1. INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) caused by human immunodeficiency virus continues to be a major health risk for mankind, ever since its discovery in 1981. Human immunodeficiency virus (HIV) epidemic caused infections in about 36.7 million people with an incidence of 2.1 million new infections in 2015 (UNAIDS global AIDS update, 2016). In India, 2.1 million people were HIV infected with a prevalence rate of 0.26%, while the incidence is about 85000 new infections every year (India HIV Estimates 2015 Technical Report, NACO). Though the rate of HIV transmission and new HIV infections were reduced every year through antiretroviral treatment (ART) and highly active antiretroviral treatment (HAART) medications and various social awareness programs, eradication is still not possible with successful therapy or vaccination and thus remains a concern.

HIV infection occurs by transmission of virus through sexual intercourse, transfusion of infected blood and blood products and mother-to-child transmission during pregnancy, at child birth or through breast feeding (Girard et al., 2011). It is observed that 50% of HIV transmission occurs through newly infected individuals (Hollingsworth et al., 2008; Brenner et al., 2007) because of their higher plasma viral load (PVL) levels seen during the early stages of infection (Wawer et al., 2005).
HIV infection and progression to AIDS generally includes an acute/primary phase that lasts for months, followed by a phase of clinically latency that typically lasts for years and then AIDS-defining illness caused ultimately by the collapse of immune system. Based on the time taken for the progression of disease HIV infected individuals are classified. Rapid progressors (10% to 15%) experience an unusual rapid progression to AIDS within 2 to 3 years of primary infection (Pantaleo and Fauci, 1996; Phair, 1994). Typical progressors accounts for the majority (70% to 80%) of HIV infected individuals, who experience a long period of clinical latency of upto 6 to 8 years (Buchbinder et al., 1994; Lifson et al., 1991). A characteristic course of HIV infection can be observed in typical progressors (Pantaleo and Fauci, 1996).

A small (<5%) group of HIV infected individuals do not experience progression of disease for an extended period of time are called Long-term non-progressors (LTNP). These people have CD4+ T-cell counts that are within the normal range and are stable over time in the absence of treatment (Gaardbo et al., 2012; Deeks and Walker, 2007; Pantaleo and Fauci, 1996). CD4+ T-cell count decreases when the rate of destruction exceeds the rate of production. LTNP may have differences in production rate compared to the destruction rate in order to maintain normal CD4+ T-cell counts.

Non-progression in LTNP might be due to viral or host factors. HIV viruses that have weaker viral fitness and that cannot evade host immune
responses might help in non-progression (Poropatich and Sullivan Jr, 2011). Viral strains from LTNP which are less evolved and less capable of escaping host immune responses has been reported (Sandonís et al., 2009; Wang et al., 2003). Host factors consist of both genetic and immunological factors. Major histocompatibility complex (MHC) loci mutations, polymorphism in HIV co-receptor genes and polymorphic immunoregulatory genes present in the MHC region might be the significant genetic factors associated with HIV disease progression (International HIV Controllers Study et al., 2010; Paranjape, 2005).

Immunological factors that contribute to disease non-progression include both innate and adaptive immune response mechanisms. Innate immunity plays a significant role in controlling HIV infection during initial stages and hence more crucial in acute and primary stages of HIV infection (Paranjape, 2005). Plasmacytoid dendritic cells (PDC) and natural killer (NK) cells are the two predominant cell types of innate immune mechanisms. PDC were reported to have the ability to express interferon-\(\alpha\) (IFN-\(\alpha\)) and loss of these cells is associated with increase in viremia and progression to AIDS (Soumelis et al., 2001). NK cells are capable of eliminating virus infected cells without prior sensitization and MHC restriction. LTNP have been shown to possess NK cells that produce significantly elevated levels of interferon-\(\gamma\) (IFN-\(\gamma\)) by which NK cells mediate control of HIV infection (Vieillard et al., 2010; O’Connor et al., 2007).
In adaptive immune responses broadly neutralizing antibodies (bNAb) and HIV-specific T-cell responses play significant role in controlling HIV infection. LTNP shown to possess weak bNAb responses compared to HIV infected patients with high viremia and it has been attributed to reduced antigenic stimulation of B-cells (Doria-Rose et al., 2010; Pereyra et al., 2008).

Elimination of HIV-infected host cells by CD8+ T-cells responses strongly correlates with immune control in LTNP. CD8+ T-cell responses were observed to coincide with decline in viral replication during acute HIV and simian immunodeficiency virus (SIV) infections (Nemes et al., 2010; Allen et al., 2000). Evidences have shown that, functionality of CD8+ T-cells might be responsible for the extended replication control of HIV in LTNP (Betts et al., 2006) because of which considerable attention has been directed towards HIV-specific CD8+ T-cells (Ndhlovu et al., 2013; Mothe et al., 2012; Gea-Banacloche et al., 2000). Presence and prolonged maintenance of strong broadly directed HIV-specific CD8+ T cell responses during chronic phase were reported to be more in LTNP compared to progressors (Poropatich and Sullivan, 2011; Boaz et al., 2002; Migueles et al., 2002). However, conflicting results have also been reported questioning the possible role of CD8+ T cell responses in viral control and its relation with HIV disease non-progression (López et al., 2008; Benito et al., 2003). Defects in phenotypic (Ghiglione et al., 2014; Appay et al., 2002; Champagne et al., 2001) and functional properties (Kostense et al.,
of HIV-specific CD8+ T-cells and their inability to expand \textit{in vitro} (Benito \textit{et al.}, 2003) have also been described. Large body of evidence suggests that HIV-specific cellular responses succeed in few and fail in most people (Migueles and Connors, 2015).

Viral replication driven generalized immune activation is now established as the main mechanism behind CD4+ T-cell depletion (Choudhary \textit{et al.}, 2007). Loss of regenerative capacity of immune system due to high T-cell turnover is caused by accelerated proliferation, expansion, and death of T-cells during the course of HIV infection (Deeks \textit{et al.}, 2004). Susceptibility of T-cells to HIV-1 infection is reduced with less CD4+ T-cell activation rates and it can lead to better disease prognosis (Poropatich and Sullivan, 2011). Activation profile of LTNP were similar to SIV infected sooty mangabeys and African green monkeys which also showed no signs of increased immune activation or high T-cell turnover despite high viral loads (Broussard \textit{et al.}, 2001). Contrarily, there are also reports stating that there are no differences in immune activation between elite controllers (EC) and LTNP (Whittall \textit{et al.}, 2011) and EC, LTNP and progressors (Vieillard \textit{et al.}, 2010).

Regulatory T-cells (T-regs) play varied roles that differ in various stages of HIV infection (Phetsouphanh \textit{et al.}, 2014; Chevalier and Weiss, 2013). T-regs have the ability to limit T-cell activation rates, which is the main mechanism behind T-cell dysfunction and depletion (Phetsouphanh \textit{et al.}, 2014; Chevalier and Weiss, 2013).
al., 2014; Moreno-Fernandez et al., 2011) and thus shows a beneficial role. On the other hand T-regs inhibit effector T-cell responses during early HIV infection (Kinter et al., 2004) and may suppress HIV-specific responses that in turn inhibit T-cell responses to HIV and increase viral persistence, leading to immune exhaustion (Phetsouphanh et al., 2014; A. Kinter et al., 2007; A. L. Kinter et al., 2007) and thus becomes detrimental. In patients who are under successful ART, a significant decrease in T-regs frequency or even normal to that of HIV negative controls were reported (Montes et al., 2011; Xing et al., 2010). In the case of LTNP and EC, frequencies of T-regs were reported to be similar (Angin et al., 2012; Shaw et al., 2011) or even lower compared to uninfected controls (Schulze Zur Wiesch et al., 2011; Owen et al., 2010).

A separate phenotype of CD4+ T-cells called follicular helper CD4+ T-cells (Tfh) expressing high levels of CXCR5 receptor were described (Kim et al., 2001; Breitfeld et al., 2000; Schaarli et al., 2000). Tfh cells promote antigen-specific B-cell development and its maturation (Wang et al., 2016) by providing help to B-cells in germinal centres of secondary lymphoid organs and are crucial for GC formation, immunoglobulin class-switch recombination, somatic hyper-mutation, and differentiation of B-cells into memory B-cells and plasma cells (Crotty, 2011). In HIV infection, Tfh plays a central role in generating efficient neutralizing and non-neutralizing antibody responses and thus becomes an essential factor in developing an effective vaccine (Petrovas and Koup, 2014; Phetsouphanh et
Hence an effective functioning of Tfh cells are required for an efficient humoral response. Impact of HIV infection towards frequencies and functions of Tfh cells during various types of disease progression were poorly understood.

HIV infection results in phenotypic perturbations of B-cells, which include over-representation of activated, exhausted, and terminally differentiated B cells associated with HIV viremia (Moir et al., 2001); over-representation of immature/transitional B cells associated with HIV-induced CD4+ T-cell lymphopenia (Malaspina et al., 2007); and reduced representation of CD27+ memory B-cells associated with most stages of HIV infection (Moir et al., 2010). Reduced CD27+ memory B-cells results in accelerated differentiation of B-cells into plasma cells affecting B-cell developmental regulation and B-cell composition in peripheral blood (Yong Chong et al., 2004). Growing evidence suggests that the HIV-specific antibodies activity mediated through the Fc-receptor, such as antibody dependent cellular cytotoxicity (ADCC), have an important role in controlling HIV infection (Aziz et al., 2015). Presence of ADCC responses in breast milk have been suggested to reduce mother to child transmission (Mabuka et al., 2012) and ADCC pressure have been shown to generate viral escape mutants (Chung et al., 2011). Hence a considerable performance of B-cells is required for establishing resistance against HIV infection.
Pathogenesis of HIV-1 infection also depends on the expression of β-chemokine receptors present on the surface of CD4+ T-cells, since it is used by HIV-1 strains as co-receptors for their entry and critical to establish persistent infection. β-chemokines such as macrophage inflammatory protein-1β (MIP-1β), monocyte chemoattractant protein-1 (MCP-1) and regulated on activation, normal T-cell expressed and secreted (RANTES) bind to these receptors and may play an important part in controlling the extent of HIV infection (Ramalingam et al., 2008). In addition to chemokines, changes in plasma cytokine levels are also important with respect to disease progression. Since HIV is associated with opportunistic infection, persistent inflammation due to HIV or opportunistic infections, are always possible. Inflammation on the other hand promotes increased viral replication, viral entry, and immune dysfunction in HIV (Haissman et al., 2009).