ORIGINAL PAPER

The prevalence of HTLV-1 co-infection among people living with HIV in a tertiary care hospital in Tehran: a cross-sectional study

Elnaz Shahmohamadi[1], Ali Akbari Sari[2], Esmaeil Mehraeen[3], Malihe Hassan Nezhad[4], Amirali Karimi[1], Pegah Mirzapour[5], Peyman Mirghaderi[1], Zahra Pashaei[5], Hossein Keivani[6], Minoo Mohraz[5], SeyedAhmad SeyedAlinaghi[5]

[1]School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[2]Department of Health Management and Economics, School of Public Health, Tehran University of Medical Sciences (TUMS), Tehran, Iran
[3]Department of Health Information Technology, Khalkhal University of Medical Sciences, Khalkhal, Iran
[4]Department of Infectious Diseases, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran
[5]Iranian Research Center for HIV/ AIDS, Iranian Institute for Reduction of High-Risk Behaviors, Tehran University of Medical Sciences, Tehran, Iran
[6]Department of Virology, School of Medicine, Iran University of Medical Sciences, Tehran, Iran

Abstract

Introduction: Human immunodeficiency virus (HIV) and human T cell leukemia/lymphoma virus type 1 (HTLV-1) share similar routes of transmission and both target T cells. HTLV-1 may negatively affect the course of disease in people living with HIV, but previous evidence is conflicting. Therefore, we aimed to investigate the prevalence of HIV/HTLV-1 co-infection, routes of transmission, and patients' CD4+ counts.

Material and methods: 184 HIV-positive individuals were recruited for this cross-sectional study from the Counseling Center for Behavioral Diseases of Imam Khomeini Hospital in Tehran. Serum samples were analyzed using enzyme-linked immunosorbent assay (ELISA) for anti-HTLV-1.

Results: The mean age of participants was 40.12 ± 11.6 years, and all cases were negative for HTLV-1 infection. Participants were diagnosed on average about 78 months (6 years) ago, and the mean CD4+ count of the participants was 669.22 cells/μl (SD = 284.2). Using ELISA screening, none of the participants from Tehran in various age groups showed concurrent HTLV-1 infection (0 percent).

Conclusions: Co-infection with HTLV-1 is negligible in HIV-infected patients in Tehran, Iran. Our data also showed that the most common route of HIV transmission among our study subjects was heterosexual contact (56.4%).

HIV AIDS Rev 2024; 23, 2: 136-140
DOI: https://doi.org/10.5114/hivar/148096

Key words: HIV, HTLV-1, co-infection, prevalence.

Address for correspondence: SeyedAhmad SeyedAlinaghi, Iranian Research Center for HIV/AIDS, Iranian Institute for Reduction of High-Risk Behaviors, Tehran University of Medical Sciences, 1419733141 Tehran, Iran, phone: +98-2166947984, e-mail: s_a_alinaghi@yahoo.com

Article history:
Received: 13.11.2021
Received in revised form: 03.04.2022
Accepted: 06.04.2022
Available online: 21.05.2024

International Journal of HIV-Related Problems
HIV & AIDS Review

Introduction

Human immunodeficiency virus (HIV) belongs to the family of retroviruses and has two important sub-types, i.e., HIV-1 and HIV-2 [1]. HIV-1 is more common worldwide, and demonstrates higher pathogenicity compared with HIV-2 [1-3]. Although HIV incidence and mortality are decreasing, they still impose a great burden worldwide. The latest global burden of disease (GBD) study estimated 2 million new HIV cases and 0.86 million deaths worldwide in 2019, with 36.8 million people living with HIV (PLWH) [4]. Similar to HIV, human T cell leukemia/lymphoma virus (HTLV) also comprises two main sub-types, HTLV-1 and HTLV-2 [3], both showing T cell proliferation properties. Moreover, HTLV-1 infection may precipitate adult T cell leukemia/lymphoma (ATLL) and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) [2, 3].

HIV and HTLV share similar routes of transmission, including parenteral and vertical [3]. Therefore, their co-infection is possible in patients with mutual risk factors [5]. Also, both HTLV and HIV target T lymphocytes, and this phenomenon increases the importance of their co-infection [6]. Some studies found higher CD4+ counts in PLWH co-infected with HTLV-1 rationalized by HTLV-1 T cell proliferative features [7, 8], but others found no significantly different CD4+ counts [9, 10]. Previous studies also produced conflicting results regarding the effects of HIV/HTLV-1 co-infection on progression to acquired immunodeficiency syndrome (AIDS) [11]. Various authors suggested faster progression to AIDS co-infected individuals, while others declared the opposite [6, 12]. Isache *et al.* [13] found a poorer responses to antiretroviral treatments and worse outcomes in a case report of PLWH co-infected with HTLV-1. Therefore, it seems that HTLV-1 might induce important adverse outcomes in PLWH, but studies are reporting conflicting results [1].

All the afore-mentioned features emphasize the importance of identifying HIV/HTLV-1 co-infection and its effects on PLWH. Hence, in the present study, we aimed to investigate the prevalence of this co-infection, routes of transmission, and patients' CD4+ counts.

Material and methods

For this cross-sectional survey, 184 patients were recruited from the Counseling Center for Behavioral Diseases of Imam Khomeini Hospital in Tehran between January and June, 2021. This center has the highest records of HIV-positive patients in Iran, and serves as the main referral center for these cases. Patients were eligible for the study if they were over the age of 18 years and diagnosed with HIV seropositive status. The study was approved by the Research Ethics Committee of Tehran University of Medical Sciences (approval number: IR.TUMS.VCR.REC.1398.845), and all included individuals signed written informed consent to participate in the study. To ensure participants' confidentiality, all information were collected and tagged with proper identification codes. Data were gathered using a standard researcher-made questionnaire consisting of demographic status and history of any current illness and medication.

Measures and instruments

Samples were collected in vacuum tubes and analyzed for HTLV-1 virus with ELISA according to instructions provided by the kit's manufacturer (DiaPro®, Milan, Italy). Suspicious samples were tested with real-time PCR. Additionally, CD4+ count was determined through flow cytometry using a standard protocol and defined as cells/mm^3.

Statistical analysis

The investigated variables included age, gender, transmission modes, duration of diagnosis, antiviral medication, CD4+ count, and viral load. Data analysis was performed using SPSS version 26 presented as mean ± SD or, if indicated, as an absolute number and percentage.

Results

The study included 113 males and 71 females (61.4% and 38.6%, respectively), with the mean age of 40.12 years. The participants were diagnosed on average about 78 months (6 years) ago. Time elapsed since date of diagnosis of the participants in months is shown in the histogram chart in Figure 1.

The findings of this study showed that 104 (56.5%) participants became infected through sex with the opposite sex, and 41 (22.3%) through injecting drug use. The method of infection transmission was reported in 17 participants as unknown (Figure 2).

Furthermore, 177 participants reported using antiviral therapies to combat their illness (Table 1). The types of antiviral treatment are shown in Table 2.

The results of this study showed that the lowest CD4+ level among the participants was 131 cells/µl, and the mean CD4+ count of the individuals was 669.22 cells/µl (SD = 284.2). In addition, the lowest viral load was 42 copies/ml, and

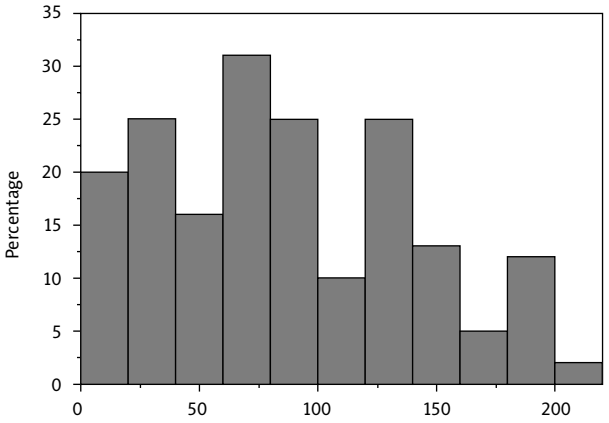

Figure 1. Time elapsed since date of diagnosis in months

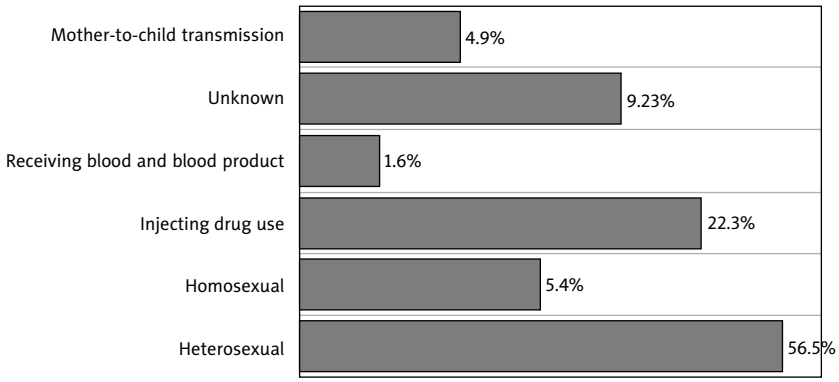

Figure 2. Transmission modes

the highest was 1,093,186 copies/ml. Moreover, the average number of viruses was 145,456 copies/ml, with a SD of 5,685 copies/ml. HTLV-1 was measured first by ELISA test in all samples and then with PCR test in suspicious cases, which was negative for all the participants in the study.

Discussion

Given that in HIV-1 patients, the HTLV-1 co-infection results in a rapid progression to AIDS and an increased risk of adult T cell lymphoma/leukemia, it is necessary to investigate the rate of this co-infection, especially in endemic regions [3]. The HTLV-1 virus is a member of a retrovirus family, which includes HIV, and both share similar transmission routes [3]. Due to comparable epidemiology, co-infection of these two viruses is common [14]. In the present study, out of 184 HIV-positive patients from Tehran in various age groups, none displayed simultaneous HTLV-1 infection using ELISA screening (0%). This outcome might stem from the fact that HTLV-1 infection is infrequent in the general population of Iran (0.02%) [15]. In previous studies, the prevalence of HTLV-1 infection showed discrepancies, ranging from 0% to 17.2% [14, 16-23]. Based on the present results and those of previous studies, HTLV-1 infection is rare in HIV-infected patients in Tehran, Iran.

The prevalence of co-infection differs depending on the region and group of individuals. Iran is one of the endemic regions of HTLV-1 [24]. Mashhad, the capital of Razavi Khorasan Province, with a 3% of prevalence in the general population is considered HTLV-1 endemic region [25]. The main routes of HIV transmission are unprotected sex and mother-to-child [26]. In addition, the HTLV-1 virus is mostly transmissible by unprotected sexual intercourse and breastfeeding [27]. In this study, the rates of mother-to-child and sexual intercourse transmissions were 4.9% and 56.5%, respectively. In other words, there was a high probability of co-infection in less than two-thirds of the sample population. Similar to the findings of this research, a study including 339 female sex workers in Brazil reported HIV and HTLV-1 rates of 2.3% and 1.7%, respectively, with no concurrent infections reported [28]. Moreover, Ramezani *et al.* [14] studied 180 HIV-positive individuals in Tehran, and found that all cases and controls were negative for HTLV-1 infection. Because HTLV and HIV have similar transmission and the same tropism for T lymphocytes, their co-infection is more likely to occur than previously thought. One reason for the lack of accurate statistics is that HTLV testing is not routinely performed in HIV clinics.

Evidence showed direct and indirect interactions between HIV and HTLV-1. HIV infection upregulates by virions and proteins of HTLV-1 by activating CD4+ [29]. Results

Table 1. Use of antiviral treatment

Antiviral treatment	*n* (%)
Yes	177 (96.2)
No	7 (3.8)
Total	184 (100.0)

Table 2. Types of antiviral treatment (*n* = 177)

Type of drug used	Atazanavir	Kaletra	Nevirapin	Efavirenz	Cobavir	Lamivudine	Tenofovir	Raltegravir	Truvada	Dolutegravir	Vonavir
n	1	10	5	14	15	6	2	7	50	40	98
%	0.5	5.6	2.8	7.9	8.5	3.4	1.1	3.9	28.2	22.6	55.3

of peripheral blood mono-nuclear cell (PBMC) cultures demonstrated that HIV and HTLV-1 have potential activation effects on each other. In case of co-infection with HIV, antigen production and concentration of HTLV-1 mRNA increase [30]. In addition, replication of HIV through activation of HIV LTR stimulates the tax protein of HTLV-1 [31]. In PLWH, those with HTLV-1 co-infection tend to be in more advanced stages of the infection compared with HIV patients without co-infection [18].

Both HIV and HTLV-1 infections have identical tropism for CD4+ T cells. With this in mind, a considerable interaction between them is expected. Studies are contradictory; some claim that the HTLV-1 co-infection worsens the progression to AIDS, and some do not [32, 33]. In-vitro studies revealed that the HTLV-1 infection can lead HIV to transform from M-tropic to T-tropic virus, which is a representative of progressive HIV disease [34]. Other studies reported that HLTV-1 causes an increase in HIV viral replication in latent reservoirs through vigorous activation of cytokines [29, 35].

The current research has several limitations. In this cross-sectional study, the impact of HTLV-1 infection on HIV and disease progression was not assessed. A longitudinal study with a control group might clarify this entity. Another drawback of this study is that we lost a great population because of a drop in the referral number of patients due to the concurrency of COVID-19 pandemic. Also, HIV patients showed a decreased intention to participate in the study due to the pandemic. Moreover, as there are discrepancies in the prevalence of HTLV-1, enrolling participants from one center only may be another drawback of this study.

Conclusions

In the general population of Iran, the HTLV-1 infection is insignificant among HIV-positive patients. However, due to differences in rates of HTLV-1/HIV co-infection between different populations and its importance, future multi-provincial studies investigating the prevalence and impact of HTLV-1 co-infection on patients with HIV are suggested.

Disclosures

1. Institutional review board statement: The study was approved by the Ethics Committee of Tehran University of Medical Sciences, with approval number: IR.TUMS.VCR.REC.1398.845.
2. Assistance with the article: The authors would like to thank the staff of the counseling center for their help.
3. Financial support and sponsorship: This study was supported by the Tehran University of Medical Sciences (grant No.: 98-02-55-43568).
4. Conflicts of interest: None.

References

1. Shahmohamadi E, SeyedAlinaghi S, Karimi A, Behnezhad F, Mehraeen E, Dadras O. HIV/HTLV-1 co-infection: a systematic review of current evidence. HIV AIDS Rev 2021; 20: 158-165.
2. Beilke MA, Theall KP, O'Brien M, Clayton JL, Benjamin SM, Winsor EL, et al. Clinical outcomes and disease progression among patients coinfected with HIV and human T lymphotropic virus types 1 and 2. Clin Infect Dis 2004; 39: 256-263.
3. Brites C, Sampalo J, Oliveira A. HIV/human T-cell lymphotropic virus coinfection revisited: impact on AIDS progression. AIDS Rev 2009; 11: 8-16.
4. Jahagirdar D, Walters MK, Novotney A, Brewer ED, Frank TD, Carter A, et al. Global, regional, and national sex-specific burden and control of the HIV epidemic, 1990-2019, for 204 countries and territories: the Global Burden of Diseases Study 2019. Lancet HIV 2021; 8: e633-e651. DOI: 10.1016/S2352-3018(21)00152-1.
5. Rosadas C, Menezes MLB, Galvão-Castro B, Assone T, Miranda AE, Aragón MG, et al. Blocking HTLV-1/2 silent transmission in Brazil: current public health policies and proposal for additional strategies. PLoS Negl Trop Dis 2021; 15: e0009717. DOI: 10.1371/journal.pntd.0009717.
6. Brites C, Goyanna F, França LG, Pedroso C, Netto EM, Adriano S, et al. Coinfection by HTLV-I/II is associated with an increased risk of strongyloidiasis and delay in starting antiretroviral therapy for AIDS patients. Braz J Infect Dis 2011; 15: 6-11.
7. Ribeiro ML, Gonçales JP, Morais VMS, Moura L, Coêlho M. HTLV 1/2 Prevalence and risk factors in individuals with HIV/AIDS in Pernambuco, Brazil. Rev Soc Brasileira Med Trop 2019; 52: e20180244. DOI: 10.1590/0037-8682-0244-2018.
8. Richey JD, Chen BJ, Deng AC. Indolent, waxing and waning cutaneous presentation of HTLV-1-associated adult T-cell leukemia/lymphoma in an HIV-1-positive patient. J Cutaneous Pathol 2018; 45: 171-175.
9. Assone T, Kanashiro TM, Baldassin MPM, Paiva A, Haziot ME, Smid J, et al. In vitro basal T-cell proliferation among asymptomatic human T cell leukemia virus type 1 patients co-infected with hepatitis C and/or human immunodeficiency virus type 1. Braz J Infect Dis 2018; 22: 106-112.
10. de Oliveira EH, Oliveira-Filho AB, Souza LA, da Silva LV, Ishak MO, Ishak R, et al. Human T-cell lymphotropic virus in patients infected with HIV-1: molecular epidemiology and risk factors for transmission in Piaui, Northeastern Brazil. Curr HIV Res 2012; 10: 700-707.
11. Bhatt NB, Gudo ES, Semá C, Bila D, Di Mattei P, Augusto O, et al. Loss of correlation between HIV viral load and CD4+ T-cell counts in HIV/HTLV-1 co-infection in treatment naive Mozambican patients. Int J STD AIDS 2009; 20: 863-868.
12. Yazdani R, Dadmanesh M, Ghorban K. First report of the prevalence of human T-lymphotropic virus type 1 (HTLV-1) for hemodialysis patients in Tehran. Arch Clin Infect Dis 2018; 13. DOI: 10.5812/archcid.65512.
13. Isache C, Sands M, Guzman N, Figueroa D. HTLV-1 and HIV-1 coinfection: a case report and review of the literature. IDCases 2016; 4: 53-55.
14. Ramezani A, Aghakhani A, Banifazl M, Boland-Ghamat Z, Foroughi M, Gachkar L, et al. Frequency of human T-Cell lymphotropic virus (HTLV) type 1 and 2 infection in HIV infected patients. Iranian J Pathol 2012; 7: 9-13.
15. Alavi SM, Etemadi A. HIV/HBV, HIV/HCV and HIV/HTLV-1 coinfection among injecting drug user patients hospitalized at the infectious disease ward of a training hospital in Iran. Pak J Med Sci 2007; 23: 510-513.
16. Phillips I, Hyams K, Wignall F, Moran A, Gotuzzo E, Sanchez J, et al. HTLV-I coinfection in a HIV-1-infected Peruvian population. J Acquir Immune Defic Syndr 1991; 4: 301-302.
17. Mehraeen E, Oliaei S, SeyedAlinaghi S, Karimi A, Mirzapour P, Afsahi AM, et al. COVID-19 in pediatrics: the current knowledge and practice. Infect Disord Drug Targets 2022; 22: e290921196908. DOI: 10.2174/1871526521666210929121705.
18. Schechter M, Moulton LH, Harrison LH. HIV viral load and CD4+ lymphocyte counts in subjects coinfected with HTLV-I and HIV-1. J Acquir Immune Defic Syndr Hum Retrovirol 1997; 15: 308-311.

19. Sobesky M, Couppie P, Pradinaud R, Godard MC, Alvarez F, Benoît B, et al. Coinfection with HIV and HTLV-I infection and survival in AIDS stage. French Guiana Study. GECVIG (Clinical HIV Study Group in Guiana). Presse Med 2000; 29: 413-416.
20. SeyedAlinaghi S, Karimi A, MohsseniPour M, Barzegary A, Mirghaderi SP, Fakhfouri A, et al. The clinical outcomes of COVID-19 in HIV-positive patients: a systematic review of current evidence. Immun Inflamm Dis 2021; 9: 1160-1185.
21. Gudo ES, Bhatt NB, Bila DR, Abreu CM, Tanuri A, Savino W, et al. Co-infection by human immunodeficiency virus type 1 (HIV-1) and human T cell leukemia virus type 1 (HTLV-1): does immune activation lead to a faster progression to AIDS? BMC Infect Dis 2009; 9: 211. DOI: 10.1186/1471-2334-9-211.
22. Oliaei S, SeyedAlinaghi S, Mehrtak M, Karimi A, Noori T, Mirzapour P, et al. The effects of hyperbaric oxygen therapy (HBOT) on coronavirus disease-2019 (COVID-19): a systematic review. Eur J Med Res 2021; 26: 96. DOI: 10.1186/s40001-021-00570-2.
23. Bessinger R, Beilke M, Kissinger P, Jarrott C, Tabak OF. Retroviral coinfections at a New Orleans HIV outpatient clinic. J Acquir Immune Defic Syndr Hum Retrovirol 1997; 14: 67-71.
24. Araujo A, Sheehy N, Takahashi H, Hall W. Concomitant infections with human immunodeficiency virus type 1 and human T-lymphotropic virus types 1 and 2. In: Brogden KA, Guthmiller JM (eds.). Polymicrobial Diseases. Washington (DC): ASM Press; 2002.
25. Mansouri Torshizi M, Khalighi AR, Fadavi Islam M, Aram R, Sabouri E, Khalilifar H, et al. Effect of human T-cell lymphotrophic virus type 1 (HTLV-1) in seropositive infertile women on intracytoplasmic sperm injection (ICSI) outcome. Iran J Reprod Med 2014; 12: 15-18.
26. Kassa GM. Mother-to-child transmission of HIV infection and its associated factors in Ethiopia: a systematic review and meta-analysis. BMC Infect Dis 2018; 18: 216. DOI: 10.1186/s12879-018-3126-5.
27. Gessain A, Cassar O. Epidemiological aspects and world distribution of HTLV-1 infection. Front Microbiol 2012; 3: 388. DOI: 10.3389/fmicb.2012.00388.
28. de Souza Lopes R, Serejo Pereira MV, Macedo da Silva R, de Luna Sales JB, Lima Gardunho DC, Cortinhas Monteiro J, et al. Molecular epidemiology of HIV-1 and HTLV-1/2 among female sex workers in four cities in the state of Para, Northern Brazil. Front Microbiol 2020; 11: 602664. DOI: 10.3389/fmicb.2020.602664.
29. Moriuchi H, Moriuchi M. In vitro induction of HIV-1 replication in resting CD4(+) T cells derived from individuals with undetectable plasma viremia upon stimulation with human T-cell leukemia virus type I. Virology 2000; 278: 514-519.
30. Beilke MA, Japa S, Vinson DG. HTLV-I and HTLV-II virus expression increase with HIV-1 coinfection. J Acquir Immune Defic Syndr Hum Retrovirol 1998; 17: 391-397.
31. Böhnlein E, Siekevitz M, Ballard DW, Lowenthal JW, Rimsky L, Bogérd H, et al. Stimulation of the human immunodeficiency virus type 1 enhancer by the human T-cell leukemia virus type I tax gene product involves the action of inducible cellular proteins. J Virol 1989; 63: 1578-1586.
32. Brites C, Sampalo J, Oliveira A. HIV/human T-cell lymphotropic virus coinfection revisited: impact on AIDS progression. AIDS Rev 2008; 11: 8-16.
33. Casoli C, Pilotti E, Bertazzoni U. Molecular and cellular interactions of HIV-1/HTLV coinfection and impact on AIDS progression. AIDS Rev 2007; 9: 140-149.
34. Moriuchi H, Moriuchi M, Fauci AS. Factors secreted by human T lymphotropic virus type I (HTLV-I)-infected cells can enhance or inhibit replication of HIV-1 in HTLV-I-uninfected cells: implications for in vivo coinfection with HTLV-I and HIV-1. J Exp Med 1998; 187: 1689-1697.
35. Leung K, Nabel GJ. HTLV-1 transactivator induces interleukin-2 receptor expression through an NF-κB-like factor. Nature 1988; 333: 776-778.