

# Impact of Interleukin 16 (IL-16) Gene Polymorphism among Seropositive Stages in HIV-1 Infected Patients in North India

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## Abstract

**Objective:** Cytokines play a major role in host immune defense system, and proinflammatory cytokines acts in both innate and adaptive immune systems. IL-16 is a pleiotropic cytokine, plays a role in inflammatory diseases and is involved in expression of several proinflammatory cytokines i.e., TNF- $\alpha$  and IL-1 $\beta$ . Previous studies reached inconclusive results regarding the role of IL-16 polymorphism on HIV-1 disease and progression. Hence, we studied its effects on HIV-1 infection and disease susceptibility.

**Aim:** This study aims to deduce the association of host genetic factors, IL-16 (rs 11556218, rs 4072111, rs 47778889) polymorphism on HIV-1 seropositive subjects in North Indian population.

**Methods:** 100 HIV-1 seropositive (HSP) subjects differentiated on the basis of disease severity (Stage I, II and III) and 150 HIV-1 seronegative (HSN) as control subjects were genotyped for IL 16 (rs 11556218 T/G, rs 4072111 C/T, rs 4778889 T/C) using Polymerase chain reaction-reaction fragment length polymorphism (PCR-RFLP) methods. Statistical analysis was done using SPSS software.

**Results:** IL 16 rs 11556218 TG, GG genotypes ( $P=0.003$  for both) and G allele was significantly associated ( $P<0.01$ ) with risk estimated to 2.5, 4.4 and 2.59 folds. For IL 16 rs 407211 T allele was seen highly protective ( $P<0.01$ ) for HIV-1.

**Keywords:** Allele; Cytokine; Disease susceptibility; Genotype; HIV infection; IL-16

## Introduction

Human immunodeficiency virus (HIV) is a blood borne 'lentivirus' (slow virus) of Retroviridae family transmitted via sexual intercourse, shared intravenous drug usage and mother-to-child transmission. HIV is a spherical virus, comprising of two copies of single stranded RNA, which codes for virus's nine genes, that is enclosed by a conical capsid composed of 2,000 copies of the viral protein p24 [1] and reverse transcriptase enzyme. This in turn is surrounded by a viral envelope, comprising of lipid bilayer, which is derived from human cell, at the time when newly formed virion derives from the cell. The virus envelope consists of proteins from the host cell, and also few copies of HIV envelope protein [1], which consists of a cap made up of three molecules namely glycoproteins (gp) 120, a stem consisting of three gp 41 molecules that anchors the structure into the viral envelop [2], and hence forms the envelope protein gp 160 (gp 120 and gp 41). This envelope protein, encoded by HIV env gene, allows the virus to attach to the target cells and fuse the viral envelope with the target cell membrane. As a result of the viral attachment, the virus envelope spike, consisting of gp 120 and gp 41 forms a dimer on fusion with cell membrane, in turn releasing the viral components, hence initiating the HIV replication cycle or the infectious cycle [2].

The universal spread of HIV-1 illustrates that the virus counteracts innate, adaptive and intrinsic immunity [3-5]. An effective depletion of activated and memory CD4<sup>+</sup> T cell in the gut is the hallmark of HIV infective during the early phases after infection [6]. Immune activation elucidates disease progression and therefore, it is the major feature in HIV-1 pathogenesis [7]. The pathogenesis against Human immunodeficiency virus (HIV) involves the replication of virus in the periphery, and thereby the disease is active and progressive to other organs of the body [8]. The viral and host factors play a major role in

the progression of disease [9]. Apart from innate immune response and genetic factors, the HIV-specific adaptive immunity also plays an important role in the progression of HIV-1 disease. There are certain Proinflammatory cytokines that are produced in the early phases of infection, acting in both innate and adaptive ways. Thus, the impact of it depends on qualitative and quantitative factors. However, over the years numerous studies have shown link between host genetics and variation in HIV infection that can modulate innate and adaptive responses.

Interleukin-16 (IL-16), a 26 kD an immunomodulatory protein, acts as a chemoattractant for CD4<sup>+</sup> cells produced by T cell, B cell, and macrophage in response to viral/bacterial invasion. This gene is located on chromosome 15 q26.3 in humans [10]. IL-16 is produced by activated CD8<sup>+</sup>T cells and in turn activates CD4<sup>+</sup> T-cells [11]. In asymptomatic HIV-1 subjects, IL-16 falls within the normal range, although a significant reduction is seen with progression of HIV-1 infection when compared with levels in uninfected subjects [12,13]. It also inhibits the replication of macrophage tropic and T cell line-tropic strains of HIV in CD<sup>+</sup>8 depleted lymphocytes [14]. Several polymorphisms located

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within regulatory and coding region, can influence gene transcription causing deviation in IL 16 production [15,16].

The rate of progression of the disease varies in HIV-1 infected individuals and several SNPs play a major role in pathogenesis of HIV/AIDS. The frequency of mutation in HIV-1/AIDS varies significantly depending upon the global, ethnic and regional variations, giving each different population and region a different susceptibility profile pattern to HIV-1 infection and disease progression. Thus, the impact of it depends on qualitative and quantitative factors. However, over the years numerous studies have shown link between host genetics and variation in HIV-1 infection that can modulate innate and adaptive responses. Therefore, in the present study, we elucidated the relationship between IL 16 non-synonymous SNP C/T Ser (Serine) to Pro (Proline) substitution (rs 4072111), a T/G Asn (Asparagine) to Lys (Lysine) substitution in exon 6 (rs 11556218) and common SNP T/C located at rs 4778889 bp upstream from transcription start site variants genes in HIV-1 seropositive (HSP), HIV-1 seronegative (HSN) subjects.

## Materials and Methods

One hundred HIV-1 seropositive patients (HSP) were enrolled from the outpatients who are attending the clinics of Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow from April 2013 to September 2014. Most of the patients were from the state of Uttar Pradesh, North India. One hundred and fifty age and gender matched controls, which are healthy staff members of institute with HIV-1 seronegative status (HSN) were recruited in the study. The HIV-1 seropositive subjects were in different stages of disease progression and had no history or a less than 6-week prior history of

antiretroviral therapy. This study has been approved by Institutional Ethics Committee. Only individuals who had a minimum follow-up time of at least 6 months were included in the study. After an informed consent, 5-mL blood sample was taken in ethylene diamine tetra acetic acid (EDTA) for analysis of DNA. Demographic profiles of the study groups are given in Table 1.

## Determination of HIV-1 status and CD4+ cell count

All individuals were primarily screened with ELISA (Vironostika, HIV Uni-FormII Ag/Ab, Biomerieux, Netherlands) to check their HIV-1 status and subsequently confirmed with Western Blot (LAV Blot I, BioRad, France). CD4 cell count was measured by flow cytometer FAC Scan (Becton Dickinson Immunocytometry systems, San Jose, CA, USA) using fresh EDTA-treated whole blood at the time of recruitment.

## Genotyping methodology

The genomic DNA was extracted using 0.2-0.3 mL peripheral blood leucocytes pellet using the standard salting out method [17]. Usually ~0.1 µg genomic DNA was used for the genotyping studies. IL 16 genotyping was carried out by Polymerase chain reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) as previously described by Gao et al. [18]. The set of primers, restriction enzymes, annealing temperatures and size of the amplified and digested products used are listed in Table 2. Enzymatic digestion was performed using specific restriction endonucleases (NEB, England). Each digested products was analyzed on 3% agarose gel electrophoresis (Agarose LE, Roche, Germany).

**Table 1:** Demographic and Clinical Characteristics of the Study Groups

Characteristics:	Mean ± SD	Pvalue	Male/Female	CD4 count/µl Pvalue
HIV-1 seronegative (HSN; n= 150)				
Age	35.1 ± 7.5	ref		
Sex (M/F ratio)			1/8	
HIV-1 seropositive (HSP; n= 100)				
Age	34.3 ± 12.5	0.113		
Sex (M/F ratio)			1/1	
CD4 counts/µl				
Stage I (n= 29)				
Age	33.9 ± 14.0	0.163		
Sex (M/F ratio)			1/1	
CD4 counts/µl				<0.001
Stage II (n= 55)				
Age	35.4 ± 12.0	0.079		
Sex (M/F ratio)			1/1	
CD4 counts/µl				<0.001
Stage III (n= 16)				
Age	40.2 ± 29.8	0.256		
Sex (M/F ratio)			2/3	
CD4 counts/µl				ref

**Table 2:** Primer sequences and reaction conditions for genotyping IL 16 gene.

Polymorphism Product size (bp)	Primer sequence (5'-3')	Annealing temp(°C)	Restriction enzyme	Product size (bp)
rs11556218 T/G	F-GCTCAGGTTACAGAGTGTTCATA	58°C	Nde1	T-147+24
	R- TGTGACAATCACAGCTTGCCCTG			G-171
rs4072111 C/T	F- CACTGTGATCCCGTCCAGTC	55°C	BsmA1	T-140+24
	R- TTCAGGTACAAACCCAGCCAGC			C-164
rs4778889 T/C	F- CTCACACTCAAAGCCTTTGTTCCTATGA	59.2°C	Ahd1	T-280
	R- CCATGTCAAACGGTAGCCTCAAGC			C-246+24

## Statistical analysis

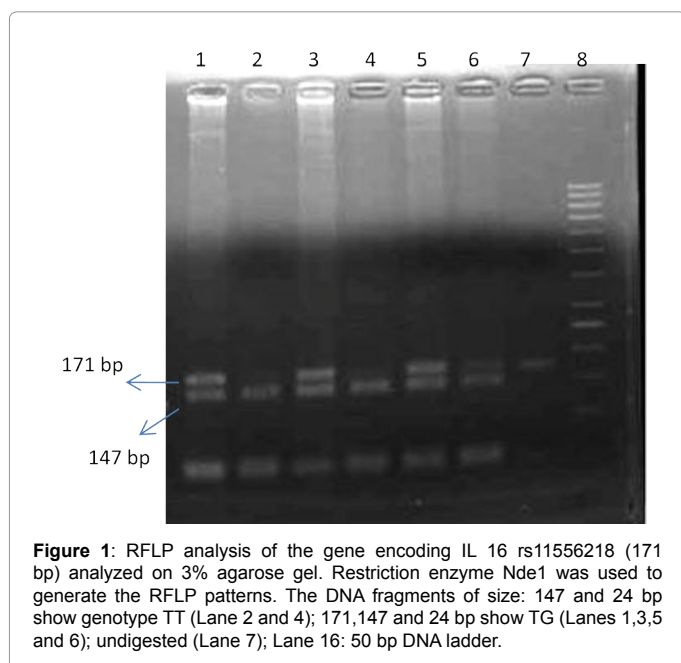
Statistical analysis was done by SPSS software version 16 (SPSS, Chicago, IL). Direct gene counting method was used to determine the frequency of genotypes and alleles. The Fisher's exact or  $\chi^2$  test was used to determine differences in allele/genotype frequencies of IL 16 genetic variants. Odds ratios (OR) and its 95% confidence interval (CI) were calculated to access the risk conferred by a particular allele and genotype. Observed and expected genotype frequencies were compared by  $\chi^2$  test to check deviation from Hardy Weinberg Equilibrium. P value <0.05 was considered to be statistically significant. The sample size was calculated using the QUANTO ver. 1 program (<http://hydra.use.edu/gxe>).

## Results

**Demographic result:** 100 HIV seropositive (HSP) group were studied including 51 males (51%) and 49 (49%) females. The HIV seronegative (HSN) group consisted of 150 healthy individuals including 95 (63.4%) male and 55 (36.6%) female patients. Depending on their CD4+ T-cell counts and based on their clinical symptoms, HIV-1 patients were divided into three subgroups, as per the Centers for Disease Control and Prevention (CDC) criteria. The three groups were as follows: Stage I (n=29; asymptomatic HIV-1 patients in CDC category A1 to A3), Stage II (n=55 symptomatic HIV-1 patients without AIDS in CDC category B1 to B3), and Stage III (n=16; symptomatic HIV-1 patients with AIDS (CDC) criteria [19,20] (Table 1) and were genotyped for IL 16-rs 11556218 T/G, rs 4072111 C/T and rs 4778889 T/C polymorphism. The genotypic frequencies distribution of IL 16 rs 11556218, rs 4072111 and rs 4778889 were in Hardy-Weinberg equilibrium (P>0.05).

## Genotyping results

**Association between IL 16 rs 11556218 T/G polymorphism with HIV-1/AIDS disease progression:** The electrophoresis gel picture depicting the polymorphism has been shown in (Figure 1). The frequency of TT genotype and T allele was significantly higher in HSP when compared to HSN (73% vs 48.7% or 84% vs 67%). Also,



TG and GG were associated with the risk (P=0.003 for both, OR=2.5, CI=1.38-4.5 and OR=4.4, CI=1.58-12.25). G allele exerts high risk when compared with HSP (P<0.01, OR=2.59, CI=1.652 – 4.048) as illustrated in Table 3. Simultaneously, the dominant (TG+GG) model play a significant role on the disease (Table 3) (P<0.01). Furthermore, comparison in between different stages of HIV seropositive individuals revealed that there was no significant difference between T and G allele when seen in Stage I and Stage II with respect to Stage III (P=0.780, OR=1.26 CI=0.397-4.024) for Stage I and (P=1.0, OR=0.919, CI=0.309-2.738) for Stage II (Table 4).

**Association between IL 16 rs 407211 C/T polymorphism on HIV/AIDS transmission:** The electrophoresis gel picture depicting the polymorphism has been depicted in (Figure 2). Heterozygous genotype (CT) was associated with the disease when compared with HSN (P=0.037, OR=0.54, CI=0.312-0.94). Furthermore, considering C as a reference allele, a significant correlation was detected between the presence of T allele and HIV disease (P<0.01, OR=0.47, CI=0.323-0.686) with T playing a protective role with respect to the disease (Table 3). Also there was non-significant association between C and T alleles at different stages of HIV infection (Table 4).

**Insignificant effect of IL 16 rs 4778889 T/C promoter polymorphism and HIV transmission:**

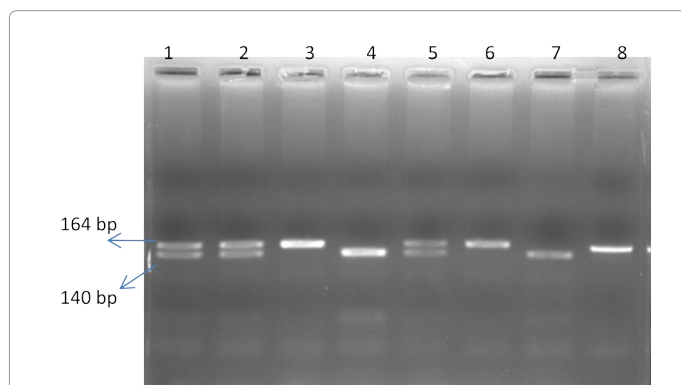
The electrophoresis gel picture depicting the polymorphism has been illustrated in Figure 3. The allelic frequencies and genotypic distribution for rs 4778889 T to C promoter polymorphism has been illustrated in Table 3. The genotypic frequency was in agreement with Hardy Weinberg equation (P>0.05). There was slightly less frequency of mutant homozygous C genotype in HIV infected as compared to HIV

**Table 3:** Genotypic and allelic distribution of IL 16 gene polymorphism among HIV seropositive (HSP) and HIV seronegative (HSN) individuals.

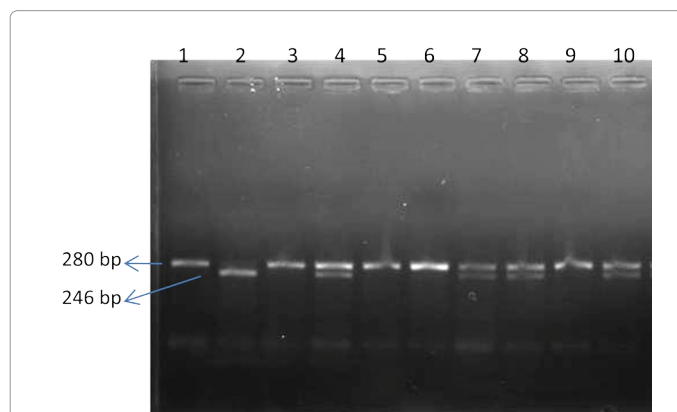
Genotype	HSP	HSN (n=100) (%)	P-value (n=150) (%)	OR	95% CI
<b>IL 16 rs 11556218 T/G</b>					
TT	73 (73.0)	73 (48.7)	ref		
TG	22 (22.0)	55 (36.7)	0.003	2.5	1.38 – 4.5
GG	5 (5.0)	22 (14.6)	0.003	4.4	1.58 – 12.25
<b>Dominant model</b>					
TT	37 (73.0)	73 (48.7)	ref		
TG + GG	29	77	0	2.9	1.65 – 4.9
T	168 (84.0)	201 (67.0)	ref		
G	32 (16.0)	99 (33.0)	0	2.59	1.652 – 4.048
<b>IL 16 rs 407211 C/T</b>					
CC	40 (40.0)	77 (51.3)	ref		
CT	48 (48.0)	50 (33.3)	0.037	0.54	0.312 – 0.94
TT	12 (12.0)	23 (15.4)	1	0.99	0.449 – 2.2
<b>Dominant model</b>					
CC	40	77	ref		
TC + TT	60	73	0.093	0.63	0.379 – 1.1
C	128 (64.0)	204 (68.0)	ref		
T	72 (36.0)	96 (32.0)	0	0.471	0.323-0.686
<b>IL 16 295 T/C (rs 4778889)</b>					
TT	83 (83.0)	129 (86.0)	ref		
TC	14 (14.0)	14 (9.3)	0.308	0.64	0.292-1.4
CC	3 (3.0)	7 (4.7)	0.745	1.5	0.378 – 5.9
<b>Dominant model</b>					
TT	83	129	ref		
CC+TC	17	21	0.59	0.79	0.396-1.595
T	180 (90.0)	272 (90.7)	ref		
C	31 (10.0)	28 (9.3)	0.068	1.67	0.970-2.884

**Table 4:** Distribution of IL 16 promoter gene/alleles among HIV seropositive North Indian individuals classified on the basis of severity of the disease.

Genotype	Stage I (n=29)	Stage II (n=55)	Stage III (n=16)	Stage III vs Stage I			Stage III vs Stage II		
				P value	OR	C.I (95%)	P value	OR	C.I. (95%)
IL 16 1156218 T/G									
TT	19 (65.5)	42(76.4)	12 (75.0)		reference			reference	
TG	9 (31.0)	10(18.2)	3 (18.8)	0.402	1.89	(0.426-8.434)	0.95	0.952	(0.225-4.023)
GG	1 (3.5)	3 (5.4)	1 (6.2)	1	0.78	(0.045-13.550)	0.89	0.857	(0.082-9.009)
T	47 (81.0)	94 (85.5)	27 (84.4)		reference			reference	
G	11 (19.0)	16 (14.5)	5 (15.6)	0.78	0.780	1.26 (0.397-4.024)	1	0.919	(0.309-2.738)
IL 16 rs 407211 C/T									
CC	8 (27.6)	24 (43.6)	8 (50.0)		reference			reference	
CT	16(55.2)	25 (45.4)	7 (43.8)	0.221	2.28	(0.609-8.579)	0.77	1.19	(0.374-3.793)
TT	5 (17.2)	6 (11.0)	1 (6.2)	0.223	4.38	(0.407-47.017)	0.55	2	(0.208-19.227)
C	32 (55.0)	73 (66.4)	23(71.8)		reference			reference	
T	26 (44.8)	37 (33.6)	9 (28.2)	0.175	2.08	(0.821-5.023)	0.67	1.29	(0.545-3.080)
IL 16 295 T/C									
TT	27 (93.0)	43 (78.0)	13 (81.3)		reference			reference	
TC	1 (3.5)	11 (20.0)	2 (12.5)	2.262	0.24	(0.020-2.904)	0.54	1.663	(0.326-8.481)
CC	1 (3.5)	1 (2.0)	1 (6.2)	0.615	0.48	(0.028-8.321)	0.41	0.302	(0.018-5.176)
T	55 (94.8)	97 (88.2)	28 (87.5)		reference			reference	
C	3 (5.2)	13 (11.8)	4 (12.5)	0.191	0.38	(0.080-1.825)	1	0.938	(0.283-3.105)



**Figure 2:** RFLP analysis of the gene encoding IL 16 rs407211 (164 bp) analyzed on 3.5% agarose gel. Restriction enzyme Nde1 was used to generate the RFLP patterns. The DNA fragments of size: 164, 140 and 24 bp show genotype TC (Lane 1, 2, and 5); 140 and 24 bp show TT (Lanes 4 and 7); 164 bp show genotype CC (Lane 3 and 6); undigested (Lane 8).



**Figure 3:** RFLP analysis of the gene encoding IL 16-295 (280 bp) analyzed on 2% agarose gel. Restriction enzyme Ahd1 was used to generate the RFLP patterns. The DNA fragments of size: 280 bp show genotype TT (Lane 3, 5, 6 and 9); 280, 246 and 34 bp show TC (Lanes 4, 7, 8, 10); 246 and 34 bp show genotype CC (Lane 2); undigested (Lane 1).

non infected individuals. There was no significant difference between CC genotype ( $P=0.745$ ,  $OR=1.5$ ,  $CI=0.378-5.9$ ) and TC genotype ( $P=0.308$ ,  $OR=0.64$ ,  $CI=0.292-1.4$ ) and also the two allelic forms of HIV seropositive subjects when compared with the HIV seronegative subjects and hence, no association of it with HIV-1 susceptibility. The dominant model also had insignificant association with HIV infection. Different clinical stages were also not in association with HIV-1 infection and disease severity (Table 4). Therefore, this result suggests that there was no association of this substitution (T to C) in the promoter region at 295 positions with HIV disease progression.

## Discussion

In our case-control study, for IL 16 we selected a common SNP, rs 4778889, located at 295 bp position upstream of transcription start site [21] and also, simultaneously two other SNPs (rs11556218 and rs4072111), to deduce their association in HIV-1 seropositive and seronegative individuals. The two later SNPs are located in exon region (rs 11556218 and rs 4072111) and rs 11556218 T/G resulting in asparagine/lysine and rs 4072111 C/T in serine/proline amino acid substitution.

According to the recent studied models, it has been found that genetic factors causes imbalance in the production of pro- and anti-inflammatory cytokine production along with the disturbance in the immune response against any bacterial/viral infection. Also, resistance against HIV infection has generated rationalism at biological and genetical level explaining differential susceptibility against HIV infection. Therefore, mutations in the cytokine genes lead to a greater understanding of host genetic factors playing a role in the susceptibility to HIV-1 infection and rate of disease progression and also in the development of several immune related diseases [22].

To the best of our knowledge this is the first study carried out on North Indian population to reveal the impact of IL 16 polymorphism in HIV-1 Seropositive subjects. In the present study we studied SNP of IL 16 gene, which is a proinflammatory cytokine, which is secreted by various type of cells and functions in recruitment of CD4+ immune cells at the site of inflammation. The main findings of our study were IL 16 rs 11556218 TG, GG and G were associated with the risk of HIV-1

infection. Also, rs 4072111 CT genotype and T allele were in significant association with the risk of the disease. Furthermore, we did not find any correlation of IL 16 with the different stages of HIV-1 on the basis of CD count [23]. Also, we did not get a significant impact of IL 16 rs 4778889 SNP with the susceptibility of the disease.

IL 16 gene is a pleiotropic cytokine that acts as a chemoattractant and modulates T cell activation [24] and is an important mediator in inflammatory disease and autoimmune diseases [25,26] which is involved in regulating the expression of other proinflammatory cytokines by macrophage system [27]. The present results revealed that 11556218 TG, GG and G allele had a significant effect in the risk of HIV-1 susceptibility and disease progression, which is in concordance with the results of study, on chronic hepatitis B infection [28], colorectal and gastric cancer [18], hepatocellular carcinoma [29], ischemic stroke [30] with the risk of developing the disease. This nonsynonymous polymorphism was also reported by Xue et al. [31] to be associated with increased risk of developing Systemic lupus erythematous. Also in our study the dominant model TG+GG genotype (TG+GG vs TT= P<0.01) was highly significantly associated with the progression of HIV, which is consistent with the previous study reported by Mo et al. [32].

For IL 16 rs 4072111 C/T nonsynonymous SNP, CT genotype and T allele were significantly associated with the decreased risk of HIV-1, similar to the findings of Luo et al. [33] on osteoarthritis subjects. Similar results were also obtained by Liu et al. [30] but there the T allele was not in significance with the risk of ischemic stroke. Also, Gao et al. [18] suggested decreased risk of CRC and GC. In conjunction to ours, a previous study by Romani et al. [28] shows only T allele significance when comparing chronic HBV patients with healthy donors.

On considering the action of IL 16 in inflammatory diseases, its association with inflammatory disease holds importance and attention. In our study we failed to infer any association of rs4778889 that it holds with the risk of the disease. Although this SNP is related with higher gene expression of IL 16. Some researchers have reported the insignificance of this polymorphism with the risk of periodontitis [34] and CAD [35,36]. Similarly, Akesson et al. [37] reported no association of it with asthma and disease severity in Australian population. Contradictory, to this some reports are there where it is involved in the severity of developing allergic contact dermatitis [38] Graves' disease [39]. These reports suggest that the role of IL 16 is different in different diseases.

This study provides an insight into association of IL 16 rs 11556218 G and rs 4072111 T alleles association to HIV infection with 2.49 risk in progression and 0.47 folds in protective nature for HIV-1. Apart from this there are several limitation of this study. Firstly, our HIV-1 seropositive sample size was relatively small and therefore the study's statistical power may have been limited. The expansion of such studies with larger sample size is required. Also, the variation in the polymorphism results can be due to the ethnicity differences, therefore these association studies should be replicated to draw firm and rigid conclusions about the role of genetic risk factors in diverse ethnic population.

Hence, the overall understanding of the molecular mechanisms involved in the resistance to viral infection remains elusive and their elucidation may provide valuable inputs for drug and vaccine designing and therapeutics of HIV-1 that provides prevention to HIV and AIDS.

#### Conflict of Interest

The authors declare that they have no potential conflict of interests.

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