6. DISCUSSION

The efficient control of viral replication has been attributed to HIV-specific CD8+ T-cell responses (Gaardbo et al., 2012). As part of these adaptive response mechanisms, CD4+ T-cell responses, CD8+ T-cell responses and neutralizing antibodies are the main factors playing a central role in viral control (Migueles et al., 2004; Paranjape, 2005). A consistent association has always been found between control of infection and CD8+ T-cell responses. During primary HIV infection, expansion of HIV-specific CD8+ T-cell responses corresponds with the decrease in viremia (Koup et al., 1994; Saez-Cirion et al., 2014). Virus infected host cells are terminated by the presence of classic CD8+ T-cell responses and gag-specific CD8+ T-cell responses have been shown to correlate well with reduced PVL (Kiepiela et al., 2007; Levy, 2009). Studies on macaque models showed in vivo depletion of CD8+ T-cells are unable to control acute SIV infection (Okoye et al., 2009) and elevated viral loads in SIV infected macaques with chronic infection (Jin et al., 1999; Schmitz et al., 1999).

Numerous studies have highlighted the importance of immune tolerance in HIV disease non-progression in LTNP. CD8+ T-cells act as potential mediations in lowering PVL levels and that it strongly correlates in facilitating immune control in LTNP (Migueles and Connors, 2010). Unlike progressors, LTNP have been found to possess robust, polyclonal T-cell responses and that are maintained for longer duration during HIV infection,
which directly correlates with their decreased viral load (Boaz et al., 2002; Migueles et al., 2002). Broadly reactive CD8+ T-cell responses against conserved sequences of env, gag and pol genes have also been reported in LTNP (Geldmacher et al., 2007; Migueles and Connors, 2010).

In this study, HIV-specific CD8+ T-cell and CD8- T-cell (probably CD4+ T-cells) responses against gag and env were analyzed in LTNP and progressors. Interestingly, there were no significant differences in the frequencies of IL-2 and IFN-γ in both CD8+ and CD8- T-cells against both gag and env peptides and many LTNP failed to mount a significant response to HIV peptides. Though contrary to many studies, this is in line with a finding revealing that the role of gag-specific CD8+ T-cells expressing IL-2 and IFN-γ in durable control of is limited (Emu et al., 2008). When only positive responders were considered, frequency of TNF-α expressing CD8-T-cell against gag and env individually, was significantly higher in LTNP. This shows a striking contrast with other studies (Altfeld et al., 2000; López et al., 2008), where TNF-α expression was shown to be significantly superior in HIV infected patients with progressive infection. Here, increasing PVL in LTNP might have played a major role in higher TNF-α expression, since LTNP with PVL >2000 also expressed significantly higher frequencies of TNF-α in CD8-T-cells against collective of both peptides. Effect of gradual CD4 T-cell depletion by means of TNF related apoptosis (Herbeuval et al., 2005) might result in increased TNF-α expression in LTNP. Another possible explanation is that 20% of LTNP involved in this study were HIV infected for more than 10
years and it is certain that they might be on the verge of losing their LTNP status as a result of compromised tolerance. This can be concluded only by longitudinal studies and quantitative analysis of TRAIL and other apoptosis related markers in LTNP comparing with other groups of HIV-infected individuals.

LTNP with PVL >2000 witnessed a spiked frequency of env-specific and both gag-specific and env-specific CD8-IFN-γ+ T-cells. IFN-γ expression by LTNP despite PVL, being elevated which is in line with other studies (Betts et al., 2006; Boaz et al., 2002; Zimmerli et al., 2005), but here it is CD8-T-cells but not CD8+ T-cells. CD8- T-cells are not classical cytotoxic T-cells, but still express IFN-γ. Helper T-cells exhibiting cytotoxicity have already been characterized in persistent viral infections (Casazza et al., 2006; Khanna et al., 1997; Zhou et al., 2007) and similar phenomenon has also been explained in PBMC from rare HIV infected individuals and LTNP (39,40). Hence, this can be hypothesized that CD8- T-cells might be stressed to perform cytolytic activities in order compensate the impaired CD8+ T-cell cytotoxic responses in LTNP (Nemes et al., 2010) which is not even seen in progressors possibly indicating the presence of completely impaired CD8+ as well as CD8- T-cells.

Contrary to other studies (Betts et al., 2006; López et al., 2008), significant elevated frequency of MIP-1β by CD8+ T-cells against env were seen in progressors, while positive correlations between gag-specific and env-specific CD8+T-cells expressing MIP-1β with CD4+ T-cell count and CD4%
were observed. Protection against HIV disease progression by $\beta$-chemokines such as MIP-1$\alpha$, MIP-1$\beta$ and RANTES differs with the relative affinity of chemokines with $\beta$-chemokine receptors of T-cells. Of the $\beta$-chemokines, MIP-1$\beta$ has a very narrower range of immunological activity in terms of binding only with CKR5 (Adams and Rlloyd, 1997; Premack and Schall, 1996; Ullum et al., 1998) and not with other C-C chemokine receptors. It should be noticed that MIP-1$\beta$ levels were elevated even in plasma of progressors. This might have also reflected at the cellular level. Evaluation of other $\beta$-chemokines along with MIP-1$\beta$ is highly required to establish the underlying mechanism behind HIV disease non-progression in LTNP. Though there were no significant differences in IL-2 expression between two groups, direct correlations of HIV-specific CD8+ T-cells expressing IL-2 with CD4% were observed in LTNP. This indicates an increased T-cell proliferation in LTNP compared to progressors.

This study did not draw any significant correlations with cytokine profile and disease non progression in LTNP. During acute infection, size or frequency of HIV-specific CD8+ T-cell responses and their negative correlation with PVL is interpreted as the effectiveness of these responses. But in persistent infection, efficacy and frequency of CD8+ T-cell responses is not clearly evaluated. It is because of the factor that proliferation of CD8+ T-cell responses occurs only in response to antigens and frequency of these responses are both a cause and an effect of the PVL. CD8+ T-cell responses that are efficient, proliferates rapidly and terminates HIV infected host cells which
results in reduction of antigenic stimulus (Bangham, 2009). Decay in the frequency of HIV-specific CD8+ T-cell responses after initiation of HAART, which suppresses PVL independent of host immune responses were strongly evidenced (Casazza et al., 2001; Kalams et al., 1999; Ogg et al., 1999). These studies clearly indicate frequency of CD8+ T-cell responses were dependent on antigen load. Similarly, in this study lower HIV-specific CD8+ T-cell responses even in LTNP with PVL <2000 due to lack of antigenic stimulus cannot be ruled out. But this can be debated on why progressors who are HAART naive cannot mount a significant response? This can possibly be explained by indicating that their basic immunological characteristics such as CD4+ T-cell counts and CD8+ T-cell counts present in lower levels which also might be of compromised quality. Hence, lower CD4+ T-cell counts might not provide adequate help for CD8+ T-cells to proliferate and mount a significant response.

This study agrees with the fact that contradictory phenomenon of CD8+ T-cell responses can only be concluded by studying critical attributes of these cells that would determine its efficiency such as CD8+ T-cell proliferation rate at a given PVL and the rate of CD8+ T-cell mediated lysis of infected cells at a given antigen load (Bangham, 2009).

Controllers usually possess a lower CD4+ T-cell activation rates than progressors (Emu et al., 2005; Owen et al., 2010; Sáez-Cirión et al., 2007), while here the LTNP with PVL <2000 had significantly decreased CD4+ T-cell
activation rates. Overall activation of CD4+ T-cells was lower in LTNP compared to progressors in this study, but when PVL categorization is applied, LTNP with PVL >2000 had high activation rates. CD4- T-cell activation rates (probably CD8+ T-cells) were quite similar in both LTNP and progressors. Categorization of LTNP with PVL could not draw any significant relevance.

Though a low CD4+ T-cell activation levels were seen in LTNP, it pulls a negative correlation with CD4%. Similarly CD4- T-cells also possess a negative correlation with CD4+ T-cell count in progressors. These factors seem contrasting when compared to other studies. Supporting these findings, elite controllers and HIV infected ART suppressed patients were reported to have similar activation rates of T-cells (Hunt et al., 2008). Even though CD4+ T-cell counts were maintained at normal levels, reports suggests that low PVL levels were strongly associated with decline in CD4+ T-cell counts and clinical progression (Mellors et al., 1997). This observation can be applied to the observations in this study to possibly explain the negative correlations observed with activation rates and CD4+ T-cell frequencies in LTNP. Moreover, this study involved participants with much higher PVL levels, establishment of association between chronic inflammation and progressive immunodeficiency in LTNP, has to be considered similar to other findings (Hunt et al., 2008; Tesselaar et al., 2003).

CD8+ T-cell activation rates might have an underlying association with gradual CD4+ T-cell depletion and clinical progression of HIV in
untreated patients. Similarly, this study also reports CD4- T-cell activation rates between LTNP and progressors which serve as a marker for immune deterioration in LTNP due to their choric nature of the infection and thus matching the CD4- T-cell activation rates with progressors. It is also observed that T-cell activation is directly associated with CD4+ T-cell decline than the extent of PVL levels in HIV-2 infected cases (Sousa et al., 2002).

Microbial translocation as a result of high plasma LPS levels were attributed for high T-cell activation and factors alike influencing the negative correlation with CD4+ T-cell counts and CD4% cannot be excluded in this study. Here, no LPS levels were measured and in addition, presence of other co-infections might have also influenced T-cell activation. Hence, data on evidences of microbial translocation and co-infections receives paramount importance even though LTNP maintained high CD4+ T-cell counts and low viral loads to decide the effects of activation in disease non-progression in LTNP. Presence of such data in this study could have been advantageous to conclude the effect of microbial translocation in T-cell activation in LTNP.

With respect to activation, it is evident from this study that CD4+ T-cell counts and PVL levels may not serve as an absolute measure of viral pathogenesis and disease non-progression. Lack of major differences in T-cell activation profile between LTNP and progression and in comparison with their respective disease progression markers might be due to the longevity of HIV infection and chronic stages of disease in which the specimens have been
collected for this cross-sectional study. Besides CD4+ T-cell counts and PVL, it is suggested that in LTNP periodic screening of T-cell activation rates must be entertained, especially during the chronic stages. This helps in ascertaining the LTNP status and provides evidences of disease progression well before CD4+ T-cell depletion. This in turn might serve as an accurate predictor of CD4+ T-cell depletion which could improvise treatment strategies of HIV infected individuals.

T-regs have to maintain a sustained equilibrium between their frequency and T-cell activation rates. Elite controllers were reported to preserve such frequencies of T-regs whereas untreated progressive HIV infection reported to have increased frequencies (Angin et al., 2012). This study reports that LTNP had decreased frequency of T-regs compared to progressors which infers that T-regs expansion is absent in disease non-progression which is quite similar to the report that finds T-regs expansion occurring during rapid disease progression (Cao et al., 2009b).

T-regs proliferates at a slower rate in vitro (Oswald-Richter et al., 2004). Studies have shown that activation results in conversion of conventional non-Tregs to T-regs (Walker et al., 2003; WanJun et al., 2003) which might alter the generation time of T-regs and also provide additional avenues of cell loss in CD4 T-cell compartment (Oswald-Richter et al., 2004). In this study, proliferation rate of T-regs might be slower in LTNP and the reduced conversion rate of T-regs from non-T-regs might have slightly altered or
unaltered the T-regs generation resulting in lower frequencies of T-regs in LTNP.

High rate of T-cell activation due to progressive HIV infection might result in high rate of non-T-regs to T-regs conversion and thus the frequencies of T-regs found to be on the higher side in progressors compared to LTNP. This fact is consistent with the findings that states, T-regs share many activation markers with activated non-T-regs (Baecher-Allan et al., 2001; Oswald-Richter et al., 2004).

Though not directly studied, this study finds that activation levels in accordance with T-regs frequencies were lower in LTNP. This lower activation levels did not the affect the T-regs frequencies in LTNP which might be contributed to less proliferation whereas in progressors higher activation levels were observed along with higher T-regs frequencies which indicate more proliferation.

Moreover, T-regs of LTNP showed significant inverse correlation with their activation rates which suggest that T-regs frequencies exists in LTNP to a level it can suppress or control higher activation rates whereas in progressors suppression of activation rates cannot be achieved by T-regs even though they are present in higher frequencies which attributes the abnormal T-cell phenomenon in progressors.
T-regs are widely noticed in HIV infection due to their nature of split personality. In one scenario, they can inhibit higher activation thereby preventing CD4+ T-cell depletion while the other scenario is that, presence of T-regs might inhibit the effector functions of T-cells and impair the immune control thereby contributing to viral replication (Chevalier and Weiss, 2013). In this study, inverse correlation of T-regs and activation in LTNP may also be partially responsible for absence of significant differences in effector function in LTNP, while in progressors, loss of effector functions can be contributed to higher depletion of CD4+ T-cells and its quality. However, this preliminary explanation would not be sufficient to completely evaluate the role of T-regs in disease non-progression for which the mechanism behind the T-regs expansion during HIV infection should be widely studied and understood.

Maturation process of high affinity antibodies requires complex interactions between Tfh and B-cells in lymphoid organs (Buranapraditkun et al., 2017). Hence, it is important to understand the role of Tfh in the generation of broadly neutralizing antibodies, which arises only in 10-20% of HIV-1 infected individuals during the course of natural infection, albeit at 2-5 years post infection and too late to protect against HIV-1 infection. Given the inaccessibility to lymphnode specimens, several studies have defined a population of such lymphocytes in peripheral circulation that might serve as a surrogate marker of Tfh activity within the lymphoid follicle (Dhaeze et al., 2015; Schmitt and Ueno, 2013). These studies defined cells that might be
related to Tfh using various combinations of phenotypic markers such as CXCR5, CXCR3, CCR6, CCR7, ICOS, and PD-1.

However a recent study identified memory PD-1-CXCR3-CXCR5+CD4+ T-cells that are highly functional for B cell help and positively correlated with the development of broadly neutralizing antibodies during HIV-1 infection (Locci et al., 2013). A subpopulation of CD25+ Foxp3+CD4+T-regs were identified that share some of the phenotypic characteristics of Tfh cells and regulate germinal centre responses by limiting Tfh and B cell activities (Sage and Sharpe, 2015). These cells were also reported to be found in peripheral circulation (Dhaeze et al., 2015). Here the frequency and phenotype of both helper and regulatory subsets of cTfh-like cells were determined in a cohort of subjects whose neutralizing antibody response had been thoroughly characterized.

Studies reported that expansion of GC Tfh occurs in both humans and primates during the course of their HIV and SIV infections respectively (Lindqvist et al., 2012; Petrovas et al., 2012). Presence of high viral loads were associated with high cTfh frequencies while there were no direct link established between individual viral load and cTfh in these studies. In this study, cTfh-like cells were significantly higher in LTNP were there is reduced PVL was observed which is similar to a recent study (Buranapraditkun et al., 2017) were controllers exhibited high cTfh frequencies. This finding suggests that cTfh-like cell frequencies replicate the dynamics of high CD4+ T-cells in
peripheral circulation which might have been independent of frequencies of Tfh cells in germinal centres.

But this higher frequency of cTfh-like cells did not correlate with broad and potent antibody response among LTNP which is in line with the study that demonstrates cTfh-like cells from chronic aviremic individuals are functionally impaired and do not provide adequate B cell help (Cubas et al., 2015). This may be due to the presence of low levels of persistent antigen in the lymphoid tissues (Hatano et al., 2009) and it was reported to be associated with functionally exhausted Tfh in lymphnode and blood (Fazilleau et al., 2007). In agreement with this, a higher frequency of cTfh-like cells among LTNP was observed in this study that associates with poor neutralization response.

Tfr were recently defined as a sub-population of CXCR5+CD4+ T cells. Like cTfh, Tfr cells express high levels of CXCR5, ICOS, and PD-1 (Sage et al., 2013). Tfr cells are thought to originate in the periphery from thymic-derived T-reg precursors, in contrast to Tfh which develop from naive FOXP3 T-cells (Linterman et al., 2011). Importantly, Tfr cells potently suppress humoral immune responses while Tfh cells stimulates them thus having opposing roles in regulating humoral immunity. Like Tfh, Tfr also present on peripheral circulation in addition to lymphnodes (Sage et al., 2013).
Elucidating the relationship between the cTfr and HIV-1 neutralization response may provide insights into the development of a broad and potent antibody response. Here, circulatory Tfr correlated with HIV-1 neutralization breadth and potency in LTNP, but did not associate with the overall HIV-1 neutralization response. This was consistent with finding that circulating Tfr frequencies did not differ significantly between the individuals with and without an efficient bNAb response (Hu et al., 2015). This phenomenon may be due to decreased suppressive capacity of circulating memory-like Tfr cells (Sage et al., 2014) when compared to the lymph node subset.

HIV replication and disease progression were marked by the loss of CD21 in B-cells of peripheral blood (Moir and Fauci, 2008). One proportion of CD21\textsuperscript{low} B-cells may transform into immature transitional CD10+ B-cells that are over-represented due to HIV-induced T-lymphopenia (Malaspina et al., 2006) while the other proportion undergoes HIV-induced activation and differentiation into plasmablasts consisting of CD27+ B-cells (Moir et al., 2001) which are classical memory B-cell subsets (Hu et al., 2015). In chronic HIV infections, absolute numbers of both classical memory B-cells populations: class switch memory B-cells and unswitched memory B-cells were reported to be deficient in peripheral circulation (Yong Chong et al., 2004; D’Orsogna et al., 2007; Hart et al., 2007).
Loss of memory B-cells in HIV infected individuals results in impaired antibody responses to vaccine antigen during effective pre-ART era were reported (Nielsen et al., 1997; Opravil et al., 1991). Such impaired antibody responses were not fully recovered even after long-term ART (Hung et al., 2010; Tebas et al., 2010). Impaired immune responses to vaccines could be a result of HIV induced phenotypic and functional B-cell perturbations (Hu et al., 2015). Impaired generation of B-cell responses might be due to lack of adequate CD4 T-cell help especially Tfh which provides essential help to B-cells in generation of high affinity antibodies in B-cell follicles (Crotty, 2014; McHeyzer-Williams et al., 2012).

Another possible mechanism behind the loss of memory B-cells is their decreased survival rate in the presence of HIV (Malaspina et al., 2008). Classical memory B-cells are hyper-activated characterized by highly spontaneous and activation-induced IgG secretion and are prone to apoptosis (De Milito et al., 2001; Titanji et al., 2003, 2005). Upregulation of Fas and Fas ligand were reported in memory B-cells which make them susceptible for Fas/FasL mediated apoptosis (Yong Chong et al., 2004; Samuelsson et al., 1997; Titanji et al., 2005; Zhang et al., 2014). Moreover, expression of Fas on memory B-cells positively correlates with microbial translocation which is emphasized by high LPS levels in HIV infected individuals (Zhang et al., 2014). Thus various mechanisms have major roles in loss of memory B-cells. Though many studies have reported the depletion of memory B-cells in chronic
stages of HIV infection, their frequencies in LTNP and other HIV controllers are not well studied.

Here, the differences in chronic stages of frequencies of CD27+ memory B-cells between LTNP and progressors were elucidated. In this study, no differences were observed in both unswitched memory B-cell and class switched memory populations in both LTNP and progressors. With respect to unswitched IgM memory B-cells, it has been reported that a decreased frequency IgM memory B-cells in association with CD4+ T-cell counts of <300 cells/µL (Barry et al., 2006) whereas it is reported to be increased in untreated HIV patients with CD4+ T-cell counts of >300 cells/µL (D’Orsogna et al., 2007). These reports are in agreement with the present study because, out of the total study population only one study participant had CD4+ T-cell counts of <300 cells/µL and also all the study participants are HAART naive but it should be noted that IgD marker were used in this study to characterize switched memory B-cells. Moreover, only 1% of LTNP produced bNAb while 51% of progressors produced bNAb. Absence of significant differences in the frequencies of switched memory B-cells between the cohorts fails to compare with the lesser production of bNAb in LTNP. Hence, this finding does not imply any possible explanations for concluding the relationship between switched memory B-cells and bNAb, especially in LTNP, since bNAb are directly proportional to high and persistent viremia in progressors. However, this study does not employ direct methods such as frequencies of IgG B-cells
or frequencies of antibody producing B-cells in germinal centres to validate the inconclusiveness of this comparison in LTNP.

Similar to switched and un-switched memory B-cells, no differences were noted in the frequencies of naive B-cells and double negative B-cells. Hence, data from this study show that B-cells might not play an important role in protective immunity and thus disease non-progression in LTNP. Even though frequencies of cTfh-like cells were significantly higher in LTNP, quality of these of cells becomes questionable. Hence IL-21 production by HIV-specific cTfh or IL-21 frequency by HIV-specific GC Tfh and HIV-specific B-cell proportions in germinal centres expressing IgG has to be compared and correlated to completely explore and summarize the role of B-cells in protective immunity that might help in developing a successful vaccine.

Importance of plasma cytokine and chemokine regulations during HIV infection in not well established. Only limited data are available about the concentrations of cytokine and chemokines in plasma and exploring their levels, especially in LTNP might help in understanding the differences at the general circulation and to an extent, preliminary conclusions can be drawn about their impact in disease severity. Hence, here concentrations of a set of anti-inflammatory and pro-inflammatory cytokines and chemokines in LTNP and progressors were analyzed.
IFN-γ has been shown to possess antiviral effects on HIV-1 macrophage infections (K et al., 2016) and enhancing antigen presenting activities (Arellano-Garcia et al., 2014). In this study, concentration of IFN-γ was significantly lower in LTNP than progressors, which is in line with the finding from a recent study where non-progressors were compared with HARRT treated progressors (K et al., 2016). In the present study, even such low levels of IFN-γ in LTNP showed a significant negative correlation with PVL. This shows that, LTNP in this study could possibly control viral replication even in the presence of lower levels of IFN-γ, yet confirmation by direct neutralization of HIV infected cells by IFN-γ are required in order to prove this hypothesis. In progressors, higher levels of IFN-γ failed to control viral replication and hence it should be noted that in progressors other opportunistic infections may also drive IFN-γ levels which might have failed its efficiency towards neutralization of HIV infected cells.

IL-2 level in plasma did not differ significantly between LTNP and progressors and it is present at lower levels in both the cohorts. Reports state that IL-2 at the cellular level mirrors the quality of CD4+ T-cells and healthy immune resistance towards HIV (Boaz et al., 2002; Younes et al., 2003; Zimmerli et al., 2005). But in circulation IL-2 reported to be higher in HIV infected patients with higher viral load (Orsilles et al., 2006). IL-2 levels signifies CD4 T-cell proliferation during HIV infection while this study does not provide any significant relevance of IL-2 in disease non-progression in both cellular as well as circulation levels even in LTNP. Previous studies in our own
center failed to provide evidence for the hypothesis that ART initiation might reverse IL-2 expression by CD4+ T-cells (data not published). Hence, IL-2 might not be capable marker of measuring disease non-progression in the setting where this was performed.

Mean levels of TNF-α were near to undetectable levels in LTNP while they were quite higher in progressors, though not significant. TNF-α levels in long term ART treated patients were reported to be similar to that of elderly patients (De Pablo-Bernal et al., 2014). Thus here, TNF-α level might have resulted in decreased inflammation in LTNP which would have lead to disease non-progression.

Opportunistic infection events and mortality have been reported to related to increased IL-6 levels in HIV infection (Lafeuillade et al., 1991). In addition, ageing and increased inflammation were also shown to be associated with IL-6 production (Aberg, 2012). Therefore lower levels of inflammation due to lower IL-6 might have helped LTNP to sustain their disease non-progression status. IL-22, a TH-17 T-cell associated cytokine mediates tissue responses during inflammation (Zheng et al., 2008) found to be negatively correlating with LPS levels in HIV infection (Arias et al., 2010). Contrary to other studies LTNP here showed lower levels of plasma IL-22 compared to progressors. This observation raises doubts in decreased IL-22 and their association with disease non-progression. It should be noted 6 out of 20 LTNP studied here had PVL >2000 and its influence in lower IL-22 levels cannot be
ignored. Also factors associated with microbial translocation were not studied here; hence justification of lower IL-22 levels in LTNP in this study cannot be achieved. Low levels of IL-22 in LTNP negatively correlated with PVL, since direct relationships cannot be drawn in this study, the correlations could be attributed to the contributions of other T-cell factors such as activation and regulation.

Regulation of chemokines during HIV infection and their exact role in HIV pathogenesis remaining obscure might be due to the fact that multiple chemokines have different effects on viral pathogenesis (Suresh and Wanchu, 2006). These chemokines alterations during chronic infections and in LTNP were not well studied. Hence, in the present study, the role of IP-10 and β-chemokines such as MCP-1, MIP-1β and RANTES were studied and compared.

IP-10 levels in HIV-exposed seronegative sex-workers have been shown to be lower compared with HIV negative and seropositive individuals, suggesting a protective role of lower levels (Lajoie et al., 2012). Inhibition of IP-10 during T-cell activation were reported to enrich T-cell activities (Ramirez et al., 2014). IP-10 level in plasma were significantly lower in LTNP in comparison with progressors. This might have lead to lower levels of IP-10 induced apoptosis. In this study, decreased levels of IP-10 might be a result of lesser viremia in LTNP which might have caused lesser migration CD4+ T-cells (Foley et al., 2005) and CD8+ T-cells (Padovan et al., 2002) to
the sites of inflammation. Moreover it might have helped in lesser CD4+ T-cell activation rates in LTNP compared to progressors. Thus here, lower IP-10 level in LTNP might have played a protective role in disease non-progression.

Studies have suggested high levels of MIP-1α, MIP-1β, RANTES and MCP-1 might upregulate HIV replication in macrophages and monocytes by recruiting activated target cells (Canque et al., 1996; Conant et al., 1998; Lu et al., 1998; Schmidtmaierova et al., 1996). These chemokines have been detected in the cerebrospinal fluid of HIV infected individuals. Upregulation of chemokine expression by immune cells might result in local and systemic effects that contribute significantly to the HIV pathogenesis (Suresh and Wanchu, 2006).

Here, LTNP showed a significant increase in MCP-1 levels while RANTES levels were significantly higher in progressors and no change was observed in MIP-1β levels between LTNP and progressors. Higher levels of chemokines might result in higher monocyte infiltration in inflammation sites. But the specific chemokine which has the potential role in blocking HIV entry thus contributing disease non-progression in LTNP is not known. Hence, analyzing chemokines along with their binding capacity to CCR5 co-receptor must be studied to conclude the role of chemokines in disease non-progression in LTNP.