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Interleukin-7 receptor gene polymorphism at +1237 locus and its effect on susceptibility to opportunistic infections among HIV and AIDS patients in Limpopo Province, South Africa

A. Samie[1], G.T. Moloro[1] and T.C. Nangammbi[2]

[1]Molecular Parasitology and Opportunistic Infections Program,
Department of Microbiology, School of Mathematical and Natural Sciences,
University of Venda, Thohoyandou, Limpopo Province,
South Africa
[2]Department of Nature Conservation, Faculty of Science,
Tshwane University of Technology, Private Bag, Pretoria, Gauteng Province,
South Africa

Corresponding author: A. Samie
E-mail: samie.amidou@univen.ac.za

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ABSTRACT. Over the past decade, an increasing number of studies have demonstrated correlations between host genetics and susceptibility to diseases. However, few studies have investigated the effects of host genetics on the occurrence of opportunistic infections among human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) patients. In the present study, the frequency of the interleukin (*IL*)-*7Rα* +1237 A/G single nucleotide polymorphisms was determined in relation to opportunistic infection occurrence among HIV and AIDS patients in the Vhembe District. Demographic, clinical,

and socioeconomic status data were collected from patients using a structured questionnaire. Genomic DNA was extracted from mouthwash samples using the QIAmp Blood Mini Kit. Genotyping of the *IL-7Rα* +1237 gene was conducted using a sequence-specific polymerase chain reaction method. We found that the *IL-7Rα* +1237 genotype distribution in our study population differed from those in European populations with a predominance of the A/G genotype. Individuals carrying the A/G genotype primarily suffered from chest pain (χ^2 = 5.016, P = 0.025), while individuals carrying the G/G genotype were protected from chest pain but had a higher prevalence of sexually transmitted disease (23 *vs* 16.9%); however, the difference was not statistically significant (P = 0.435). Individuals carrying the A/A genotype were more susceptible to diarrhea (32 *vs* 13.6%) (P = 0.034). Our data will support gene therapy and may be used to modify the course of diseases among HIV patients as well as the general population. Further studies using larger populations are needed to confirm these hypotheses.

Key words: Human immunodeficiency virus; Limpopo Province; Interleukin-7; Opportunistic infections; Single nucleotide polymorphisms; +1237 locus

INTRODUCTION

Interleukin-7 (*IL-7*) is a 25-kD glycoprotein encoded by the *IL-7* gene, which is involved in regulating the secreted signaling molecule lymphopoiesis, which is produced by stromal cells. It is the most recently cloned bone marrow-derived cytokine regulating T-cell homeostasis through a CD4+-driven feedback loop (Gougeon and Chiodi, 2010). The biological effects of *IL-7* are mediated via the hematopoietic *IL-7* receptor (*IL-7R*) complex, *IL-7* receptor α chain, which binds *IL-7* and thymic stromal lymphopoietin and the *IL-2* receptor γ chain; it has been found to be a cofactor for V(D)J rearrangement of T-cell receptor beta during early T-cell development (Muegge et al., 1993). Recent studies have shown that polymorphisms at specific loci on the *IL-7Rα* were risk factors for a number of diseases, including multiple sclerosis, type 1 diabetes, rheumatoid arthritis, primary biliary cirrhosis, inflammatory bowel disease, atopic dermatitis, inhalation allergy, sarcoidosis, and graft-versus-host disease (Sombekke et al., 2011; Mazzucchelli et al., 2012; Kreft et al., 2012).

Human immunodeficiency virus (HIV) is a lentivirus that causes acquired immunodeficiency syndrome (AIDS), a condition in humans in which gradual failure of the immune system allows life-threatening opportunistic infections and cancers to thrive (Palella et al., 1998). These conditions constitute a major health problem worldwide, particularly in Southern Africa where an estimated 22.9 million people in the region are living with HIV; this accounts for approximately two-thirds of the world total (Geldmacher et al., 2012). In South Africa, HIV/AIDS is a prominent health concern, and 310,000 individuals died from this disease in 2009 (Gobind and Ukpere, 2014). Most untreated people infected with HIV-1 eventually develop AIDS and die from opportunistic infections (Migueles and Connors, 2010). Opportunistic infections are responsible for HIV/AIDS-related morbidities and mortalities. Factors affecting the occurrence of specific infections and their distribution in the HIV-infected populations

are not clearly understood. It has been suggested that the genotypes of individuals may play an important role in the susceptibility to different infectious and non-infectious diseases (Foroughi et al., 2012).

Recent genetic studies have shown that host genetics play a major role in the progression of HIV infection, and some single nucleotide polymorphisms (SNPs) on the *IL-7Rα* were found to be strong associated with rapid progression (Limou et al., 2012). The sequencing of mammalian and microbial genomes has also enabled the study of how genetic variation in the host and pathogen can influence the course of infectious disease (Kiryluk et al., 2007). Several gene polymorphisms were found to be associated with diseases such as tuberculosis (TB). In a recent study in a Chinese population, a polymorphism in the *IL-6* promoter was associated with increased resistance to TB while CD14+ monocytes isolated from individuals with the GG genotype produced significantly less *IL-6* in response to *Mycobacterium tuberculosis* 19-kD lipoprotein compared to those with the CC or CG genotype (Zhang et al., 2012). In another study on the effect of the polymorphism +874 A/T of the interferon-γ gene, genotype TT had a protective effect, while genotype AA was associated with increased susceptibility to developing TB (de Albuquerque et al., 2012). However, no studies have examined the impact of these polymorphisms on the occurrence of other opportunistic infections or the general health of Southern African HIV patients. In the present study, the relationship between a polymorphism of the *IL-7Rα* gene at the +1237 locus and the occurrence of opportunistic infections among HIV and AIDS patients was examined in the Limpopo Province.

MATERIAL AND METHODS

Ethical considerations

HIV-positive patients visiting the 3 main hospitals in the region, including Tshilidzini, Donald Fraser, and Elim, as well as registered students at the University of Venda (UNIVEN) were recruited for the study. Ethical approval was obtained from the University of Venda Research and Publication Committee, the Ethics Committees of the different hospitals, and the Department of Health in Limpopo. The aims and objectives of the study were clearly explained to the patients and a written consent form was obtained before beginning the study. Patients were mostly from the surrounding villages and were in different stages of HIV infection, except for the sero-negative university students. All interviews were confidential and identifiers such as name of the patients were not collected to protect their identity.

Sample collection and DNA purification

A total of 166 participants were recruited for the present study. Data on the demographical, clinical, and socioeconomic status were collected from the patients using a structured questionnaire. Mouthwash samples were collected from consenting participants and genomic DNA was purified using the QIAmp Blood Mini Kit (Qiagen, Hilden, Germany) following manufacturer instructions.

Sequence-specific primer polymerase chain reaction (PCR)

Genotyping of the +1237A/G locus was achieved using the common primer *IL7*Rex4F2

(5'-GTGACTTGCAGAGGAGATGA-3') and 2 allele-specific primers Rex4R1t (5'-TTGGCT CCTTCCCGATAGAT-3') and *IL-7*Rex4R2c (5'-TGGCTCCTTCCCGATAGAC-3'). PCRs were carried out in 25-µL volumes as previously described by Shamim et al. (2006). Amplifications were performed on a GStorm PCR System (VACUTEC, Pretoria, South Africa). Ready-mix *Taq* polymerase (Fermentas, Vilnius, Lithuania) was used in the PCR with the following cycling conditions: pre-denaturation at 96°C for 10 min, a touch-down procedure of 25 s at 95°C, followed by annealing for 45 s at temperatures decreasing from 55°C (4 cycles) to 50°C (25 cycles), and an elongation step at 72°C for 40 s; samples were stored at 10°C. PCR success was evaluated by electrophoresis for fragment separation on a 1.5% agarose gel stained with ethidium bromide and band sizes representing individual alleles were visualized under an ultraviolet transilluminator.

Data analysis

Statistical Package for Social Science v. 18.01 (SPSS, Inc., Chicago, IL, USA) was used to analyze the results, and the difference was considered significant if the P value was less than 0.05. The chi-square, crude odds ratio, and 95% confidence interval were used to determine the potential differences in the distribution of alleles.

RESULTS

Demographic and clinical information of the study population

Of the total population of 119, 28.6% were males and 71.4% were females. Most samples (49.6%) were from Donald Fraser hospital followed by Tshilidzini, Elim, and UNIVEN, respectively. Most patients were aged 25-45 years, followed by 40-80 years, and very few were less than 25 years. Through the use of a questionnaire, patients were asked about general symptoms experienced at the time they went for testing, at the time they started antiretroviral treatment, and at the time the survey was being conducted. Of all patients, 81 (71.7%) indicated that they went for testing because they had an infection or condition. The most common infections or symptoms included pain, diarrhea, TB, and sexually transmitted disease (Table 1).

IL-7R +1237 gene polymorphism distribution in relation to immunological and virological characteristics of the patients

Of the 3 genotypes of the *IL-7R* +1237 gene, genotype A/G (64.7%) was the most common, while the other genotypes occurred at equal distributions (17.6%). There was no significant association between the immunological characteristics of patients collected at the time of interview and the genotype distribution, although there were slight differences. For example, very low CD4 count (fewer than 50 cells/µL) was more common among patients carrying the A/A genotype, while at the level of CD4 count of 200 cells/µL, there was no difference. However, lower viral load values were observed among patients carrying the A/A genotype (Table 2).

Table 1. Socio-demographic characteristics and common opportunistic infections and symptoms among the HIV and AIDS patients attending treatment centers and participating in the study.

Demographic characteristics	Characters	Frequency	Percent
Gender	Male	34	28.6
	Female	85	71.4
	Total	119	100.0
Hospital or Study Fields	Donald Fraser	59	49.6
	Elim	24	20.2
	Tshilidzini	30	25.2
	UNIVEN	6	5.0
	Total	119	100.0
Age group (years)	0-24	10	8.4
	25-45	67	56.3
	46-80	42	35.3
	Total	119	100.0
Marital status	Divorced	12	10.0
	Married	38	32.0
	Single	52	43.7
	Widow	17	14.3
	Total	119	100.0
Common opportunistic infections and clinical symptoms	Infection at time of testing	81	71.7
	All pain at testing	21	19.1
	Diarrhea	25	22.1
	Fever	32	32.0
	Fatigue	41	41.0
	Weakness	40	40.0
	Loss of weight	13	14.9
	Abdominal pain	37	37.4
	Tuberculosis infection	30	26.5
	Current chest pain	27	24.1
	Current cough	31	27.7
	Pain in the chest	42	37.2
	STD	30	26.5

UNIVEN = University of Venda; STD = sexually transmitted disease.

Table 2. Distribution of *IL-7R* +1237 genotypes in relation to immunological and virological characteristics of the patients.

Variables	Characteristics		Total	χ^2	OR (95%CI)	P value
Very low CD4 count	CD4 >50	CD4 <50				
G/G	17 (21.8%)	4 (18.2%)	21 (21.0%)	0.13	0.79 (0.23-2.67)	0.713
A/G	53 (67.9%)	14 (63.6%)	67 (67.0%)	0.14	0.82 (0.31-2.22)	0.704
A/A	8 (10.3%)	4 (18.2%)	12 (12.0%)	1.02	1.94 (0.52-7.18)	0.312
	78	22	100			
CD4 count	CD4 <200	CD4 >200				
G/G	13 (21.0%)	8 (18.2%)	21 (19.8%)	0.12	0.83 (0.31-2.23)	0.723
A/G	40 (64.5%)	29 (65.9%)	69 (65.1%)	0.02	1.06 (0.47-2.39)	0.882
A/A	9 (14.5%)	7 (15.9%)	16 (15.1%)	0.03	1.11 (0.38-3.25)	0.844
	62	44	106			
Viral load	Viral load <25 copies	Viral load >25 copies				
G/G	2 (11.8%)	2 (22.2%)	4 (15.4%)	0.49	2.14 (0.24-18.59)	0.482
A/G	11 (64.7%)	6 (66.7%)	17 (65.4%)	0.11	1.09 (0.19-6.01)	0.920
A/A	4 (23.5%)	1 (11.1%)	5 (19.2%)	0.58	0.41 (0.03-4.31)	0.445
	17	9	26			

χ^2 = chi-square; OR = odds ratio; 95%CI = 95% confidence interval. Significance at $P < 0.05$.

Distribution of *IL-7Rα* +1237 polymorphism in relation to opportunistic infections among HIV and AIDS patients

Patients were asked if they had infection at the time they went for testing for HIV (the

time they first learned that they were infected with the virus). We examined whether there was an association between the different infections and the different genotypes of the *IL-7R* gene at the locus +1237 A/G. Patients carrying the G/G genotype appeared to have fewer infections, and approximately 28% of these patients did not have an infection at the time of HIV testing, while approximately 15% of them had an infection at the time of testing. However, the difference was not statistically significant. Patients were also asked if they had any sexually transmitted diseases in addition to HIV. Of all the patients who answered this question, 30 (26.5%) responded yes. However, there was a significant difference in relation to genotype distribution between the patients indicating that they had a sexually transmitted disease and those who did not. Patients were also asked about diarrhea; the AA genotype was significantly associated with diarrhea (P = 0.034). The AA genotype was common among patients that did not have physical pain at the time of testing; however, the difference was not statistically significant (P = 0.110; Table 3).

Table 3. Distribution of *IL-7Rα* +1237 polymorphism in relation to opportunistic infections among HIV and AIDS patients.

Variables	Characteristics		Total	χ^2	OR (95%CI)	P value
Infection at time of testing	Did not have infections at testing	Had infections at testing				
G/G	9 (28.1%)	12 (14.8%)	21 (18.6%)	2.68	0.44 (0.16-1.19)	0.101
A/G	17 (53.1%)	55 (67.9%)	72 (63.7%)	2.16	1.86 (1.05-8.41)	0.141
A/A	6 (18.8%)	14 (17.3%)	20 (17.7%)	0.03	0.91 (0.31-2.61)	0.854
	32	81	113			
Diarrhea	Did not have diarrhea	Had diarrhea				
G/G	18 (20.5%)	3 (12.0%)	21 (18.6%)	0.92	0.53 (0.14-1.97)	0.338
A/G	58 (65.9%)	14 (56.0%)	72 (63.7%)	0.82	0.65 (0.26-1.62)	0.363
A/A	12 (13.6%)	8 (32.0%)	20 (17.7%)	4.50	2.98 (1.05-8.413)	0.034
	88	25	113			
Body pains at testing	Had no pains	Had pains				
G/G	15 (16.9%)	5 (23.8%)	20 (18.2)	0.55	1.54 (0.48-4.85)	0.457
A/G	57 (64.0%)	15 (71.4%)	72 (65.5%)	0.41	1.40 (0.49-3.97)	0.522
A/A	17 (19.1%)	1 (4.8%)	18 (16.4%)	2.55	0.21 (0.02-1.69)	0.110
	89	21	110			
Fatigue	Did not feel fatigue	Felt fatigue				
G/G	11 (18.6%)	6 (14.6%)	17 (17.0%)	0.27	0.74 (0.25-2.21)	0.600
A/G	42 (71.2%)	26 (63.4%)	68 (68.0%)	0.67	0.70 (0.30-1.64)	0.413
A/A	6 (10.2%)	9 (22.0%)	15 (15.0%)	2.63	2.48 (0.81-7.63)	0.105
	59	41	100			
STD	Did not have STD	Had STD				
G/G	14 (16.9%)	7 (23.3%)	21 (18.6%)	0.61	1.50 (0.53-4.17)	0.435
A/G	54 (65.1%)	18 (60.0%)	72 (63.7%)	0.24	0.81 (0.34-1.90)	0.621
A/A	15 (18.1%)	5 (16.7%)	20 (17.7%)	0.03	0.91 (0.29-2.75)	0.863
	83	30	113			

STD = sexually transmitted disease.

Distribution of *IL-7Rα* +1237 polymorphism in relation to TB and related symptoms among HIV and AIDS patients

Patients were asked about TB as well as related symptoms such as cough and chest pain. Although there was no statistically significant difference in the distribution of the different genotypes and the report of TB among patients, the G/G genotype frequency was significantly higher among patients without chest pains (P < 0.05). In addition, a higher percentage of these patients did not have TB, although the difference was not significant (P = 0.388). The patients carrying the G/G genotype also reported cough at testing less frequently (20.4%),

while there were no patients with this genotype who reported coughing at the time of testing (χ^2 = 2.993, P = 0.084) (Table 4). All this indicates that the homozygote G/G might have a protective effect against chest pain and coughing and therefore might have a slower evolution to TB disease compared to the heterozygotes with A/G who had significantly more chest pain (P = 0.034) and more cough.

Table 4. Distribution of *IL-7Rα* among HIV and AIDS patients in relation to TB and related conditions.

Variables	Characteristics		Total	χ^2	OR (95%CI)	P value
Tuberculosis	No TB	Has TB				
G/G	17 (20.5%)	4 (13.3%)	21 (18.6%)	0.74	0.59 (0.18-1.94)	0.388
A/G	51 (61.4%)	21 (70.0%)	72 (63.7%)	0.69	1.46 (0.59-3.59)	0.404
A/A	15 (18.1%)	5 (16.7%)	20 (17.7%)	0.03	0.91 (0.29-2.75)	0.863
	83	30	113			
Cough at testing	Was not coughing at testing	Was coughing at testing	Total			
G/G	20 (20.4%)	0	20 (18.2%)	2.993	0.86 (0.79-0.94)	0.084
A/G	62 (63.3%)	10 (83.3%)	72 (65.5%)	1.904	2.90 (0.60-13.99)	0.168
A/A	16 (16.3%)	2 (16.7%)	18 (16.4%)	0.001	1.02 (0.25-5.12)	0.976
	98	12	110			
Current cough	Not coughing	Currently coughing				
G/G	16 (19.8%)	5 (16.1%)	21 (18.8%)	0.19	0.78 (0.26-2.35)	0.660
A/G	50 (61.7%)	21 (67.7%)	71 (63.4%)	0.35	1.30 (054-3.12)	0.554
A/A	15 (18.5%)	5 (16.1%)	20 (17.9%)	0.08	0.84 (0.28-2.56)	0.768
	81	31	112			
Pain in the chest	No pain	Have pain in the chest				
G/G	18 (25.4%)	3 (7.1%)	21 (18.6%)	5.78	0.22 (0.06-0.82)	0.016
A/G	40 (56.3%)	32 (76.2%)	72 (63.7%)	4.49	2.48 (1.05-5.81)	0.034
A/A	13 (18.3%)	7 (16.7%)	20 (17.7%)	0.04	0.89 (0.32-2.45)	0.825
	71	42	113			
Current chest pain	No pain in the chest currently	Have pain in the chest currently				
G/G	20 (23.5%)	1 (3.7%)	21 (18.8%)	5.28	0.12 (0.01-0.98)	0.021
A/G	49 (57.6%)	22 (81.5%)	71 (63.4%)	5.01	3.23 (1.11-9.35)	0.025
A/A	16 (18.8%)	4 (14.8%)	20 (17.9%)	0.22	0.75 (0.22-2.47)	0.636
	85	27	112			

Currently means at the time of the survey (2009-2010).

DISCUSSION

HIV infection is characterized by progressive immunodeficiency, which is reflected by a steady decline in the number of CD4+ T-cells. Disease progression varies considerably from patient to patient. Although more than 99% of human DNA sequences are the same, variations in DNA sequences can have a major impact on how humans respond to disease and environmental factors such as bacteria, viruses, toxins, chemicals, drugs, and other therapies. This makes SNPs valuable for biomedical research and for developing pharmaceutical products or medical diagnostics (Weiner and Hudson, 2002).

A lack of the beneficial effect of *IL-7* during HIV-1 infection may be due to the loss of *IL-7Rα* in most T-cells. Decreased expression of *IL-7Rα* is observed both for CD4+ and CD8+ T-cells during HIV-1 infection (Gougeon and Chiodi, 2010). Because of weak or impaired signaling in the immune response, HIV individuals may die, mostly resulting from manifestations of opportunistic infections. In our study population, the *IL-7Rα* +1237 genotype distribution differed from those found in European populations, which showed a predominance of the A/G genotype. In a study by Shamim et al. (2006), the AA and AG genotypes appeared in similar frequencies (45%), while only 11% of the study population had the GG genotype. This indicates a difference in the distribution of these genotypes depending on the population studied.

The progression of HIV disease varies according to the genetic makeup of the patient. In our study, there was no correlation between genotype and CD4 count or viral load. Although some of the participants had a low viral load, few of the HIV participants in our study carrying the A/G allele of the genotype +1237 A/G had a CD4+ count lower than 200 cells/μL, while most patients with the same allele had CD4+ counts greater than 50 cells/μL. Other studies have demonstrated that extremely low numbers of T-cells in the peripheral blood may fail to express major histocompatibility complex (MHC) gene products (MHC Sequencing Consortium, 1999). MHC genes are highly polymorphic, which plays a very important role in the resistance to pathogens. T-cell abnormalities allow opportunistic pathogens to take advantage of the suppressed individual's immune system, which in HIV individuals creates a greater possibility of early death (Hoe et al., 2010).

TB is a very common opportunistic infection among patients with HIV and AIDS worldwide (Abdallah et al., 2011). Although the distribution of genotypes of specific genes was found to be associated with the occurrence or evolution of TB, no studies have considered the effect of *IL-7R* polymorphisms on TB. In the present study, we found that fewer patients with the G/G and A/A genotypes had TB compared to patients carrying the A/G genotype, but the difference was not statistically significant. Therefore, the *IL-7Rα* +1237 genotypes are associated with TB. However, there was a significant association between the A/G genotype and chest pain, while the G/G genotype generally protected against chest pain among the patients ($P < 0.05$). A previous study by Ben-Selma and Boukadida (2012) showed that the reduced functional polymorphism 1142G→A encoded by *IL-23R* influences the outcome of disease severity of active pulmonary TB in Tunisian patients. Similarly, Verma et al. (2012) found that the C allele of the *IL-12*Rβ2 promoter significantly impacted TB among Indian patients. Randhawa et al. (2011) conducted a different study in South Africa and found that TLR1/6 polymorphisms modulate Th1 T-cell polarization through genetic regulation of monocyte *IL-10* secretion in the absence of *IL-1* among TB patients. This is the first time that the *IL-7Rα* +1237 genotypes have been associated with general symptoms such as chest pain.

Our study showed that individuals carrying the A/G allele of the +1237 A/G genotype suffered from diarrhea and chest pains; however, there is no evidence suggesting that these symptoms were side effects of antiretroviral treatment. Importantly, visible changes in the health of an HIV-positive person on antiretroviral treatment can be vital in reducing stigma, particularly when HIV is associated with death. Young et al. (2012) found that although the relationship between genetics and pain is not well understood, it is clear that a number of genes play a critical role in determining sensitivity or susceptibility to chronic pain. Previous studies have indicated that cytokine genes are candidates for controlling human susceptibility to infection and pain. A previously known functional polymorphism (-819) of the *IL-10* gene associated with regulation of *IL-10* serum levels was also associated with the development of leishmaniasis skin lesions in a Brazilian population sample from the northeastern state of Bahia (Salhi et al., 2008).

A previous study by Nielsen et al. (2005) indicated that significant individual variability is observed in both pain threshold and the susceptibility to chronic pain conditions; a portion of this variation can be explained by variation within specific genes. Single functional SNPs or combinations of SNP alleles that are generally inherited together (haplotypes) can contribute to increased or decreased susceptibility to pain (Foulkes and Wood, 2008). One of the most extensively studied pain candidate genes is *catechol-O-methyltransferase* (*COMT*), the product of which is known to be involved in the inactivation of dopamine, epinephrine,

and norepinephrine neurotransmission and is associated with variations in experimental and clinical pain behavior (Andersen and Skorpen, 2009). Only a few studies have examined the effects of gene polymorphism on pain in general as well as diarrhea. In a study conducted in Finland, Solovieva et al. (2004) showed that carriage of the *IL-1* RNA (1812) allele was associated with pain occurrence, the number of days with pain, and days with limitation of daily activities. Carriage of the *IL-1betaT* (3954) allele was associated with the number of days with pain. In our study, the A/G genotype was associated with chest pain, which may be a manifestation of several infections or disease conditions. By studying stretches of DNA that harbor a SNP associated with a disease trait, researchers can identify relevant genes associated with a disease. In the future, appropriate drug treatment can be determined in advance of treatment by analyzing a patient's SNP profile (Weiner and Hudson, 2002).

In this study, we showed that the distribution of the *IL-7Rα* genotypes in our study population in Northern South Africa was different from those found in other populations such as Europeans. This is the first study to determine the distribution of the *IL-7Rα* genotype in the South African community and to show that HIV-positive individuals carrying the A/G allele of the +1237 A/G genotype were more susceptible to chest pain and had higher levels of TB, while patients carrying the A/A genotype were more susceptible to diarrhea. The study provides data that will support gene therapy and probably modify the course of diseases among HIV as well as the general population. Further studies are needed to confirm this hypothesis in larger populations.

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