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Evaluation of factors affecting survival of HIV/AIDS patients using Cox and extended Cox models

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Abstract

Introduction: Acquired immune deficiency syndrome (AIDS) is a global viral disease that is increasing in populations with high-risk behaviors. Identifying factors prolonging survival of human immunodeficiency virus (HIV)-positive patients is imperative, and retrospective cohort studies with survival analysis approach are most applicable in research. The present study aims to determine an assessment of survival of HIV/AIDS-positive patients and its' related factors.

Material and methods: The present retrospective cohort study was conducted based on medical records of HIV-positive patients visiting Behavioral Diseases Counseling Centers in Kermanshah during 1996-2018. Cox and extended Cox regression models were applied for univariate and multivariate analyses. Data were analyzed using STATA-14.

Results: The likelihood of one-, five-, and ten-year survival from the time of HIV diagnosis until AIDS stage was found as 0.87, 0.69, and 0.54, respectively, and the likelihood of one-, five-, and ten-year survival until AIDS-related death was estimated as 0.75, 0.44, and 0.21, respectively. The risk of disease progression to AIDS was greater in women and in patients with tuberculosis comorbidity. Receiving antiretroviral therapy reduced the risk of AIDS-related death by 3.9 times.

Conclusions: The main correctable factors affecting the survival of HIV/AIDS patients include early diagnosis, adherence to treatment, and receiving periodic services.

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Key words: HIV, AIDS, survival, tuberculosis.

Introduction

Human immunodeficiency virus (HIV) is one of the biggest personal and social challenges of the modern times [1]. This virus proliferates body's immune cells and gradually impairs he body's defense system, and is therefore referred to as human immunodeficiency virus and its' resultant disease as acquired immune deficiency syndrome (AIDS) [2]. White blood cells (CD4) are reduced in patients with AIDS, making them predisposed to the development of opportunistic infections [3].

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Although people have been warned about HIV and AIDS for almost forty years, this disease has claimed millions of lives so far, and millions of people are annually affected with HIV worldwide [1].

As opposed to the rest of the world, new HIV patients and HIV-related deaths increased by 31% and 64% in the Eastern Mediterranean region in 2018 compared to 2010 [4]. Modeling results revealed that almost ten thousand new cases of HIV occur in Iran every year [5], but the rate recorded in the National Comprehensive Electronic Data Management System in 2018 shows a much lower figure of around 2,132 cases [6].

According to the World Health Organization's report at the end of 2018, 71 million people had developed AIDS since the beginning of the HIV epidemic, 39 millions of whom have died, and the same report revealed that 37.9 million people worldwide, 360 thousand people in the Eastern Mediterranean region, and 66 thousand people in Iran are infected with HIV [7]. HIV is a hidden epidemic in the Middle East and North Africa, and approximately two-thirds of new infections occur in Iran, Sudan, and Egypt, respectively [8].

The bitter and obvious fact is that, despite persistent planning, 1.7 million people still developed HIV in 2018 around the world. Despite scientific advances and tremendous efforts, there is no effective vaccine for preventing HIV infection [9].

Early initiation of antiretroviral therapy (ART) despite small white blood cell (CD4) counts, nutritional support, and careful monitoring of patients right after the initiation of ART, are a huge contribution towards improving patient survival [10]. The risk of transmitting HIV to a sexual partner through unprotected sex is zero in people who have received ART in full, and in whom suppression of viral load in the blood is complete and stable [11]. Life expectancy in AIDS patients, who have continuously received ART is longer by ten years compared to those who have not received medications [12].

Survival analysis can be used to predict the prognosis of AIDS and to evaluate the treatment. Domestic studies have reported one-year survival of HIV-positive patients as 89% [13], while foreign studies have reported one-year survival of HIV-positives as 95% in women and 90% in men [14].

Given the changing pattern of the disease transmission in recent years and the increasing rates of AIDS infection through sexual contacts in Kermanshah [2] as well as the changes in the management of HIV/AIDS treatment, (without accounting for the CD4+ count and clinical signs), and since there are only a few studies on the survival rates of these patients in Iran, the present study was conducted in Kermanshah to determine the rate of survival of HIV/AIDS patients and the factors affecting the rate.

Material and methods

The present retrospective cohort study was conducted based on a data recording system using data available in the Behavioral Diseases Counseling Center of Kermanshah Province from 1996 to 2018. All HIV patients' data, irrespective of age, gender, disease stage, diagnosis date, and symptoms, were included in the present study by census sampling. Data were extracted from HIV-positive patients center, including age at first visit, gender, HIV transmission route (injection drug use, sex, mother-to-child transmission, and unknown routes), tuberculosis comorbidity, HIV stage at diagnosis (asymptomatic, symptomatic, and unknown), HIV diagnosis date, disease-free period in HIV-infected people, date of HIV progression to AIDS, date of death (if applicable), cause of death (if known), and date of initiation of antiretroviral therapy (ART). Missing patients who were excluded from follow-up, those who died for causes other than AIDS, and those who survived until the end of the study were taken as censored cases. Informed consent was obtained from patients when their medical file was created. Patients were assured about confidentiality of information, and that their names would not be mentioned in the research. Therefore, based on summarized checklist, information was collected from patients' files without mentioning their names. The study obtained an ethics code No. IR.KUMS.REC.1397.257, from the Kermanshah University of Medical Sciences. In Figure 1, individuals enrolled into the study and excluded cases based on exclusion of criteria are shown. Inclusion criteria were being 18 years of age or older, HIV-infected, and having a health record. Exclusion criteria were HIV-positive individuals living outside of Kermanshah Province, duplicate records, and lack of sufficient information about HIV/AIDS infection based on diagnostic guidelines of the Ministry of Health.

Statistical analysis

Chi-square test was used to assess the relationship of nominal and ordinal qualitative variables. Tables and graphs of longevity and probability of AIDS progression and AIDS-related death at one-year intervals were drawn in general and according to gender. Mean and median

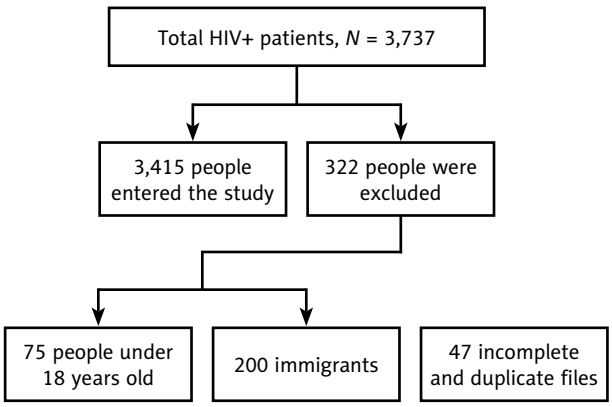

Figure 1. Total number of individuals who entered the study, and amount of those excluded based on exclusion criteria

time of survival were determined in terms of each variable. Using Kaplan-Meier curve, patients' survival curve was according to study variables in intended outcomes (from HIV diagnosis time to AIDS stage, and from AIDS stage to AIDS-related death), and was compared among subgroups using log-rank test. Given that there is no definitive cure for AIDS, it is important to know which factors affect long-term survival of patients with AIDS. One of the most suitable methods to investigate the simultaneous effect of variables on patients' survival time is Cox proportional hazards regression models. In this model, there are no assumptions about the distribution of basic risk function. The amount of hazard for one person has a fixed and specific ratio to the amount of hazard for another person; hence, the model is called proportional hazards. One of the necessary assumptions to use non-parametric Cox regression model is to establish proportional hazard (PH) assumption in each of the covariates. Therefore, the risk ratio for the two categories of explanatory variables does not depend on time. Other assumptions, distribution of occurring time of events and censorship, are independent, which means the probability of incident occurring for a person who is excluded from the study for any reason is equal to the probability of incident occurring for a person who remains in the study until the end. This is called 'uninformed censorship', and the relative risk for different categories of the variable under study is constant over time (for variables that do not change over time).

In the present study, Schoenfeld residual test, log-log survival plot against time, and goodness-of-fit test were applied to assess PH assumption. Extended Cox model is also a good method to determine independent predictors of mortality and to calculate hazard ratios even when PH assumption for some variables is not met. Therefore, multiple extended Cox model was used to verify the net effect of each variable separately on survival time after diagnosis of AIDS. Significance level was set at $p < 0.05$. Data were analyzed using STATA version 14, and significance level was set at 0.05 for all the tests.

Results

Of the 3,415 patients studied, 1,362 were in the HIV-positive (HIV-positive/AIDS-negative) phase, 1,786 in the HIV-positive/AIDS-positive phase, and 267 in the unknown (HIV-positive/AIDS) phase. In general, 2,984 patients (87.38%) were males and 431 (12.62%) were females. The participants' mean age was 33.69 ± 0.15 years, including 40.77% in the younger than 30 years age group, 40.89% in the 31-40 years age group, and 18.33% in the over 40 years age group. A total of 64.54% of the patients had primary school/junior high school education, 21.27% had high school diploma and higher qualifications, 14.19% were illiterate, and 15.6% had unknown education levels. A total of 42.84% of the patients were single, 28.52% were married, 24.22% were divorced, and 4.42% were widowed. The survival median (year) and 5-year survival probability for 1,786 patients in the HIV-positive/AIDS-positive phase are presented in Figure 2.

The likelihood of the patients' survival after one year from the time of HIV diagnosis to the AIDS stage was found as 0.87. Table 1 presents the likelihood of survival of the HIV/AIDS patients by the studied outcomes using Kaplan-Meier test.

A total of 56.54% of the patients had been infected through injection drug use, 16.57% through multiple routes (more than one high-risk behavior for developing HIV), and 13.24% through sexual contact. A total of 996 patients (29.17%) had received ART. Table 2 addresses the behavioral and clinical characteristics of HIV-positive patients by disease stage.

The assessment of proportional hazards assumption using graphic methods and Schoenfeld residuals for each variable revealed that the proportion of hazard remains

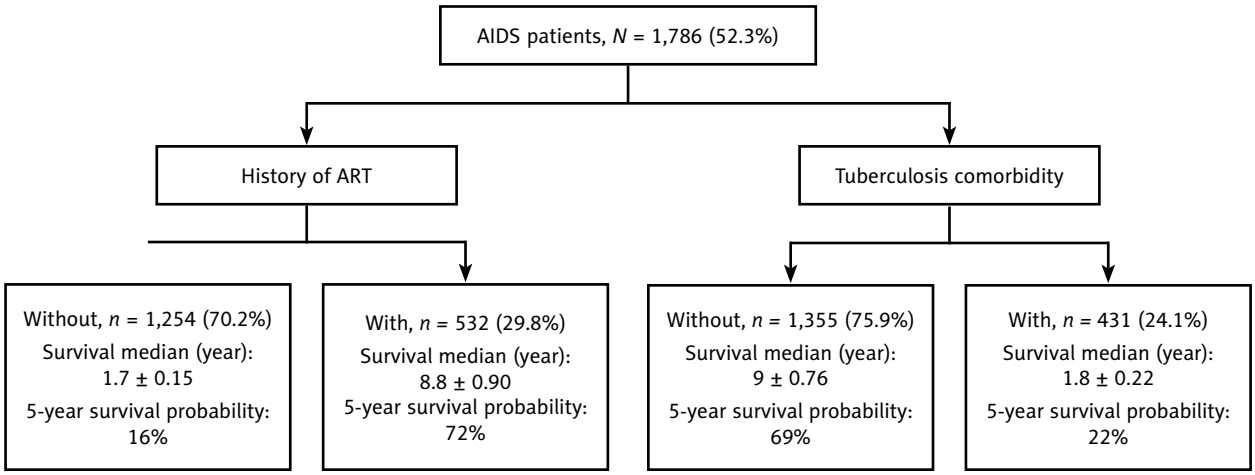

Figure 2. Median of survival and likelihood of five-year survival in terms of clinical variables in the studied outcome (from the beginning of AIDS stage until its' resultant death)

Table 1. Survival of HIV/AIDS patients by the studied outcomes

Interval	Probability of patient survival from diagnosis to AIDS stage	Probability of patient survival from AIDS stage to AIDS-related death	Probability of patient survival from HIV diagnosis to HIV-related death
One year	87% (85-88%)	75% (72-77%)	88% (87-89%)
Five years	70% (68-71%)	44% (41-47%)	64% (62-65%)
Ten years	54% (52-56%)	21% (17-25%)	41% (38-43%)

Table 2. Behavioral and clinical characteristics of the studied HIV patients by AIDS development, non-development, and unknown status

Variable	AIDS-negative, *n* (%)	AIDS-positive, *n* (%)	AIDS, *n* (%)*
TB comorbidity			
With	0 (0.00)	431 (100.00)	0 (0.00)
Without	285 (22.44)	968 (76.22)	17 (1.34)
Unknown	1,077 (62.83)	387 (22.58)	250 (14.59)
Antiretroviral therapy			
With	387 (39.00)	532 (53.30)	77 (7.70)
Without	975 (40.30)	1,254 (51.80)	190 (7.90)
Initial CD4+ (cells/mm^3)			
0-200	250 (39.40)	332 (52.30)	52 (8.30)
201-350	195 (41.10)	244 (51.50)	35 (7.40)
351-500	149 (42.00)	178 (49.30)	31 (8.70)
> 500	229 (37.70)	336 (55.50)	41 (6.80)
Disease transmission route			
Injection drug use	771 (39.93)	981 (50.80)	179 (9.27)
Sex	143 (31.64)	298 (65.93)	11 (2.43)
Mother-to-child	14 (28.00)	36 (72.00)	0 (0.00)
Multiple routes	263 (46.47)	267 (47.17)	36 (6.36)
Unknown	29 (31.87)	61 (67.03)	1 (1.10)
Other	142 (43.69)	143 (44.00)	40 (12.31)

**First measured CD4+ counts or CD4+ counts at initiation of treatment*

constant over time in all the assessed variables but ART. Cox and extended Cox regression models were used for the univariate and multivariate analyses. Table 3 demonstrates the distinct effect of each predictor variable on the hazard proportion of AIDS-related death using proportional hazard Cox and extended Cox models. According to the univariate analysis, the risk of AIDS-related death was significantly higher in men than in women, but this difference was not significant in the multivariate analysis. A significant relationship was observed between AIDS-related death and aging. Moreover, single people were found to die of AIDS sooner than married people. Also, a high school diploma and higher education reduced the risk of AIDS-related death significantly. Compared to the injection route, patients with unknown transmission routes were found to be at a lower risk of AIDS-related death. Receiving medical intervention (ART) reduced the risk of AIDS-related death significantly (Table 3).

Discussion

The present study was conducted to determine the survival and its' factors in HIV/AIDS patients. The participants' mean age was 33.69 ± 0.15 years, similar to mean age of patients in a study conducted in Tehran [15]. The USA CDC reported that the highest transmission rate is found in people aged 13-29 years old [16}. Such a high transmission rate from young people to others is mainly due to high prevalence of injection drug use and unprotected sexual relations among young people as well as their unawareness of the infection. As a result, health policy-makers should focus on and offer training programs on prevention methods for this age group. In the current study, the highest rate was found

Table 3. The effect of predictor variable on crude and extended hazard proportions of disease progression from entering the AIDS stage to AIDS-related death using Cox regression and extended Cox regression models

Variable	Frequency	Crude proportional hazard (95% CI)	*p*-value	Adjusted proportional hazard (95% CI)	*p*-value
Gender					
Female	285	1.0	< 0.001	1.0	0.47
Male	1,501	2.26 (1.75-2.91%)		0.77 (0.39-1.53%)	
Age group (year)					
0-30	715	1.0		1.0	
31-40	744	1.1 (0.95-1.25%)	0.179	1.11 (0.85-1.44%)	0.415
41-79	323	1.5 (1.25-1.75%)	< 0.001	1.70 (1.2-2.39%)	0.003
Marital status					
Single	779	1.0		1.0	
Married	539	0.65 (0.55-0.77%)	< 0.001	0.64 (0.47-0.87%)	0.005
Divorced	359	0.86 (0.72-1.0%)	0.08	0.81 (0.59-1.1%)	0.183
Widowed	114	0.55 (0.39-0.77%)	< 0.001	3.03 (1.92-4.74%)	< 0.001
Education					
High school diploma or higher	183	1.0		1.0	
Primary/junior high school	1,106	1.5 (19.22-1.77%)	<0.001	1.5 (1.12-2.03%)	< 0.006
Illiterate	404	2.19 (1.7-2.83%)	< 0.001	3.03 (1.9-4.74%)	< 0.001
Prison history					
No	727	1.0		1.0	
Yes	1,059	1.76 (1.41-2.19%)	< 0.001	1.42 (1.07-1.89%)	0.014
Drug use					
No	456	1.0		1.0	
Yes	1,330	2.9 (2.22-3.75%)	< 0.001	2.58 (1.5-4.44%)	0.001
Disease transmission route					
Injection drug use	981	1.0		1.0	
Sex	298	0.37 (0.28-0.49%)	< 0.001	1.07 (0.596-1.95%)	0.801
Mother-to-child	36	0.37 (0.18-0.74%)	0.005	1.37 (0.44-0.227%)	< 0.001
Multiple routes	267	1.31 (1.11-1.56%)	0.002	1.73 (1.31-2.27%)	0.989
Unknown	61	0.50 (0.29-0.85)	<0.001	0.22 (0.05-0.93%)	0.040
Other	143	0.92 (0.71-1.18%)	0.520	0.79 (0.46-1.4%)	0.431
Antiretroviral therapy*					
With	885	1.0		1.0	
Without	901	3.96 (3.39-4.63%)	< 0.001	1.13 (1.06-1.21%)	< 0.001
TB comorbidity					
No	968	1.0		1.0	
Yes	431	3.6 (3.03-4.27%)	< 0.001	2.95 (2.32-3.73%)	< 0.001

**Time-dependent variable*

in men. Similarly, Karimi *et al.* in Iran reported a much greater rate of infection among males [15]. Also, in the USA, the highest infection rate was reported among men, particularly homosexual men [17]. This high-rate may be due to men's high frequency of injection drug use and shared needle use in Iran. Contrary to the USA, women are more frequently infected in sub-Saharan Africa. Gender inequality, lack of access to services, and sex violence in women are the major causes for this high-rate of infection among women in these regions [18]. The most important transmission route in the present study (in the West of Iran) was injection drug use and shared needles. However, in a study by Karimi *et al.*

(in Tehran), the most important transmission route was sexual intercourse [15].

HIV is mainly transmitted through injection drug use and heterosexual intercourse in three Baltic countries (Lithuania, Latvia, and Estonia), but through homosexual intercourse, particularly among homosexual men, in North America and Western Europe. In the USA, 67% of new HIV cases in 2015 were reported among homosexual men [19]. Awareness of the main transmission routes can greatly contribute to planning for HIV transmission prevention.

According to the present study, 29% of the identified patients had received ART, and 33% of those treated had managed to control their viral load, which is in accordance with the results of a study conducted in India by Mukund Bhaskar [20]. At present, ART is required to be initiated in all adults living with HIV regardless of their clinical stage or CD4+ count [20], and the results are far from the 90-90-90 target [21].

According to Karimi *et al*., about 42% of patients in Tehran received antiretroviral therapy [15]. The difference in the results of this and the present study could be due to injection drug users' negligence of ART and adherence to protocol. Coverage of ART differs across countries and is, for instance, 83% in Western and Central Europe and 43% in the Middle East and North Africa [22]. The low percentage of ART in the current study could lead to adverse consequences. The enormous global success against HIV includes the use of antiretroviral medications to reduce mother-to-child transmission of HIV [23]. Therefore, low percentage of ART use can increase or prevent the reduction in transmission through this route.

In the present study, the cumulative one-, five-, and ten-year HIV/AIDS survival was 88%, 64%, and 41%, respectively. Respective values were reported as 77%, 68%, and 61% in Liuzhoa, China, as reported by Guo [24], showing a higher 10-year survival rate. Melissa Marzan reported a six-year survival rate of 87% [25]. This difference in values could be due to the low antiretroviral therapy coverage in the present study.

The likelihood of one-, five-, and ten-year survival from the time of HIV diagnosis until AIDS stage was 0.87, 0.69, and 0.54, respectively, and the likelihood of one-, five-, and ten-year survival from the time of HIV diagnosis until AIDS-related death was estimated as 0.75, 0.44, and 0.21, respectively, which concurs with the results of some studies [14]. The likelihood of one-, five-, and ten-year survival until AIDS-related death was lower in the present study than that reported by Mirzaei for the entire population of Iran (0.90, 0.74, and 0.55), Hatami in Isfahan (0.96, 0.66, and 0.53), and Leo in China (0.91, 0.86, and 0.79) [26]. This disparity could be due to differences in ART coverage, medical services, prevalence of TB, etc. [27].

Moreover, evaluation of life expectancy in HIV-positive patients in Iran showed a little difference among provinces. The difference between the highest and lowest life expectancy was 18 years [28], which is consistent with the difference in human development index among provinces [29]. Therefore, differences in survival among provinces of Iran, and between Iran and other countries can be explained.

According to the results, the likelihood of five-year survival of disease progression from HIV diagnosis to the development of AIDS was 25% higher in men compared to women. In other words, women in this study had developed AIDS sooner than men. Since HIV is transmitted through a sexual route in 71% of the affected women (84.5% through sex with the spouse, and 15.5% through sex with non-spouse partners), women are likely to have noticed their disease later, which delayed diagnosis and loss of opportunity to reduce harms [30]. About 54% to 70% of individuals infected through the sexual route did not have any knowledge about their HIV infection. Such patients often have a high-risk of death, with little chance of obtaining early medical services [31]. Treatment of patients with late-diagnosed HIV is thus one of the major challenges of physicians [32].

Similar to studies conducted by Kheirandish in Tehran, Hatami in Isfahan, and Abdel Hanan in Bangladesh, the present study showed that the history of sharing needles was significant among the patients with a history of imprisoning. Patients with a prison history had a substantial role in spreading HIV, and sharing needles was the main cause of their infection [3]. In agreement with previous studies, the present study showed that 95.53% of those reporting a history of imprisonment and staying in rehabilitation centers in Kermanshah, had a history of needle sharing.

The present findings showed that the risk of AIDS-related death was significantly higher in patients who had been infected through injection and through more than one high-risk behavior compared to those who had been infected through a sexual route, which concurs with previous findings [33]. According to the results obtained by other researchers, people over the age 50 years are at a greater risk of progression to AIDS and AIDS-related death than younger people [24, 33]. In line with previous studies, the present research also showed that age is a good predictor of the progress of AIDS. In the multivariate analysis, the over-50 age group was 1.8 (range, 1.37-2.4) times more at risk of HIV-related death compared to the younger-than-30 age group. In other words, death occurs 1.8 times sooner in HIV-positive people over the age of 50 compared to HIV-positive people younger than 30 years.

High mortality rates in people with AIDS who have TB comorbidity, even in developed countries with good access to healthcare services and ART, indicate that the active diagnosis of TB in AIDS patients and AIDS in TB patients is an effective measure for reducing mortality [34]. The present study showed that the patients with TB comorbidity were at a significantly higher risk of AIDS progression and AIDS-related death compared to the HIV-positive patients without TB. Previous studies have also shown that the risk of AIDS-related death in patients with TB was significantly higher compared to those without TB, who lived in areas with a low prevalence of HIV and moderate TB burden [33]. Such evidence reveals the importance of prevention and

treatment of TB in HIV-positive patients according to their region of residence and TB burden.

In the present study, a significant relationship was found between a low level of education and an increased risk of AIDS progression and death, which agrees with previous findings [33].

Herein, the lack of ART use was associated with the risk of mortality. Various studies have shown an association of ART with a 54%-92% reduction in mortality among these patients [34].

Limitations

One of the limitations of the present study was its' retrospective cohort design. The accuracy of the recorded information and incompleteness of the files may reduce validity of the results because the quality and accuracy of estimates and associations depend on quality of the recorded data, and we could not verify the accuracy of data, which may cause information bias. Prospective cohort data would be more dependable for survival analysis. Another limitation of the study was that we used the time of HIV diagnosis to estimate the patients' survival rate from the time of diagnosis to the onset of AIDS, which could underestimate the survival rate, because some patients were diagnosed at the end stage of the infection.

Conclusions

In this study, a substantial proportion of the participants developed advanced-stage disease (i.e., AIDS) in the first year. The accumulation of outcome in the first year is due to delayed diagnosis of the disease. The most important factors affecting the survival of HIV/ AIDS patients include the importance of timely diagnosis, early initiation of ART, screening for TB, and periodic measurement of CD4+ in HIV-positive patients. In the past, the majority of HIV/ AIDS patients were men with injecting drug use, but cases of HIV infection through sex, even in people who have not engaged themselves in a high-risk sexual relationship, have been gradually growing. People unaware of their infection unintentionally transmit HIV to their spouses; women can also infect their own newborns and cause an increased spread and incidence of HIV.

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Conflict of interest

The authors report no conflict of interest.

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