

Trend Analysis of HIV/AIDS Burden in Iran: Results from the Global Burden of Disease 2017 Study

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Title: *Trend analysis of HIV/AIDS burden in Iran: results from the Global Burden of Disease 2017 study*

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Abstract

Despite global efforts, HIV/AIDS is still one of the major public health problems in the entire world. In this context, assessing the burden of this disease in different parts of the world is of great importance. In this study, we aimed to investigate the trends of HIV/AIDS incidence and mortality in Iran in the period 1990- 2017.

The HIV/AIDS burden data including age-standardized incidence rate (ASIR) and mortality rate (ASMR) was extracted from the Global Burden of Diseases 2017 study for total Iranian population and by gender from 1990 to 2017. The trend analyses was performed using joinpoint regression modeling approach.

The obtained results showed that in year 2017 the HIV/AIDS ASIR and ASMR were, respectively, more than 12 and 10 times of these rates in year 1990. Also, the estimated average annual percent change (AAPC) was 9.8% and 8.7%, respectively for ASIR and ASMR. In this period of time, women have experienced sharper slope of ASIR and ASMR trends compared to Iranian men.

The increasing trend of HIV/AIDS burden is a serious alarm for the Iranian health policy makers. To achieve the UNAIDS goals, there is an urgent need for an efficient national action plan which breaks the HIV/AIDS taboo in the society, promote access to HIV testing and prevention facilities especially among the key populations and provides care and treatments for all infected people.

Introduction

Acquired Immunodeficiency Syndrome (AIDS) is known as one of the most important health challenges in different parts of the world¹. Although a short time has passed since the first case of Human Immunodeficiency Virus (HIV) infection, the world has faced with an epidemic for which there is no definitive or specific cure yet². AIDS is not limited to a certain geographical region or race, and all social groups, especially the youth, are vulnerable to it³. The overall rate of people living with HIV is rising throughout the world due to extending the Antiretroviral Therapy (ART) coverage, challenging human communities with its health-related, socio-economic, cultural, and political consequences^{1,4}.

Since the outset of this epidemic, 75.7 million people have become infected with HIV, and 32.7 million people have died as a result of AIDS-related diseases. In 2019, there were 38 million people living with HIV/AIDS all over the world, including 1.8 million children less than 14 years. Despite these worrisome statistics about the HIV/AIDS in different parts of the world, there is some good news about reducing the burden of this disease in recent decade. New cases of HIV were 2.8, 2.1 and 1.7 million in years 1998, 2010 and 2019, respectively (a reduction of 40% over two last decades and about 20% reduction over the last decade). In addition, about 700,000 AIDS-related deaths were recorded globally in 2019 comparing with 1.1 million deaths in 2010 (about 36% reduction)⁵.

Depending on the study population, study period and the main outcome under study, the published research in the field of HIV/AIDS burden in Iran have reported different patterns in the trend of incidence, prevalence, mortality and DALY rates. For instance,

a study by Noori et al. showed that the burden of HIV/AIDS has dramatically increased from 1990. This disease was known as the 152nd leading cause of disease burden in 1990, while it was ranked as 37th cause in year 2010⁶. In another study by Moradi et al., they reported non-significant increase in HIV/AIDS incidence and mortality rates in the period 2008-2016⁷. A trend analysis between 1990 and 2015 by Moazen et al. revealed that the HIV/AIDS mortality had a peak in 1995 followed by a steady decline until 2015⁸. A number of studies are also available in the different Iranian key populations which show a downward trend in the HIV/AIDS burden over the last decade⁹⁻¹¹. Regarding these controversial findings, we decided to use the Global Burden of Disease (GBD) data set as one of the most comprehensive and reliable sources in the field of disease burden and apply more advanced statistical approaches to model the trend of HIV/AIDS incidence and mortality rates over the period 1990-2017 in our country, Iran.

Methods

Data Sources

In this research, we extracted the HIV/AIDS incidence and mortality rates from the GBD 2017 study⁸. The GBD estimates and reports the burden of disease indices (including incidence, prevalence, mortality, years of life lost, years lived with disability, and disability-adjusted life years) for a wide range of diseases and injuries by gender and age group for 195 world countries between 1990 and 2017. The GBD data base is an open access source which is freely available for any research-related activities. In the present study, we used the aggregated age- standardized HIV/AIDS incidence and

mortality rates per 100,000 Iranian people for total population and by gender from the GBD data base in the period 1990-2017. Since no personal data was used in this research, informed consent was neither required nor necessary.

Ethical consideration

This research was conducted based on the data from GBD 2017 study which is an open access online data source. The ethical aspects of the present study was approved by the Ethics Committee of the Iran University of Medical Sciences (project code: 99-1-2-18396, Ethics code: IR.IUMS.REC 1399.979).

Statistical analysis

Joinpoint regression modeling is a well-known statistical technique for the analysis of trend data. In this statistical approach, a log-linear Poisson regression is utilized in which the change points are identified using the Monte Carlo permutation test. In order to capture the jump locations (change points) in the trend data, a segmented linear regression model is fitted¹³. More formally, suppose a set of observations $(x_1, y_1), (x_2, y_2), \dots, (x_n, y_n)$, where x_i represents the study time points and y_i indicates the HIV/AIDS incidence or mortality rates. The joinpoint regression model is defined as:

$$y_i = \beta_0 + \beta_1 x_i + \gamma_1 (x_i - \tau_1)^+ + \dots + \gamma_k (x_i - \tau_k)^+ + \varepsilon_i, \quad i = 1, \dots, n$$

where $\tau_k, k = 1, 2, \dots, K$ represents the location of change point, K shows the number of change points, and ε_i indicates the error term of the model. In addition, β_0, β_1 and $\gamma_1, \dots, \gamma_k$ indicate the regression coefficients. Here, the notation $(x_i - \tau_k)^+ = x_i - \tau_k$ if $x_i - \tau_k > 0$, and $(x_i - \tau_k)^+ = 0$ otherwise. In the present study, the regression

coefficients and the number of change points were estimated using the mythology introduced by Kim *et al*¹⁴. To interpret the estimates, some useful indices such as Annual Percent Change (APC) and Average Annual Percent Change (AAPC) can be reported. Clearly, the APC shows the annual percent change of the HIV/AIDS incidence or mortality rates and the AAPC is a summary measure of the trend over a fixed interval (1990-2017). This index enables us to interpret the average APCs over a period of time using a single measure. The joinpoint regression modeling was performed using the Join point Regression Program version 4.8.0.1 (Statistical Research and Applications Branch, National Cancer Institute)¹⁵. P-values less than 0.05 were considered statistically significant.

Results

Table 1 shows the trend of HIV/AIDS age-standardized incidence rate (ASIR) and age-standardized mortality rate (ASMR) in Iranian population by gender for some specific years. In addition, Figure 1 displays these trends for the time period under the study, separately for male, female and total population. Regarding these, one can observe that the HIV/AIDS ASIR has increased from 0.29 in 1990 to 3.58 per 100,000 in 2017. This means that the HIV/AIDS ASIR in 2017 was more than 12 times of this rate in the starting point of the study. Moreover, the HIV/AIDS ASIR in year 2017 was 7.6 and 28.5 times of this rate in year 1990, respectively for male and female populations. Over this period of time, the HIV/AIDS ASMR has increased from 0.09 in 1990 to 0.90 per 100,000 in 2017. Also, it was found that the HIV/AIDS ASMR has increased from 0.14 in 1990 to 1.01 in 2017 for men and from 0.04 in 1990 to 0.77 per 100,000 in 2017 in women. This means that the HIV/AIDS ASMR in 2017 was about 7.2, 19.2 and 10 times of this rate in 1990, respectively in male, female and total Iranian population.

Table 1. Trend of HIV/AIDS ASIR and ASMR in Iranian population by gender

| Index | Gender | Year | | | | | | |
|-------|--------|------|------|------|------|------|------|------|
| | | 1990 | 1995 | 2000 | 2005 | 2010 | 2015 | 2017 |
| ASIR | Male | 0.45 | 0.65 | 1.58 | 1.45 | 2.09 | 2.96 | 3.43 |
| | Female | 0.13 | 0.20 | 0.56 | 0.72 | 1.38 | 2.85 | 3.71 |
| | Both | 0.29 | 0.42 | 1.08 | 1.09 | 1.74 | 2.91 | 3.58 |
| ASMR | Male | 0.14 | 0.23 | 0.39 | 0.68 | 0.80 | 0.96 | 1.01 |
| | Female | 0.04 | 0.07 | 0.13 | 0.26 | 0.36 | 0.62 | 0.77 |
| | Both | 0.09 | 0.15 | 0.26 | 0.47 | 0.58 | 0.79 | 0.90 |

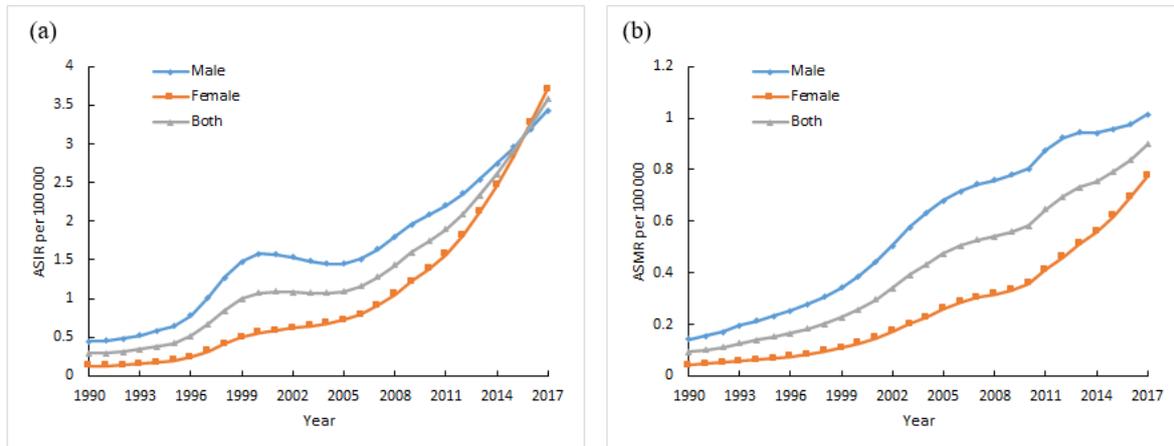


Figure 1. HIV/AIDS ASIR and ASMR trend in Iranian population from 1990 to 2017 (a: ASIR, b: ASMR)

In the next step of data analysis, to capture the observed turning points in ASIR and ASMR trends (Figure 2), we fitted different joinpoint regression models to the data, separately for males, females and total population. The modeling process has led to different turning points and APCs for these trends. Table 2 and Figure 2 show the results of fitting six joinpoints regression models to the HIV/AIDS ASIR and ASMR trends data. The fitted model to the total population ASIR data has resulted in four significant joinpoints in years 1992, 1995, 1999, and 2006, which leads to five periods with different trends. In this context, the obtained results could be interpreted in terms of the estimated APCs and AAPC. The estimated APCs show annual percent change of 3.7, 10.7, 25.3, 1.4 and 10.9 in HIV/AIDS ASIR, respectively in the time intervals of 1990-1992, 1992-1995, 1995-1999, 1999-2006 and 2006-2017. Moreover, the estimated AAPC implies a mean annual rise of 9.8 percent in HIV/AIDS ASIR for total Iranian

population. The interpretation of the estimates based on the fitted models for males and females is quite similar. Here, comparing the estimates for males and females tells us that Iranian women had higher APC values than men in all the determined time intervals with the F/M AAPC ratio of 1.7.

Table 2. Joinpoint regression estimates for HIV/AIDS ASIR and ASMR data in Iranian population from 1990 to 2017

| Segments | Total population | | Males | | Females | |
|----------------|------------------|--------------------|-----------|--------------------|-----------|--------------------|
| | Year | APC (95 % CL) | Year | APC (95 % CL) | Year | APC (95 % CL) |
| ASIR | | | | | | |
| Trend 1 | 1990-1992 | 3.7* (0.5, 7.1) | 1990-1992 | 3.7* (0.2, 7.3) | 1990-1992 | 4.0* (1.1, 7.0) |
| Trend 2 | 1992-1995 | 10.7* (7.3, 14.3) | 1992-1995 | 10.1* (6.4, 13.9) | 1992-1995 | 12.1* (9.0, 15.4) |
| Trend 3 | 1995-1999 | 25.3* (23.3, 27.3) | 1995-1999 | 25.1* (23.0, 27.2) | 1995-1999 | 27.6* (25.8, 29.4) |
| Trend 4 | 1999-2006 | 1.4* (0.9, 1.9) | 1999-2005 | -1.3* (-2.1, -0.6) | 1999-2006 | 6.1* (5.6, 6.6) |
| Trend 5 | 2006-2017 | 10.9* (10.7, 11.2) | 2005-2017 | 7.4* (7.2, 7.6) | 2006-2017 | 15.3* (15.1, 15.5) |
| AAPC | 1990-2017 | 9.8* (9.3, 10.3) | 1990-2017 | 7.8* (7.3, 8.4) | 1990-2017 | 13.3* (12.9, 13.8) |
| ASMR | | | | | | |
| Trend 1 | 1990-1998 | 10.1* (9.4, 10.8) | 1990-1999 | 10.2* (9.6, 10.7) | 1990-1998 | 10.3*(9.9, 10.8) |
| Trend 2 | 1998-2004 | 14.0* (12.5, 15.4) | 1999-2004 | 13.7* (11.9, 15.6) | 1998-2003 | 16.7* (15.4, 18.0) |
| Trend 3 | 2004-2017 | 5.5* (5.2, 5.8) | 2004-2013 | 4.2* (3.6, 4.8) | 2003-2006 | 12.9* (9.0, 17.0) |
| Trend 4 | - | - | 2013-2017 | 1.6 (-0.0, 3.3) | 2006-2009 | 4.5* (0.9, 8.3) |
| Trend 5 | - | - | - | - | 2009-2017 | 11.2* (10.8, 11.6) |
| AAPC | 1990-2017 | 8.7* (8.3, 9.1) | 1990-2017 | 7.5* (7.0, 7.9) | 1990-2017 | 11.4* (10.7, 12.0) |

* Significant at alpha=0.05

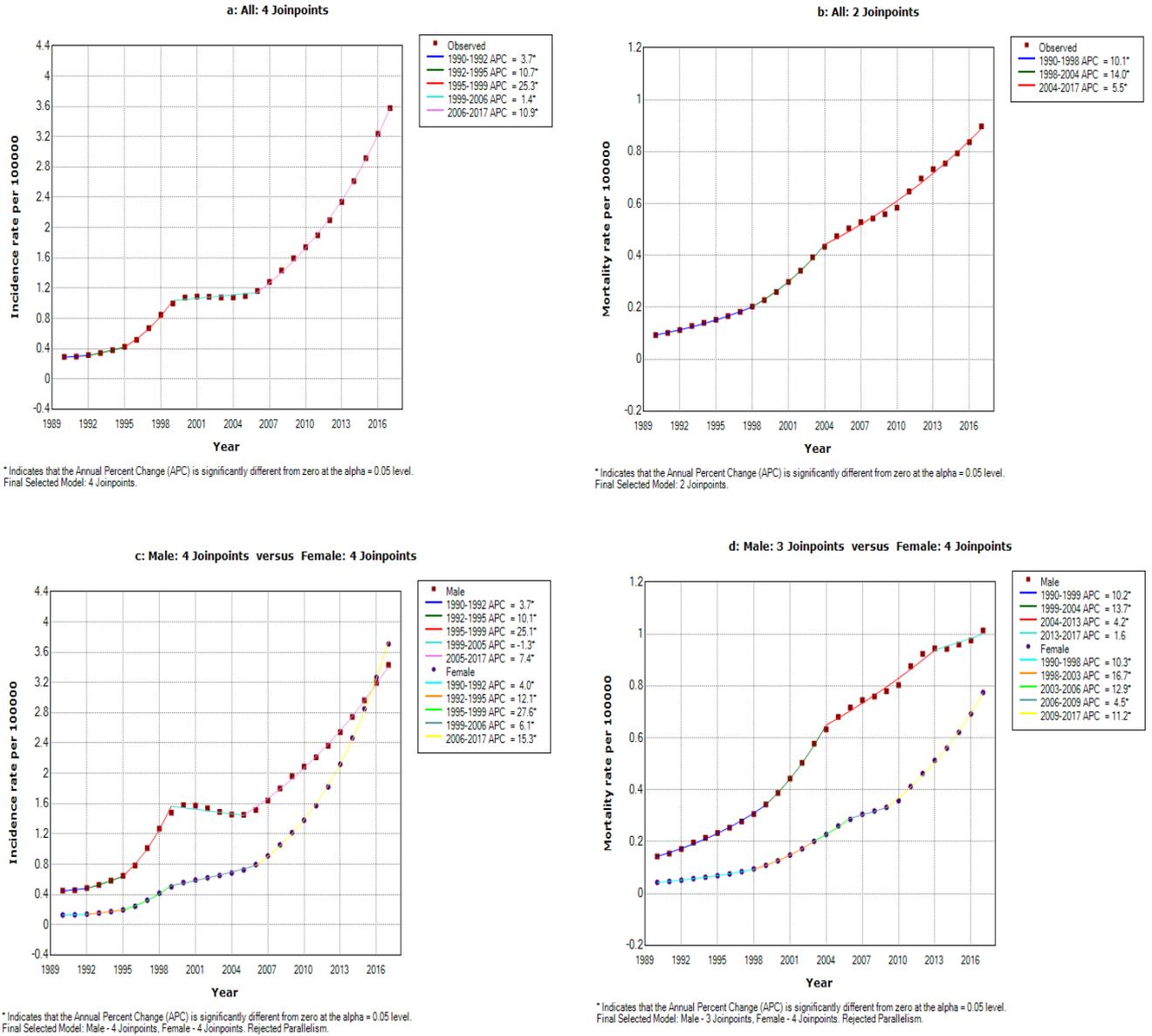


Figure 2. Model-based estimates of HIV/AIDS ASIR and ASMR over 1990-2017 (a: total population ASIR, b: total population ASMR, c: ASIR by gender, d: ASMR by gender)

Based on the fitted model to the total population ASMR data, two significant joinpoints were identified in years 1998 and 2004 which leads to three periods with different trends. The estimated APCs show annual percent change of 10.1, 14.0 and 5.5 in HIV/AIDS ASMR, respectively in the time intervals of 1990-1998, 1998-2004 and

2004-2017. The estimated AAPC suggests a mean annual rise of 8.7 percent in HIV/AIDS ASMR for total Iranian population. The F/M AAPC ratio of 1.5 was also estimated based on the fitted models.

Discussion

In recent years, higher accessibility to HIV preventive and diagnostic services, more efficient treatments and medications and promoting the level of patients' care made HIV/AIDS more manageable and increased the survival rate of the patients dramatically. However, it is still remains as one of the major health problems throughout the world. According to the World Health Organization (WHO), the HIV/AIDS key populations can be defined as males who have sex with males, people who inject drugs, prisoners and people in other closed settings, sex workers and their clients and transgender people¹². These key populations play an important role in the current status of HIV/AIDS burden in our country, Iran. In general, our findings in the present study revealed an ascending trend for incidence and mortality of this disease in Iran over the past three decades. Some of the important reasons for these upward trends in Iranian population are as follow:

First, drug trafficking was a major problem for the Iranian governments in the previous decades because of its geographical location and about 2000 *km* border with the most important opium producer country in the world, i.e. Afghanistan which produces more than 80% of global heroin. Also, Iran has a long common border with Pakistan as one of the major transit countries for illegal drugs in the world. According to some reports,

more than 75% of the produced narcotic drugs in Afghanistan is smuggled through Iran and Pakistan¹⁷. The increasing rate of narcotic addiction, especially through sharing the injection instruments, is the result of the high purity and availability of heroin with a low price in Iran which has led to increasing in the number of drug user prisoners. As a result, the injection of narcotics is the most common route of HIV/AIDS transmission in Iran. However, a considerable reduction in the number of Iranian infected individuals was reported by two different studies among people who inject drugs in the recent years. They suggested that this reduction is a consequence of developing extensive harm reduction programs in Iran^{9, 11}.

Second, AIDS is a taboo in Iran due to religious beliefs and cultural norms, and people with HIV/AIDS are faced with stigma and prejudice. Therefore, people usually hide their disease from others which subsequently leads to an increase in the risk of HIV/AIDS transmission. Hiding diseases due to social stigma will also result in lack of public access to counseling and diagnostic services in high-risk groups. Thus, late detection of HIV will lead to the progression of the disease to AIDS, and increasing the risk of transmission and early mortality^{8, 18}.

Third, regarding the defined key populations by the WHO, males who have sex with males, sex workers and their clients as well as transgender people are three sub-populations who constantly stigmatized by other people, especially by conservative and religious parts of the population. In addition, prostitution and homosexuality are illegal in Iran, and some homosexual activities might be sentenced to death penalty. Consequently, people's fear of disclosure and social stigma motivates them to hide these kinds of activities. As a result, a considerable number of HIV/AIDS patients in these

key populations do not receive preventive, therapeutic, and supportive services, and this increases the risk of infection in population.

Finally, some other reasons may be contributed in increasing trend of HIV/AIDS incidence in Iranian population. Progress in diagnostic techniques, shortage of educational and preventive programs, having unprotected sexual intercourse with the spouse or with others, lack of knowledge, attitude and practice among people who infected with HIV and people's unawareness of their infection with HIV/AIDS (less than 40% Iranian patients are unaware of their infection) are some of these reasons^{19, 20}.

Comparing the changes in the annual incidence of HIV/AIDS tells us that the highest annual percentage change was related to the third period (1995-1999) with APC=25.3 and the fourth period (1999-2006) had the lowest change with APC=1.4. The marked increase in the incidence rate in the third period may be due to the second wave of epidemic which started from 1991 among addicted people to narcotic injection with high risk behaviors like sharing infected syringes and needles. In this period of time, more than 80% of the HIV cases were addicted to drug injection and unfortunately this situation was extended to the prisons^{11, 21}. In the last decade of the previous century, most of activities in HIV monitoring system have been focused on identification of high-risk places such as prisons and places of narcotic use and reporting the detected HIV/AIDS cases in these areas.

In addition, the lowest rate of increase in HIV/AIDS incidence in the fourth period was probably due to the national strategic plan for HIV infection control. In this period of

time, the triangular clinics (to prevent AIDS, drug addiction, and sexually transmitted diseases) was started in Kermanshah Province and expanded to other parts of the country. After establishment of Voluntary Counseling and Testing (VCT) centers in most provinces and cities, the distribution of disposable syringes and needles in prisons and the promotion of educational programs led to more success in reducing infection in injecting drug users and prevented the vast transmission of HIV in the society²². As a result of administration of these programs, the percentage of HIV/AIDS cases among injecting drug users was reduced from more than 80% in 1991 to about 60% in 2013²¹.

Following the considerable reduction in the annual rate of HIV/AIDS incidence over the fourth period, the annual incidence rate had a sharp raise with an APC of 10.9 over the fifth period (2006-2017). This upward trend may be attributed to the third wave of epidemics resulting from unprotected sexual intercourse. The use of amphetamine-type stimulants might be considered as one of the main reasons for increasing rate of unprotected sexual behaviors, especially among the younger individuals in this period of time²².

In the present study, we found that the HIV/AIDS incidence rate in Iranian women was remarkably lower than men, while Iranian women had higher annual percent changes over the study period (the estimated F/M AAPC ratio of 1.7). These findings are in agreement with the obtained results from a study in 2014 that reported a noticeable increase in the trend of identifying new cases among women. According to their reports, the percentage of infection in the newly identified female cases has increased from 4% in 2001 to 22% in 2011^{21, 7}. Women are at risk of HIV/AIDS especially in marital relations. Some studies in Iran have shown that 3/4 of women with HIV/AIDS have

been infected by their spouses²³. Gender inequality and gender-based violence, absence of comprehensive sexual and reproductive health services, illiteracy and lack of knowledge and practice about preventive behaviors are some of possible reasons for the increased women's vulnerability to HIV/AIDS²⁴. In addition, poverty drives some women to prostitution, which increases the risk of HIV/AIDS infection. The growing number of HIV/AIDS cases among women will also increase the risk of contagion between mother and child, as another important transmission route of this disease.

The results of the present study indicated that the mean HIV/AIDS mortality rate has annually increased over the study period by 8.7% for the total population, 7.5% for men, and 11.4% for women. Apparently, the rising number of mortality cases might be attributed to people's lack of awareness of their HIV/AIDS infection and hiding the disease due to social stigma, as well as the inadequate coverage of antiretroviral therapy^{18, 19}.

Regarding the mean annual changes in HIV/AIDS mortality rates, it was found that the highest and lowest changes were related to the second (1998-2004) and third (2004-2017) periods, respectively with APC=14 and APC=5.5. The small increase in HIV/AIDS mortality rate in the last 14 years of the study could be due to improving the awareness about HIV/AIDS among patients and the entire society, promoting the level of patients' care as well as wider use of ART in Iran.

Similar to the findings for the HIV/AIDS incidence, our results showed that the HIV/AIDS mortality in female patients was lower than males over the period 1990-2017. However, female patients have experienced sharper slope of annual increase in

death from HIV/AIDS compared to males (AAPC of 11.4 in women versus AAPC of 7.5 in men).

According to our calculations on GBD 2017 data, the HIV/AIDS mortality in the Middle East and North Africa (MENA) region has a rising trend, with an AAPC of 7%. With an AAPC of 8.7%, Iran stands above the average annual percent change of HIV/AIDS mortality estimated for the MENA countries. According to the Joint United Nations Programme on HIV and AIDS (UNAIDS) reports in 2019, global HIV/AIDS incidence has declined by 23% compared to 2010 and 40% reduction has been observed compared to the peak in 1998. In addition, deaths from HIV/AIDS have decreased by 39% and 60%, respectively from the peak in 2004 and 2010 compared to 2019. Although this decline seems to be a hopeful global message, it is not adequate to achieve the 90-90-90 goals for 2020⁵.

Here, it should be noted that lack of access to local comprehensive and reliable data about burden of HIV/AIDS in Iran is the most important limitation of our work. In addition, the HIV/AIDS burden data sets are highly confidential in our country and the independent researchers have limited access to them. Thus, we used the estimated data by the GBD 2017 study as an international open access source to achieve our goals. Despite this limitation, our work is the first research in analyzing the HIV/AIDS burden over the span of almost three decades in Iran. Using an advanced statistical technique (joinpoint regression model) for analyzing the GBD data could be thought as another strength point of the present study.

Conclusions

In general, our findings indicated that the HIV/AIDS incidence and mortality had a growing trend over the period 1990-2017 in Iran. These findings seem to be worrisome, since the global trend of HIV/AIDS burden had a downward trend from 2010. Poverty, stigma and other social and cultural inequalities play important roles in upward trend of HIV/AIDS in our country. To achieve the 90-90-90 goal of UNAIDS, the Iranian health policymakers should put more efforts on promoting the knowledge of patients and the entire society about this disease and improving the access to prevention and control facilities, especially in the key populations, as well as providing the proper care and treatment for the infected individuals.

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Availability of data and materials: The HIV/AIDS burden data is freely accessible in the GBD compare website (available at <http://ghdx.healthdata.org/gbd-results-tool>). Requests for additional information should be addressed to the corresponding author.

List of Abbreviations

AIDS: Acquired Immunodeficiency Syndrome

HIV: Human Immunodeficiency Virus

GBD: Global Burden of Disease

ASIR: Age-Standardized Incidence Rate

ASMR: Age-Standardized Mortality Rate

APC: Annual Percent Change

AAPC: Average Annual Percent Change

WHO: World Health Organization

ART: Antiretroviral Therapy

VCT: Voluntary Counseling and Testing

MENA: Middle East and North Africa

UNAIDS: Joint United Nations Programme on HIV and AIDS

Figure legends

Figure 1. HIV/AIDS ASIR and ASMR trend in Iranian population from 1990 to 2017 (a: ASIR, b: ASMR)

Figure 2. Model-based estimates of HIV/AIDS ASIR and ASMR over 1990-2017 (a: total population ASIR, b: total population ASMR, c: ASIR by gender, d: ASMR by gender)

Figures

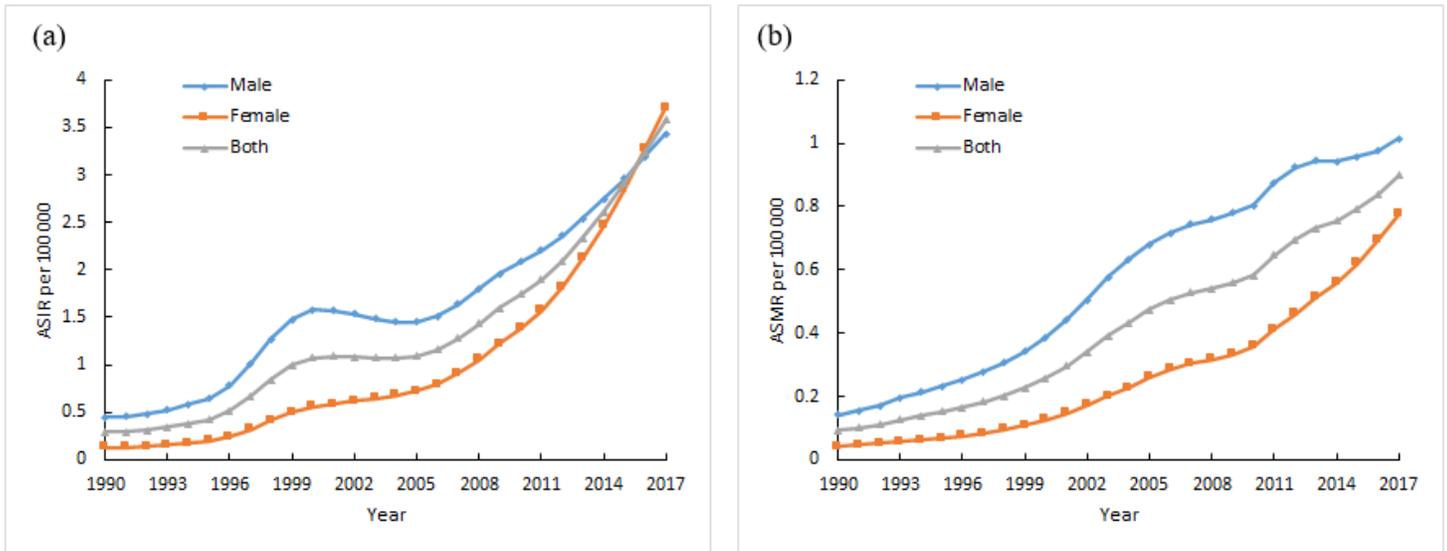
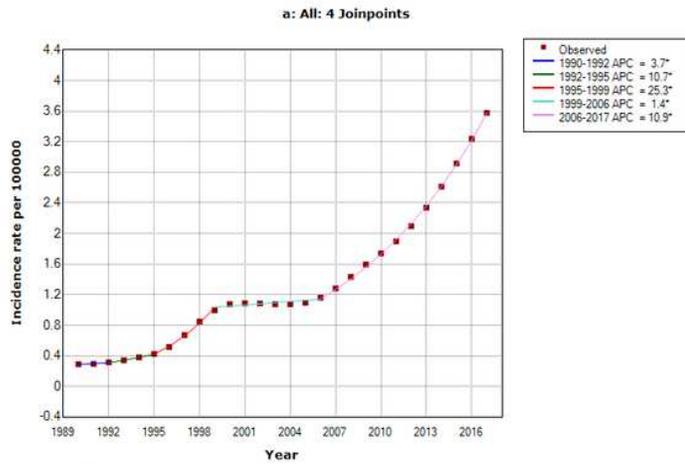
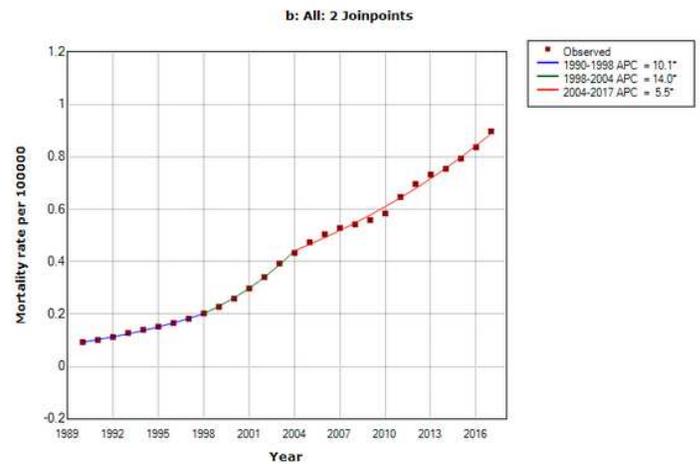


Figure 1

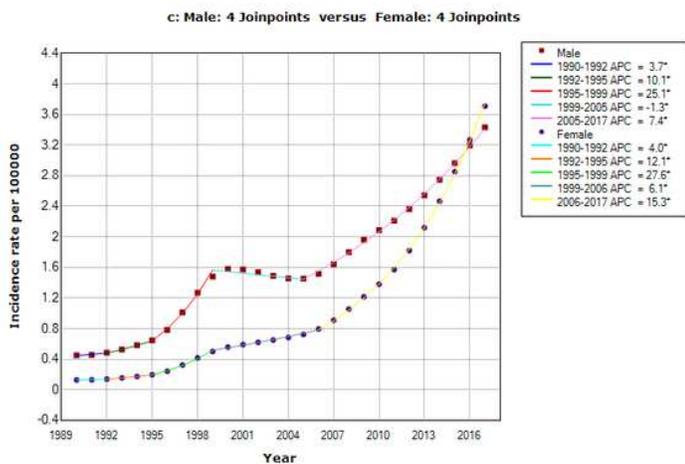
HIV/AIDS ASIR and ASMR trend in Iranian population from 1990 to 2017 (a: ASIR, b: ASMR)



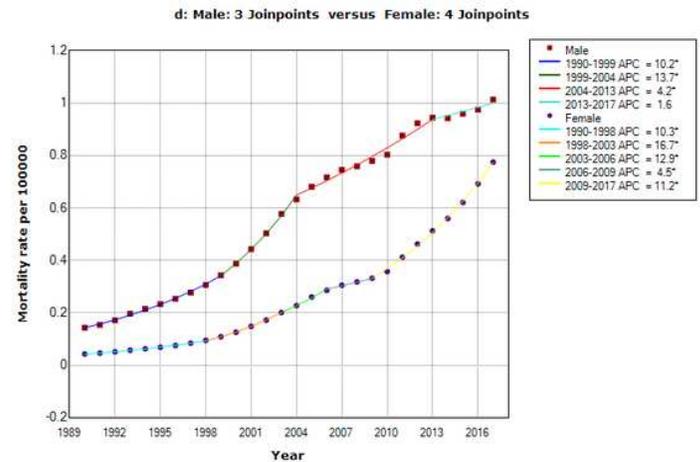
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level. Final Selected Model: 4 Joinpoints.



* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level. Final Selected Model: 2 Joinpoints.



* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level. Final Selected Model: Male - 4 Joinpoints, Female - 4 Joinpoints. Rejected Parallelism.



* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level. Final Selected Model: Male - 3 Joinpoints, Female - 4 Joinpoints. Rejected Parallelism.

Figure 2

Model-based estimates of HIV/AIDS ASIR and ASMR over 1990-2017 (a: total population ASIR, b: total population ASMR, c: ASIR by gender, d: ASMR by gender)