Summary and Conclusions
Dendritic cells (DCs) are most versatile antigen presenting cells that are central to induction and regulation of adaptive immune responses. DCs reside in different tissues and mucosae as immature cells and possess capacity to acquire, process and present antigens to T cells; induce tolerance in self reactive T cells, interact with B and NK cells and play a very significant role in antiviral innate immune response. Such a large degree of functional plasticity in DCs can be attributed to a combination of specialized DC subtypes, their distribution in tissues, different maturation stages and various functional/effector molecules.

Sexual transmission across the genital mucosa is the main route of HIV infection and accounts for 80% of the infections worldwide. Immature DCs residing within the epithelial surfaces (Langerhans cells, LCs) and sub epithelial surfaces (dermal DCs) are believed to be the initial targets for HIV-1 after mucosal exposure and to be involved in early events in primary HIV infection in the mucosa (Morrow et al., 2007). The DC-HIV interaction may result in processing and presentation of the virus particles (Larsson et al., 2002), or rapid internalization into non-lysosomal compartments (Geijtenbeek et al., 2000b) or productive infection of DCs (Turville et al., 2004). Transmission of HIV from DCs which are not infected but have engulfed the virus is called as trans transmission while the transmission of de novo virus particles is known as cis transmission. While DCs can help in transport of virus they are also important for DC-T cell interaction for generating adaptive immune response specific to HIV. In this way, the central role of DCs in stimulating T-cell activation not only provides a route for viral transmission but also represents a vulnerable point at which HIV-1 can interfere with the initiation of primary T-cell immunity.

HIV interferes with DC function by affecting their T cell stimulatory capacity (Donaghy et al., 2003), cytokine secretion (Buisson et al., 2009) and expression of functionally important molecules (Andrieu et al., 2001). HIV infection also induces numerical and functional defects in the two major circulating DC subsets, myeloid DCs (mDC) and plasmacytoid DCs (pDC)
mDCs are proficient at antigen uptake and presentation while pDCs are thought to play an important role in innate immune responses to different viruses by producing interferon alpha (IFN-α) and support antigen presentation function of mDCs (Randolph et al., 2008). Groot et al found opposing roles for mDCs and pDCs during HIV infection of T cells i.e mDCs facilitate transmission while pDCs inhibit HIV replication (Groot et al., 2006a). Though a number of studies have focused on role of DCs in HIV immunopathogenesis, our understanding of DC-HIV interaction is far from complete. In this study we have concentrated on co-stimulatory molecules on DCs in HIV infection and the regulation of their gene expression and DC populations in circulation with the following specific objectives,

1. To study the mechanisms responsible for depletion of circulating mDC and pDC populations at different stages of HIV infection.
2. To study the effect of HIV infection on expression of co-stimulatory molecules CD80 and CD86 and other genes important for DC function.

**Conclusions**

*In vivo* study to assess the effect of HIV infection on circulating DC subsets (chapter 3).

1. HIV infection results not only in persistent decrease in pDC numbers by induction of apoptosis but also impede their function. Since pDCs are important mediators of innate antiviral immune response, early irreversible loss of pDCs, largely through apoptosis may be responsible for impaired innate anti-HIV immune responses.
2. Maintaining normal levels of functional pDCs by slow progressors in our study to retain functional pDCs, imply that pDCs may play an important role in HIV virus control and subsequent progression to AIDS.
3. The loss of circulating mDCs during HIV infection might be due to migration to lymphoid areas as well as apoptosis.

In vitro studies to assess effect of HIV infection on gene expression by dendritic cells

1. Reduced surface expression of CD80 and CD86 on DCs during HIV infection may be regulated at transcription level by multiple TFs, including NFκB subunits and MYB.

2. HIV infection also hampers the expression of other members of the co-stimulatory molecules (TNFRSF8, TNFRSF9, TNFRSF11B, and CD70) and this may be a major mechanism by which the virus abrogates generation of HIV-specific immune response.

3. HIV is capable of impairing DC function even without productively infecting the DCs.