CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

Mortality Causes of HIV-positive Patients: Evaluation of 31 Cases in Turkey

HIV Pozitif Kişilerde Mortalite Nedenleri: Türkiye'den 31 Olgunun Değerlendirilmesi

🆔 Sabri Atalay[1], 🆔 Hazal Albayrak Uçak[2]

[1]University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, İzmir, Turkey
[2]Ankara City Hospital, Clinic of Infectious Diseases, Ankara, Turkey

Cite as: Atalay S, Albayrak Uçak H. Mortality Causes of HIV-Positive Patients: Evaluation of 31 Cases in Turkey. J Tepecik Educ Res Hosp 2022;32(3):350-6

Abstract

Objective: The current study determines the causes of mortality in cases of human immunodeficiency virus/ acquired immunodeficiency syndrome (HIV/AIDS) in a developing country where there is no difficulty in accessing antiretroviral therapy and to determine the measures that can be taken to reduce mortality.

Methods: The study was conducted between 2003 and 2018. Patient data were extracted from patient files until 2007 and, after that date, from patient files and hospital information software. The cause of mortality was determined based on the patients' complaints at admission, clinical, radiological, microbiological, and pathological findings. The causes of mortality were studied in three groups as "HIV-related", "HIV-associated" and "other."

Results: The study enrolled 31 (10.8%) cases resulting in mortality from 287 patients followed up in our outpatient clinic. The average age of the cases was 47 (25-68) years and 27 (90%) of them were men. The cause of death of most of our patients was opportunistic infections, notably disseminated tuberculosis. Among the malignancies, AIDS-defining ones such as lymphoma and Kaposi's sarcoma were identified as the most common causes of death.

Conclusion: Deaths were most frequently caused by "HIV-related" causes such as AIDS-related opportunistic infection and AIDS-defining malignancies. For an early diagnosis of HIV/AIDS, more efforts should be made to screen risk groups and keep diagnosed patients in follow-up and treatment.

Keywords: HIV, acquired immunodeficiency syndrome, mortality, opportunistic infections, neoplasms

Öz

Amaç: Çalışmamızın amacı, antiretroviral tedaviye erişimde zorluk yaşanmayan gelişmekte olan bir ülkede insan immün yetmezlik virüsü/edinilmiş immün yetmezlik sendromu (HIV/AIDS) olgularında ölüm nedenlerini belirlemek ve mortaliteyi azaltmak için alınabilecek önlemleri belirlemektir.

Yöntem: Çalışma 2003-2018 yılları arasında gerçekleştirilmiştir. Hasta verileri 2007 yılına kadar hasta dosyalarından ve bu tarihten sonra hasta dosyalarından ve hastane bilgi yazılım sisteminden alınmıştır. Mortalite nedeni, hastaların başvuru şikayetleri, klinik, radyolojik, mikrobiyolojik ve patolojik bulgulara göre belirlenmiştir. Ölüm nedenleri "HIV ile ilişkili", "HIV ile ilişkili" ve "diğer" olmak üzere üç grupta incelenmiştir.

Bulgular: Çalışmaya polikliniğimizde takip edilen toplam 287 hastadan ölümle sonuçlanan 31 (%10,8) olgu alınmıştır. Olguların yaş ortalaması 47 (25-68) yıl olup, bunların 27'si (%90) erkekti. Hastalarımızın çoğunun ölüm nedeni fırsatçı enfeksiyonlar, özellikle dissemine tüberkülozdu. Maligniteler arasında lenfoma ve Kaposi sarkomu gibi AIDS'yi tanımlayanlar en sık ölüm nedenleri olarak belirlenmiştir.

Öz

Sonuç: Ölüme en sık AIDS ile ilişkili fırsatçı enfeksiyon ve AIDS'yi tanımlayan maligniteler gibi "HIV ile ilişkili" nedenler neden olmuştur. HIV/AIDS'nin erken teşhisi için risk gruplarının taranması ve tanı konulan hastaların takip ve tedavide tutulması için daha fazla çaba gösterilmelidir.

Anahtar Kelimeler: HIV, edinilmiş immün yetmezlik sendromu, mortalite, fırsatçı enfeksiyonlar, neoplazmlar

Introduction

Since the onset of the human immunodeficiency virus/ acquired immunodeficiency syndrome (HIV/AIDS) epidemic, a total of 84.2 million people have been infected and 40.1 million people have died. The actual number of deaths due to AIDS is the lowest ever recorded. More than three-quarters (85%) people living with HIV know their HIV status, and 28.7 million people are on antiretroviral therapy (ART). Thus, HIV-related deaths among HIV-positive people decreased from 1.9 million in 2004 to 650,000 in 2021[1]. As for the rates in the various regions, there was a decrease of 38% in Eastern and Southern Africa, 24% in Asia and Pacific countries, Western Europe and North America, 18% in Latin America and the Caribbean, and 10% in West and Central Africa. However, an increase of 22% was detected in Central Asia, Eastern Europe, North Africa, and the Middle East countries[2]. Significant progress has been made on ARTs recently. Thanks to the single tablet regimens, the treatment has been simplified, and medicines with different mechanisms of action and fewer side effects have been introduced. Thus, the incidence of opportunistic infections has reduced and the quality of life of individuals living with HIV has improved. Especially in developed countries, the causes of death among HIV-positive people are shifting from AIDS-related causes [tuberculosis (TB), cryptococcal meningitis, cerebral toxoplasmosis, etc.] to non-AIDS-related causes (sepsis, cardiovasculary diseases, non-AIDS-defining cancers, etc.). This observation has been attributed to the prolongation of life and improved quality of life with ART[3]. Turkey is a developing country and has a young population of over 80 million people. According to the data of the Turkish Public Health Agency, Department of Infectious Diseases, Sexually Transmitted Infections Unit: Although our country represents a low-endemic area, a notable increase in the number of individuals living with HIV has occurred recently, 30,293 cases reported in 1985 and 31th December 2021 and 18.8% of the cases were women[4]. In our country, patients diagnosed with HIV/AIDS are covered under general health insurance, and patients have no difficulty accessing and using ART. Therefore, causes of death can be expected to be similar to those in developed countries, but to our knowledge, studies on this subject are limited. In our country, data on the causes of mortality in HIV-positive patients are based on cohort studies. Our study aims to determine the causes of mortality in cases of HIV/AIDS in a developing country where there is no difficulty in accessing ART and to determine the measures that can be taken to reduce mortality.

Materials and Methods

The study was conducted out in patients followed up for confirmed HIV infection at the University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital between 2003 and 2018. Patient data were extracted from patient files until 2007 and, after that date, from patient files and hospital information software.

This study included cases resulting in mortality during this period. The cause of mortality was determined based on patients' complaints at admission, clinical, radiological, microbiological, and pathological findings; postmortem biopsy has not been performed. The causes of mortality were studied in three groups as "HIV-related," "HIV-associated" and "other." In the "HIV-related death" group, the primary cause of mortality is included in the list of AIDS-defining diseases, also called stage 4 by the World Health Organization (WHO). The "HIV-associated death" group included causes of mortality related to HIV but not included in the stage 4 group of WHO. Causes of death that could not be directly attributed to either of the above groups were included in the "other" group. "HIV-related" deaths are subdivided into opportunistic infections and AIDS-defining malignancies, whereas "HIV-associated" deaths are subdivided into other non-opportunistic infections, non-AIDS-defining malignancies, and chronic diseases. Parameters of demographics such as age, gender, duration of follow-up, treatment status, CD4 and viral load values, chronic diseases, recreational substance use and presence of depression of patients were also examined. Some data could not be obtained due to non-compliance with the follow-up and were evaluated on the basis of a lower number of patients. Ethics committee approval was obtained from University of Health Sciences

Turkey, İzmir Tepecik Education and Research Hospital Ethics Commitee (decision no: 2019/8-3 date: 08.05.2019).

Statistical Analysis

Descriptive statistics are given as numbers and percentages for categorical variables, and as mean and (minimum-maximum) values for continuous variables.

Results

The study enrolled 31 (10.8%) cases resulting in mortality from 287 patients followed up in our outpatient clinic. The average age of the cases was 47 (25-68) years and 27 (90%) of them were men. Based on WHO staging at the time of admission, 27 (87%) patients were at stage 4, three at stage 3, and 1 case was at stage 1. Fifteen (48.3%) patients were diagnosed late, and AIDS was diagnosed at the time of diagnosis. The duration of diagnosis and follow-up of other patients were 1-5 years in 7 cases, 6-10 years in 5 cases, and longer than 10 years in 4 cases. None of these patients were fully compliant with follow-up and treatment. The mean CD4 count of 23 patients whose records were available was 241 (11-976) cells/mm^3. Count was below 200 in 14 (45.1%) cases. The viral load of these patients was more than 100,000 copies/mL in 9 cases, while values were <50 copies/mL in only 3 cases. Twenty patients were smoking, 20 were using alcohol, and drug use was reported in 9 cases, whereas 17 cases were diagnosed with depression. The causes of mortality were identified as "HIV-related" in 30 cases, "HIV-associated" in 9 cases, and "other" in one case. More than one cause was detected in the "HIV-related" group due to the coexistence of opportunistic infections and/or malignancies suspected to cause mortality. The cause of death of most of our patients was opportunistic infections, notably disseminated TB. Among the malignancies, AIDS-defining ones such as lymphoma and Kaposi's sarcoma were identified as the most common causes of death. The causes of mortality are listed in Table 1.

Discussion

The data from the study show that "HIV-related" causes such as opportunistic infections and HIV-defining malignancies are still the most common causes of mortality in patients followed up in our hospital. This is in contradiction with the variations observed in the causes of mortality in developed countries. Whereas, in some studies, it was found that deaths due to non-HIV causes increased, and these deaths were often associated with substance abuse, hepatic, cardiovascular,

pulmonary, or non-AIDS-defining cancers[5,6]. Similarly, in a study evaluating 640 cases of mortality out of 1759, 28.9% were attributed to non-HIV-related causes, among which cancers and liver diseases were found to be the most common causes[7]. The most significant reason for this is that, in other developing countries, the patients in our study were admitted to the hospital at an advanced stage following an opportunistic infection and/or malignancy and were diagnosed late[8]. Studies conducted in our country reported mortality rates of 8.3 to 27.6%. In a study by Ozdemir et al.[9] involving 144 patients, the median CD4 + T-lymphocyte count was 214 cells/microliter and 52.1% of them were presenting AIDS. In the study, the mortality rate was reported as 31.2%, but without a reason was given. The high mortality was explained by the late diagnosis of patients and the inclusion of patients to the study before 2000, when treatment options were more limited. In a study by Erbay et al.[10] involving 70 patients, it was detected that 28.5% of the patients died, most of them at the time of first admission, and their CD4 counts were lower than those who survived. Of 9 cases diagnosed with TB, 5 have died. Other opportunistic infections reported were P. jiroveci pneumonia and oral candidiasis. In their study with 255 patients, Çerçi et al.[11] reported a mortality rate of 11.4% that was lower than that of other studies. Concerning the causes of death of 29 patients who have died, 11 patients died of septic shock, 2 patients with pneumonia, 1 patient of acute kidney failure, 1 patient of acute liver failure, 1 patient with tumor lysis syndrome and 1 patient of non-vehicle traffic accident, while the cause of death of 13 patients could not be determined.

In the study by Oliveira et al.[12], late diagnosis was associated with high mortality, and one-year survival following an AIDS-related diagnosis at the time of admission was reported as 48%. In their study conducted in Bangladesh, Shahrin et al.[13] detected that a CD4 + T-lymphocyte count of <200 cells/mm^3 was an independent risk factor for mortality. In the same study, they found that the patients who were hospitalized within the first 6 months of HIV diagnosis died more often, which was attributed to the diagnosis at an advanced stage. It is therefore necessary to develop screening programs for risk groups and to extend free-of-charge test centers for an earlier diagnosis of HIV. Besides, patients who were diagnosed early and started ART were also found to be non-compliant with follow-up and treatment. This was considered related to most patients being men, smoking, use of alcohol and narcotic drugs, and depression being present in more than half of the patients.

Table 1. Causes of mortality in patients			
Cause of mortality (number/%)			
HIV-related 21 (67.7%)	Opportunistic infection 17 (54.8%)		P. jiroveci pneumonia 5 (16%)
			Cerebral toxoplasmosis 3 (9.6%)
			Tuberculosis (TB) 7 (22.5%) Pulmonary and Extrapulmonary TB (4) Pulmonary TB (3) Meningitis (2), peritonitis (1), Meningitis and psoas abscess (1)
			Cryptococcal meningitis 2 (6.4%)
	AIDS-defining malignancy 13 (41.9%)		Lymphoma 7 (22.5%)
			Kaposi's sarcoma 6 (19.3%)
			Multiple myeloma 1 (3.2%)
HIV-associated 9 (29%)	Non-AIDS-defining malignancy 3 (9.6%)		Gastric signet ring cell lymphoma Prostate carcinoma Glioma
	Chronic disease 2 (6.4%)		Heart failure
			Cerebrovascular disease
	Other infection 4 (12.9%)		Bacterial pneumonia 4 (12.9%)
Other 1 (%3.2)	Traffic accident 1 (3.2%)		
HIV: Human immunodeficiency virus, AIDS: Acquired immunodeficiency syndrome			

It is well-established that ART reduces HIV-related morbidity and mortality. However, the patient must comply with the treatment and follow-up to achieve this. Various studies demonstrated that the patients were lost to follow-up, admitted at an advanced stage, and that these cases progressed with high mortality. In a study conducted in Tanzania, 18% of the patients were lost to follow-up 12 months after starting ART and 36% after 36 months[14]. In another review, the average rate of follow-up in Africa was 60% (46-85%) after 2 years. Missing or wrong phone number or address, switching to another treatment schedule, financial problems, deterioration, or improvement in health status were the most common reasons for being lost to follow-up. Social stigma and drug side effects have been reported less frequently[15].

Patient-related factors such as late diagnosis and admission at advanced-stage, as well as health-related factors are involved in the death of HIV-positive patients due to opportunistic infections and/or HIV-defining malignancies. Health professionals other than Infectious Specialists treating Diseases are still nervous about treating HIV-positive patients. This causes failure in interventional diagnosis and treatment procedures such as lymph node biopsy, stereotactic brain biopsy, bronchoalveolar lavage, and delays in the specific treatment of patients. In our study, opportunistic infections, which are included the "HIV-related" causes, were detected as the most common possible cause of mortality with a rate of 54.8%. TB is an endemic infection in our country and is mainly disseminated and extrapulmonary TB has emerged as the most common possible cause of mortality. This was followed by pneumocystis pneumonia (PCP), cerebral toxoplasmosis and cryptococcal meningitis. Similarly, in a study conducted in Ghana, disseminated TB, pulmonary TB and TB meningitis were detected as the most common causes of death[3]. In a study conducted in Nigeria, TB was reported as the most common cause of admission and 33.6% of deaths, and approximately half of the these were diagnosed with extra-pulmonary TB[16]. In a study conducted in Burkina Faso, TB was again the leading cause of mortality alongside with HIV resorption syndrome and anemia[17]. In our country, the current picture is similar to that in African countries. To prevent TB-related deaths, more efforts are necessary to meticulously investigate latent and active TB in every patient diagnosed with HIV, and to treat positive cases. Recently, with the health policies implemented under the name of "transformation in health", family medicine and performance system were initiated, and while many

TB dispensaries are being closed, experienced physicians working in these units have started to work in other units for financial reasons. This was considered to negatively affect TB infections in our country[18]. In our study, one of the opportunistic infections, which are the most probable cause of mortality in patients, was PCP. In our hospital, the diagnosis of PCP is often based on clinical complaints of patients and radiological imaging methods. Unfortunately, $(1{\rightarrow}3)$-β-D-glucan test, which is a sensitive and specific test in the diagnosis of PCP, and bronchoalveolar lavage is not available. This might have led to a delay in the diagnosis, albeit partially. In many other developing countries, PCP remains one of the major causes of mortality despite the availability of prophylaxis and treatment[13,19,20]. This stresses the need to keep a low threshold value to diagnose PCP and start treatment early, especially in HIV-positive people with low CD4 count who need to be hospitalized, where diagnostic means are limited. Among the "HIV-related" causes, AIDS-defining malignancies (lymphoma and Kaposi's sarcoma) were detected as the most common causes of mortality. In a study conducted in Bangladesh, the presence of malignancy in patients was associated with mortality, and AIDS-defining malignancies were most frequent. Developing surveillance programs for HIV-positive or non-AIDS-defining malignancies is essential for early diagnosis and treatment[13]. In other studies conducted in our country, malignancies were often associated with mortality. A publication reporting a mortality rate of 27.6% from the Cappadocia region reported that patients died within 6 months of diagnosis, 6 patients died of opportunistic infections and 1 of adenocarcinoma. Disseminated candida infection and military TB, carcinoma and pneumonia were identified in 3 cases whose postmortem biopsy results were available. In that study, the mortality rate was 78.6% (11/14) in the patients admitted between 1992 and 1999, compared with 11.4% (5/44) among those admitted between 2000 and 2009[21].

Study Limitations

Our study has some limitations. Although the prevalence is increasing rapidly in our country, the number of HIV-positive patients is relatively low. The number of patients evaluated was also low because the study is conducted in a single center. Because of the retrospective design of the study, the cause of mortality in patients was classified according to the most likely cause. We believe that the results of our study are significant in terms of providing a local insight into the data from our country.

Conclusion

Our study showed that the patients who progressed with mortality were often at advanced stage and admitted late to the hospital or were not complying with follow-up and treatment. Most patients had substance abuse and depression. Deaths were most frequently caused by "HIV-related" causes such as AIDS-related opportunistic infection and AIDS-defining malignancies. For an early diagnosis of HIV/AIDS, more efforts should be made to screen risk groups and keep diagnosed patients in follow-up and treatment.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital Ethics Commitee (decision no: 2019/8-3 date: 08.05.2019).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.A., H.A.U., Concept: S.A., H.A.U., Design: S.A., H.A.U., Data Collection or Processing: S.A., H.A.U., Analysis or Interpretation: S.A., H.A.U., Literature Search: S.A., H.A.U., Writing: S.A., H.A.U.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. UNAIDS. Fact sheet - Latest global and regional statistics on the status of the AIDS epidemic. https://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf. [Accessed:: 01.09.2022].

2. Guimarães MDC, Carneiro M, Abreu DMX, França EB. HIV/AIDS Mortality in Brazil, 2000-2015: Are there reasons for concern? Rev Bras Epidemiol 2017;20(Suppl 1):182-90.

3. Lartey M, Asante-Quashie A, Essel A, Kenu E, Ganu V, Neequaye A. Causes of Death in Hospitalized HIV Patients in the Early Anti-Retroviral Therapy Era. Ghana Med J 2015;49:7-11.

4. T.C. Sağlık Bakanlığı Halk Sağlığı Genel Müdürlüğü Bulaşıcı Hastalıklar ve Erken Uyarı Dairesi Başkanlığı HIV-AIDS İstatistik [Online] Website: https://hsgm.saglik.gov.tr/tr/bulasici-hastaliklar/hiv-aids/hiv-aids-liste/hiv-aids-istatislik [Accessed: 01/09/2022]. (In Turkish)

5. Sackoff JE, Hanna DB, Pfeiffer MR, Torian LV. Causes of Death among Persons with AIDS in the Era of Highly Active Antiretroviral Therapy: New York City. Ann Intern Med 2006;145:397-406.

6. Palella FJ Jr, Baker RK, Moorman AC, et. al. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. J Acquir Immune Defic Syndr 2006;43:27-34.

7. Novoa AM, de Olalla PG, Clos R, Orcau A, Rodríguez-Sanz M, Caylà JA. Increase in the non-HIV-related deaths among AIDS cases in the HAART era. Curr HIV Res 2008;6:77-81.

8. Bekker LG, Egger M, Wood R. Early antiretroviral therapy mortality in resource-limited settings: what can we do about it? Curr Opin HIV AIDS 2007;2:346-51.

9. Ozdemir B, Yetkin MA, Bastug A, et al. Evaluation of epidemiological, clinical, and laboratory features and mortality of 144 HIV/AIDS cases in Turkey. HIV Clin Trials 2018;19:69-74.

10. Erbay A, Kayaaslan B, Akıncı E, et al. Evaluation of Epidemiological, Clinical and Laboratory Features of HIV/AIDS Cases. Flora 2009;14:36-42

11. Çerçi P, İnkaya AÇ, Alp Ş, Tümer A, Ünal S. Evaluation of 255 HIV/AIDS cases: Hacettepe cohort, Ankara, Turkey. Mikrobiyol Bul 2016;50:94-103.

12. Oliveira MT, Latorre Mdo R, Greco DB. The impact of late diagnosis on the survival of patients following their first AIDS-related hospitalization in Belo Horizonte, Brazil. AIDS Care 2012;24:635-41.

13. Shahrin L, Leung DT, Matin N, et al. Characteristics and predictors of death among hospitalized HIV-infected patients in a low HIV prevalence country: Bangladesh. PLoS One 2014;9:e113095.

14. Somi G, Keogh SC, Todd J, et al. Low mortality risk but high loss to follow-up among patients in the Tanzanian national HIV care and treatment programme. Trop Med Int Health 2012;17:497-506.

15. Brinkhof MWG, Pujades-Rodriguez M, Egger M. Mortality of Patients Lost to Follow-Up in Antiretroviral Treatment Programmes in Resource-Limited Settings: Systematic Review and Meta-Analysis. PLoS One 2009;4:e5790.

16. Agaba PA, Digin E, Makai R, et al. Clinical characteristics and predictors of mortality in hospitalized HIV-infected Nigerians. J Infect Dev Ctries 2011;5:377-82.

17. Kouanda S, Meda IB, Nikiema L, et al. Determinants and causes of mortality in HIV-infected patients receiving antiretroviral therapy in Burkina Faso: a five-year retrospective cohort study. AIDS Care 2012;24:478-90.

18. Türk Tabibpleri Birliği. Verem kayıt dışına çıktı. 07.04.2011. Available at: http://www.ttb.org.tr/975yea7.

19. Schneider M, Zwahlen M, Egger M. Natural history and mortality in HIV-positive individuals living in resource-poor settings: A literature review UNAIDS Obligation HQ/03/463871. http://data.unaids.org/pub/periodical/2004/egger_unaids_hq_03_463871_2007_en.pdf. [Accessed: 21.05.2019].

20. Holmes CB, Losina E, Walensky RP, Yazdanpanah Y, Freedberg KA. Review of Human Immunodeficiency Virus Type 1-Related Opportunistic Infections in Sub-Saharan Africa. Clin Infect Dis 2003;36:652-62.

21. Alp E, Bozkurt I, Doğanay M. Epidemiological and clinical characteristics of HIV/AIDS patients followed-up in Cappadocia region: 18 years experience. Mikrobiyol Bul 2011;45:125-36.