of X4 virus variants.
3.) Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) p50/RelA heterodimer and components of canonical NF-κB pathway can initiate HIV transcription by binding to the enhancer region located at -104 to -80 within 5’ LTR region (Duh et al., 1989; Alcamí et al., 1995; Sgarbanti et al., 2008).

In order to understand the interactions of these factors and longitudinal immunological changes during HIV-1 disease progression and *M.tuberculosis* co-infection, different cohorts of HIV-1 infected individuals at different stages of HIV-1 infection were recruited in this study, including those individuals who are co-infected with pulmonary tuberculosis (PTB).