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CLINICAL MICROBIOLOGY - RESEARCH PAPER

CCR5-Δ32 gene variant frequency in the Turkish Cypriot population

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Abstract

Recent UNAIDS reports (December 2019) indicate that 37.9 million people have been affected by HIV infection around the globe in 2018, of which 1.7 million are cited as new infections. Human immunodeficiency virus-1 (HIV-1) requires both the CD4 receptor, as the primary receptor, and a chemokine co-receptor to gain entry into the cell. In addition to the WT allele for C–C motif chemokine receptor 5 (CCR5-wt), there is another allele with a 32 bp deletion in the protein coding region (CCR5-Δ32). Individuals who are homozygous for the mutant allele are resistant towards M-tropic HIV infections. In the current study, we aimed to determine the CCR5-Δ32 allele frequency in the Turkish Cypriot population with 326 subjects, 141 men (43.1%) and 185 (56.9%) women. The region of the CCR5 gene containing the Δ32 deletion was amplified using flanking primers. The CCR5 gene Δ32 allele frequency was calculated at 3% and only observed in heterozygous individuals. We hope that our current publication could be a point of dialog between the physicians, the government officials and the public set up a more modern and well-structured HIV screening program in an effort to control and hopefully eliminate HIV from the Turkish Cypriot population.

Keywords CCR5-Δ32 · HIV · Allele frequency · Turkish Cypriots · Public health policy

Introduction

Human immunodeficiency virus (HIV) is a virus from the family Retroviridae, genus Lentivirus. HIV epidemic is one of the worst epidemics of the modern times. By destroying the CD4-positive T lymphocytes, HIV is able to make the body lose its ability to fight infection and disease due to an extremely low CD4 cell count. This condition is known as acquired immunodeficiency syndrome (AIDS). According to the latest UNAIDS data from the 2019 factsheet and the WHO statistics, 37.9 million people were affected by HIV infection around the globe in 2018, of which 1.7 million are new infections. Unfortunately, by the end of June 2019, only 24.5 million (23.3 million according to WHO) people have been reported to have access to antiretroviral therapy (ART) according to UNAIDS, which is a greatly improved number compared to the 8 million in 2010 [1–5]. According to the recent speech by the Executive Director of UNAIDS, nearly 350,000 people have died of AIDS just in the first 6 months of 2020 [6]. Despite the improved access to ART, drug-resistant HIV is present in individuals with or without treatment, making HIV suppression without drugs an urgent necessity [7].

HIV-1 requires both the CD4 receptor, as the primary receptor, and a chemokine co-receptor to gain entry into the cell [8]. There are two different tropisms of HIV-1 depending on the type of chemokine co-receptor they utilize for attachment. Macrophage-tropic (M-tropic) HIV-1 is more likely to be present in early infections, preferring primary cultures of macrophages, and uses C–C motif chemokine receptor 5 (CCR5) chemokine co-receptors for attachment. On the other hand, the T cell-tropic (T-tropic) strain, which requires the C-X-C motif chemokine receptor 4 (CXCR4) chemokine co-receptors for attachment, will appear in late stage infections, preferring primary cultures of $CD4^+$ T cells and established T cell lines, and will cause a faster decline in the number of CD4-positive T cells [9–11]. The CXCR4 and the CCR5 are both members of

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the G protein coupled receptor (GPCR) family, with seven transmembrane domains that are structurally similar to each other. Both receptors have chemokines as their ligands and play a role in multiple cellular processes such as development, angiogenesis, immune response, and leukocyte trafficking. More specifically, the CCR5 receptor has the CC (or β) chemokines as their ligands [9, 12, 13].

CCR5 WT (CCR5-wt) protein is 352 amino acids long, with 7 membrane spanning regions, 3 extracellular domains, and 3 cytoplasmic domains. One of the other functions of this protein is to target leukocytes to the site of inflammation. In addition to the WT allele, there is another allele with a 32 bp deletion in the protein-coding region (CCR5-Δ32). The shorter protein encoded by this allele could not be observed on the cell surface [10]. The WT nucleotide sequence of the protein-coding region and the resulting protein sequence are shown in Fig. 1 together with the location of the deletion on the nucleotide sequence. The 32 base pair deletion will lead to a frameshift and therefore cause a much shorter protein. Individuals who are homozygous for the mutant allele are resistant towards HIV infections. However, this resistance is not absolute and is only for the M-tropic HIV strains. These individuals will not have the same resistance towards the T-tropic HIV strains [8, 10, 14]. Additionally, people who are heterozygous for the CCR5-Δ32 allele will show a slower progression to AIDS when compared to homozygous WT individuals [1]. The CCR5 knock-out mice developed normally. However, the mice had difficulty in clearing Listeria infections and partial macrophage dysfunction. The CCR5 may also play an important role in graft-versus-host disease through its downmodulation of the T cell-dependent immune response. As CCR5 has a role in decreasing the T cell-related immune response, absence of CCR5 may increase the chance for graft-versus-host disease. This connection remains unclear. Individuals who are homozygous mutant may also have a higher chance of death as a result of West Nile Virus infections [9, 10].

CCR5-Δ32 first came to light in 2009, in what is referred to as the "Berlin Patient". Stem cell transplant using CCR5-Δ32/CCR5-Δ32 cells was performed to treat leukemia in this patient. Following the transplant, the HIV infection in the blood and the bone marrow became undetectable without the use of antiretroviral treatment. A second similar case was mentioned in literature in 2019.

Recently, a paper detailing the CCR5-Δ32 allele frequency in 87 countries has been published. DKMS (Germany, Poland, and UK) which collects samples from potential hematopoietic stem cell donors has implemented the genotyping routine to newly registered donors [7, 8, 10]. New techniques are being developed to knockdown CCR5 expression by gene therapy with the help of zinc-finger nuclease (ZFN), CRISPR/Cas9, and transcription activator-like effector nuclease (TALEN) systems [15]. Yu et al. have created a double-knockout system for both the CXCR4 and CCR5 genes in the circulating CD4+ cells using the CRISPR/Cas9 system which could potentially lead to more functional HIV prevention [16]. In light of the

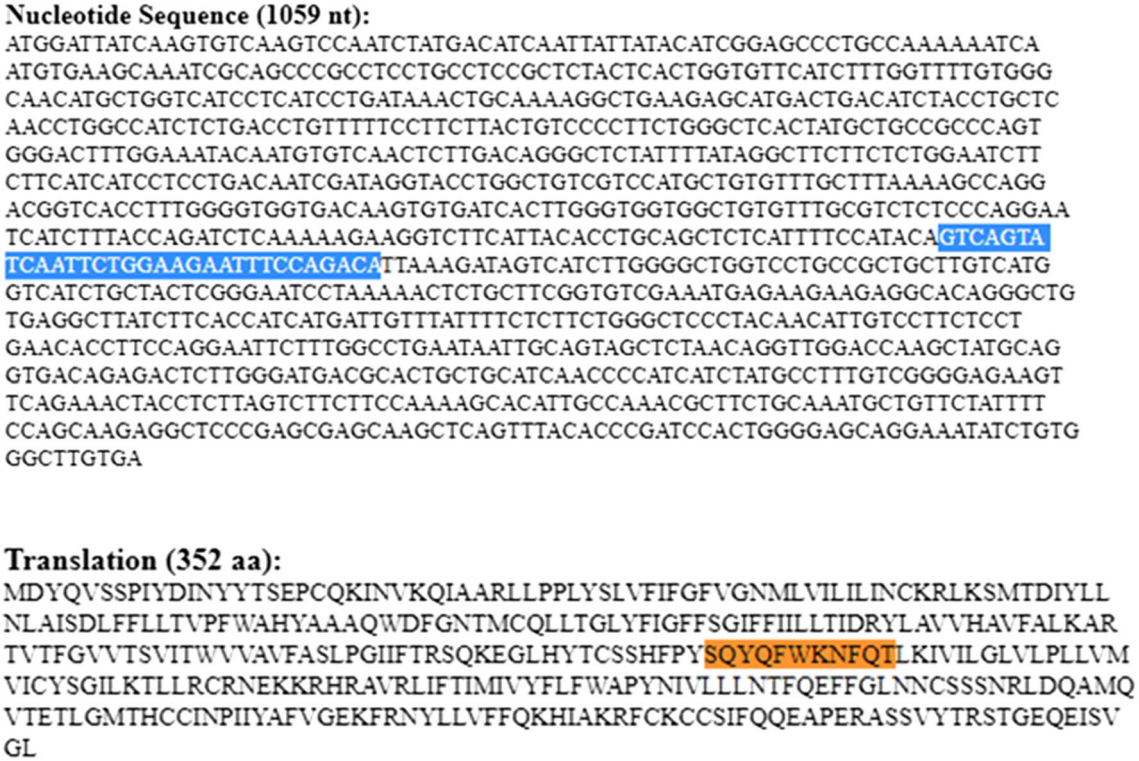

Fig. 1 The nucleotide sequence and the protein sequence for CCR5. The blue-highlighted region shows the 32-base deletion and the orange shows the corresponding amino acids that will be deleted

recent COVID-19 pandemic, it has also come to our attention that CCR5 cytokine receptor is upregulated in COVID-19 patients and is emerging as a possible target in clinical trials for COVID-19 treatment [17].

UNAIDS data for Cyprus from 2017 states that individuals, from all age groups, living with HIV in Cyprus, are less than 1000. The number of people living with HIV has been increasing gradually since 1990. However, there has been a decrease in the AIDS-related deaths since 2014. These statistics probably only reflect the Republic of Cyprus and do not include the Turkish Cypriots living separately on the north side of the Island. According to the ministry of health statistics for the Turkish Cypriots, since 1997, there have been a total of 68 cases reported. All of these are Turkish Cypriots citizens, since if a non-Turkish Cypriot is detected to be HIV positive in North Cyprus, it is grounds for deportation. Thirteen new cases have been identified in 2017 and 2018 in North Cyprus. The highest number of cases detected was in 2014 and 2015, with 11 and 10 cases, respectively. Only five of the Turkish Cypriot HIV-positive cases are female [18, 19].

In the current study, we aimed to determine the CCR5-Δ32 allele frequency in the Turkish Cypriot population. We hope that this study will be a valuable addition to the literature and will also help the health authorities from the public health perspective. Neither the Greek Cypriots nor the Turkish Cypriot populations were part of the extensive study by Solloch et al. [10]. However, a Greek population only study was reported in 1997 [20].

Materials and methods

Study population

The study population is made up of 326 Turkish Cypriots, of which 141 are males and 185 are females. The volunteered subjects have been defined as Turkish Cypriots who have been living on the island at least for the past three generations. Furthermore, due to the small size of population, the subjects which are related, such as first degree relatives, were eliminated from the study. There were no other restrictions set up for the study population. An ethical approval for the study was obtained from the Near East University Scientific Research Ethics Committee (YDU/2019/68-791). Informed consent was obtained from each participant.

Molecular genotyping

Blood samples collected in tubes containing ethylenediaminetetraacetate (EDTA from participants. QIAamp DNA Blood Mini Kit (Qiagen Inc., Valencia, CA, USA) was used for genomic DNA extraction. The region of the *CCR5* gene containing the Δ32 deletion was amplified using the following flanking primers: 5′-CAAAAAGAAGGTCTTCATTACACC-3′and 5′-CCTGTGCCTCTTCTTCTCATTTCG-3′. The expected fragments from the WT and the Δ32 allele were 189 and 157 bp, respectively (Fig. 2). The PCR reactions were prepared using the 2X PCR Master Mix by Thermo Scientific (K0171) with the final primer concentration at 20 pmols for each primer. The DNA amount used was around 10 ng. The PCR protocol was the same as Angelis et al. [14]. A homozygous WT individual will only display the 189 bp band, a heterozygous individual will display both the 189 and the 157 bp band, and a homozygous mutant individual will only display the 157 bp band. Fragments obtained from PCR were separated in 3% agarose gels which contained ethidium bromide for visualization. By using UV-treated solutions, designated pipettes and pipette tips, a class II laminar hood and DNA/DNAse-free plasticware and reagents, the risk of contamination was decreased to a minimum.

Statistical analysis

The Hardy-Weinberg equilibrium (HWE) was evaluated by the goodness-of-fit χ^2 test to calculate genotype distributions and allele frequencies, where a $p < 0.05$ was considered to indicate significant disequilibrium. The GraphPad Prism software was used (GraphPad Software, Inc., San Diego, CA, USA) to perform for the data analysis. HWE exact test was performed using the website https://www.cog-genomics.org/software/stats.

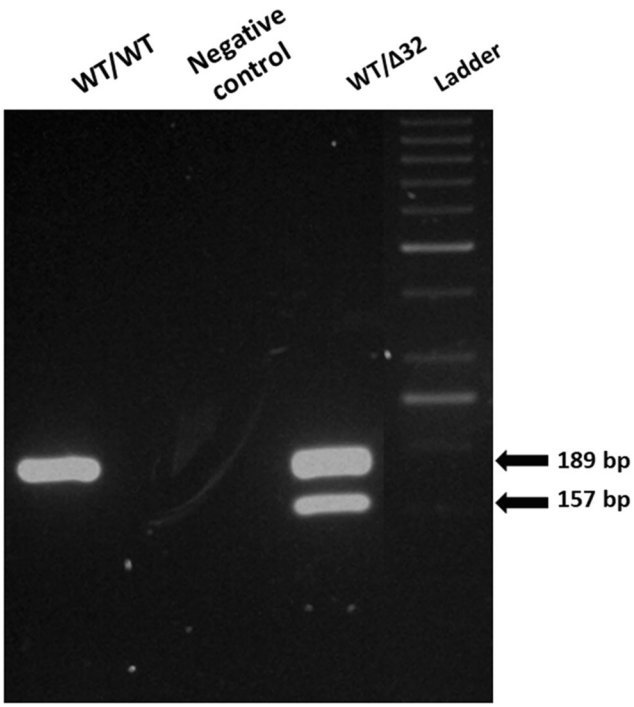

Fig. 2 CCR5 genotypes in Turkish Cypriot individuals. WT allele is expected at 189 bp and the Δ32 allele is expected at the 157 bp. Lane 1 represents a homozygous wild-type genotype (fragment of 189 bp), lane 2 is the negative control for the PCR reaction (no bands as expected), lane 3 represents a heterozygous genotype (fragments of 189 bp and 157 bp)

Results

The subjects were made up of 326 Turkish Cypriots of which 141 are men (43.1%) and 185 (56.9%) are women. Genotype distributions and allele frequencies of the *CCR5* gene Δ32 variant are shown in Table 1. Distribution of the *CCR5*Δ32 genotype was in agreement with the Hardy-Weinberg equilibrium ($P = 0.587$, $X^2 = 0.293$). The *P* value using the HWE exact test was 0.618. The calculated *CCR5 gene* Δ32 allele frequency was 3% and only the allele was observed in heterozygous individuals. Therefore, the allele frequency of the wild-type *CCR5* allele was 97%. No *CCR5*Δ32 homozygous Turkish Cypriots were detected in the studied cohort.

Discussion

CCR5 delta 32 mutation has been studied extensively in many ethnic groups and the allele can be seen more frequently in northern European populations. The allele frequency decreases as you move south and east. The lowest allele frequency is seen in South and South east Asia and the Sub-Saharan Africa. CCR5-Δ32 allele is thought to have arisen from a single origin. IT is thought that the Vikings might be responsible for dissipating the mutant allele. The more you move away from the old Viking lands, the lower you see the frequency. Different selective pressures in different populations such as smallpox might have made it possible to see higher frequencies in Europe [10, 14, 21]. Only 2–3% of the white population is CCR5-Δ32/CCR5-Δ32. No obvious phenotype is observed in these individuals [9].

Up to 87 countries have been analyzed with regards to their CCR5-Δ32 allele frequency. Cyprus was not one of those countries. The statistics given by the UNAIDS website do not include Turkish Cypriots as they live separately. Also, the previous publication by Christodoulou only provides the data for Greek Cypriots [18, 20]. In order to contribute to the CCR5-Δ32 allele frequency literature in a time where the CCR5 delta 32 is becoming a hot topic again and to provide a much-needed statistic for the Turkish Cypriot population, 326 Turkish Cypriots were studied to determine their CCR5-Δ32 allele status. This would also provide valuable information from the public health standpoint and help set up a more structured approach to HIV testing. A total of 326 people provided us with a good sample number considering the small population of Turkish Cypriots (approx. 286,000) [22].

Distribution of the *CCR5*Δ32 allele was in agreement with the Hardy-Weinberg equilibrium ($P = 0.587$, $X^2 = 0.293$) in the Turkish Cypriot population. The *P* value using the HWE exact test was 0.618. The two *P* values were in agreement with each other. The *CCR5 gene* Δ32 allele frequency was calculated to be 3% and only observed in heterozygous individuals. This number is also close to the 2.9% reported for the Greek Cypriot population [20]. No individuals homozygous for the *CCR5*Δ32 allele were detected. Perhaps a much larger test population would have made it more likely detect a homozygous mutant individual. Failure to detect a homozygous mutant individual in other studies as well would indicate how small the allele frequency is for the *CCR5*Δ32 allele in reality (observed) as compared to the expected. The allele frequencies of neighboring countries such as Turkey, Greece, Egypt, Israel, Syria, and Lebanon (Fig. 3) are approximately 3%, 5%, 2%, 10%, 3%, and 2%, respectively [10, 23, 24]. The Turkish allele frequency has also been cited around 6% in earlier studies, which is higher than what Solloch has reported [10, 21, 25]. Therefore, it is safe to say that the allele frequency of the Turkish Cypriots is compatible with the neighboring countries. When we look at other European Mediterranean countries such as Spain, Italy, and France (8%, 6%, and 10% respectively), we can see that the Turkish Cypriot population allele frequency of 3% would follow the rule of going down as we move southward and eastward. Turkish Cypriot population is a relatively isolated population from the rest of the world as there are restrictions on travel to and from the north of the island. The population that most interacts with the Turkish Cypriots is the Turkish population and their allele frequency is 3–6%. The Turkish Cypriot and Greek Cypriot populations have physically lived separately between 1974 and 2003. After 2003, with the opening of the border between

Table 1 Genotype distribution and allele frequencies of the CCR5 gene variants. Hardy-Weinberg equilibrium test results of observed and expected genotypes (homozygotes/heterozygotes) of 326 Turkish Cypriot subjects are given at the top portion of the table. The bottom shows the allele frequencies for each allele

CCR5	wt/wt	wt/ Δ32	Δ32/ Δ32	X^2	*P* value	*P* value HWE exact test
Observed	307	19	0	0.293	0.587	0.618
Expected	307.08	18.4	0.3			
f (wt)	0.97	97%				
f (Δ32)	0.03	3%				

wt wild type, *f* frequency

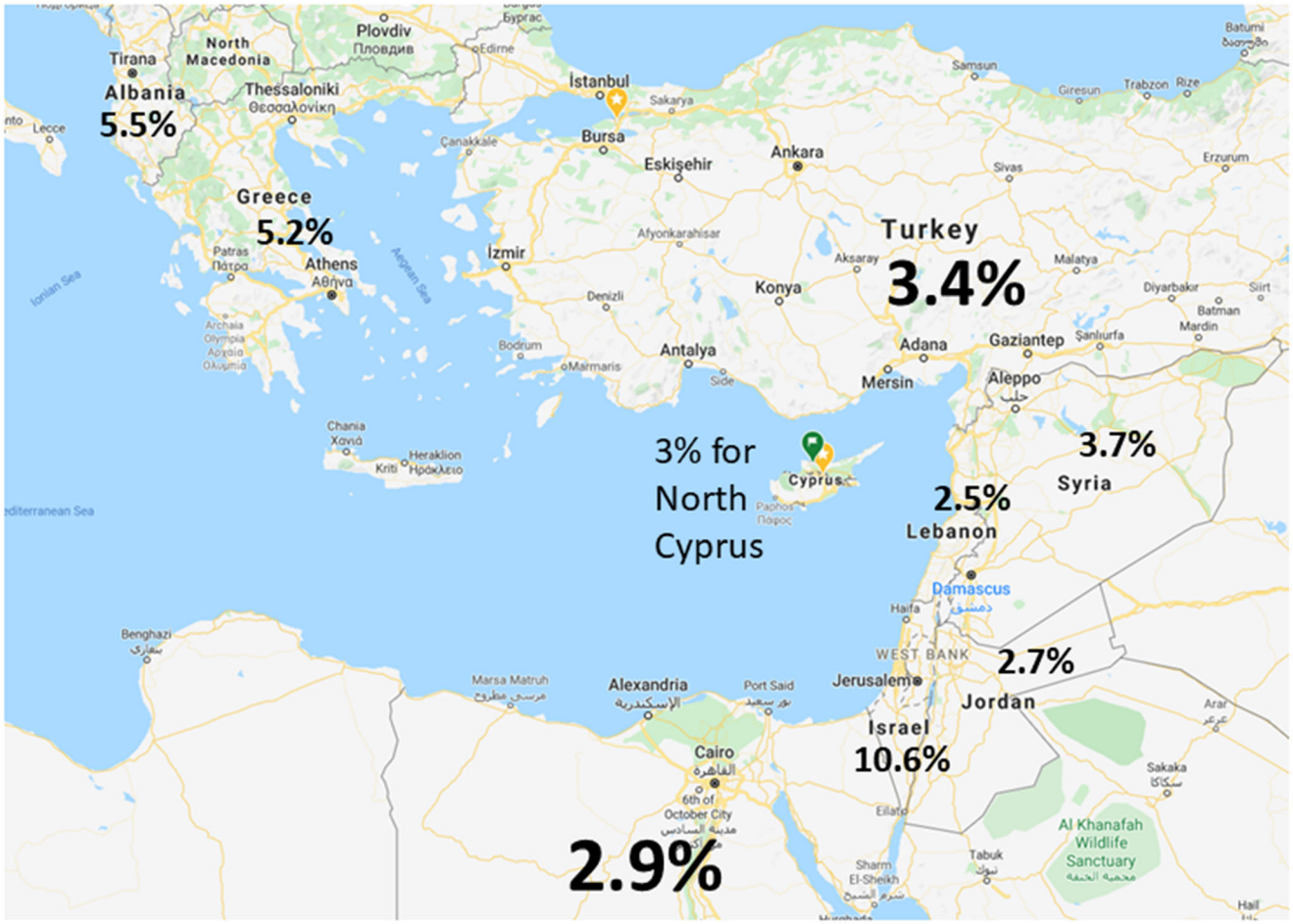

Fig. 3 Map of Cyprus and the neighboring countries with the respective CCR5-Δ32 allele frequencies. Map image is taken from Google Maps

the two sides, despite being able to interact with each other, interethnic marriages and relationships are still at a very low number (commonly known stigma). There are no official statistics available on the issue as this is a very political and contentious issue. However, as a document by the Interpeace and 'Cyprus 2015' Initiative states, the Greek Cypriot population does not look too favorably towards interethnic marriages even to other non-Orthodox Christians [26].

Turkish Cypriot population has only had 68 HIV/AIDS cases since 1997 and 2017 with only 5 deaths. For 2018, there are some conflicting numbers being announced for HIV-positive cases. One source indicates 129 cases whereas the other one indicates only 27 cases. Both of these numbers are obtained from news articles and cannot be found on any official publication. One of the sources is citing the 2018 HIV analysis report and the other one is citing a source from the Medical Board. According to the Medical Board sources, the 2019 number for the HIV cases is 74 [27, 28]. North Cyprus is a big tourist destination and is also home for many international students from many different countries including some African countries where the HIV infection rate may be very high. The same article is pointing out that the HIV-positive report rate may be low in North Cyprus due to couple of reasons. One of the reasons is the stigma attached to being HIV positive in such a small population whereas the second reason is the fear of being deported for foreigners. This may be dangerous as it may cause the disease to advance and be passed on to other people [27].

As the results of our study suggest, most of the Turkish Cypriot population is at greater risk of HIV infection and faster disease progression due to a very low frequency of the Δ32 allele. People are avoiding testing due to the stigma attached to HIV/AIDS in addition to the threat of deportation from the country if you are a foreigner. By keeping the greater risk in mind and using studies like ours, a dialog with health authorities must begin in order to develop a more structured and up-to-date strategy for testing and preventing HIV with the hopes of eliminating HIV/AIDS from the Turkish Cypriot population. Another component of preventing HIV is a more serious dialog between the physicians, the government officials, and the public to better face the challenges posed by HIV to the public. Ignoring the problem, stigmatizing the issue, and not having a policy on the issue are not an option if we

want to take HIV/AIDS seriously. Additionally, having such statistics available for the Turkish Cypriot population would also create a more complete outlook of the region. Even though Turkish Cypriot administration is not internationally recognized, diseases such as HIV know no boundaries or politics. Our current publication could serve as a starting point of dialog for this issue and a warning for people to take HIV infection more seriously.

Authors' contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Umut Fahrioğlu, Mahmut Çerkez Ergören, and Gamze Mocan. The first draft of the manuscript was written by Umut Fahrioğlu and Mahmut Çerkez Ergören and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability All data generated or analyzed during this study are included in this published article.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval Ethical approval for the study was obtained from the Near East University Scientific Research Ethics Committee (YDU/2019/68-791).

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication Not applicable.

Code availability Not applicable.

Abbreviations *AIDS,* Acquired immunodeficiency syndrome; *ART,* Antiretroviral therapy; *CCR5,* C–C motif chemokine receptor 5; *CXCR4,* C-X-C motif chemokine receptor 4; *GPCR,* G protein coupled receptor; *HIV,* Human immunodeficiency virus; *M-tropic,* Macrophage-tropic; *TALEN,* Transcription activator-like effector nuclease; *T-Tropic,* T cell tropic; *ZFN,* Zinc-finger nuclease

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