Shift to older ages of HIV/AIDS deaths and its gender difference: inference derived from Vital Statistics of Japan

Hiroshi Yoshikura

Received: January 7, 2019. Accepted: March 29, 2019
Published online: April 26, 2019
DOI:10.7883/yoken.JJID.2019.005
Shift to older ages of HIV/AIDS deaths and its gender difference: inference derived from Vital Statistics of Japan
Hiroshi Yoshikura*
National Institute of Infectious Diseases

*Corresponding author
Postal address: Policy Planning and Communication Division, Department of Environmental Health and Food Safety, Ministry of Health Labour and Welfare, 1-2-2, Kasumigaseki, Chiyoda-ku, Tokyo 100-8916
Telephone number:03-3503-1111
FAX number 03-3503-7965
Mail Address:Yoshikura-hiroshi@mhlw.go.jp; Yoshikura@nih.go.jp
Running head: HIV/AIDS and aging
Keywords: HIV/AIDS; aging; death; thymic involution; gender difference

Summary
Death of HIV/AIDS patients <54 years old declined from 1995 to 2000; from 2000 on, however, the deaths of the HIV/AIDS patients >55 years old started increasing. Though deaths directly linked to infections declined since 2005, those related to malignancy, encephalopathy, interstitial pneumonia, wasting syndrome, etc. persisted. For all of HIV/AIDS (mainly males), ATL, CJD and general population, age of death shifted to older ages by 5 years in 10 years from 1999-2004 to 2010-2017. Among them, only HIV/AIDS patients and general population exhibited unequivocal gender difference. As of 2011-2016, the median of the deaths of the HIV/AIDS patients was 52.5 years for males and 70 years for females, while the median of the deaths of the general population was 75 years for males and 85 years for females. Male HIV/AIDS patients died 22.5 years earlier and female HIV/AIDS patients 15 years earlier than the general population. A common denominator of HIV/AIDS deaths and the deaths among the general population could be CD4+ T cells. CD4+ T cells were primary targets of HIV infection and decline of naive CD4+ T cells was a hallmark of aging.

Introduction
We previously reported that the median of the ages of HIV/AIDS deaths was 40-44 years in 1995-1998 and 50-54 years in 2014-2016; survival time of the HIV/AIDS patients became longer by 10 years in twenty odd years. Importantly, however, the life span of the Japanese population too became longer by 10 years (1), which raised a question whether the shift of the HIV/AIDS deaths toward the older ages by 10 years was due to the anti-retroviral therapy (ART) or not.

In order to answer the question, we examined the ages of the deaths caused by other diseases, adult T cell leukemia (ATL) and Creutzfeldt-Jakob disease (CJD). These two diseases were chosen because the timing of infection or diagnosis was relatively uniform. ATL was caused by HTL-1 mostly transmitted maternally (2, 3) and 5-10% of the virus carriers developed ATL (https://www.niid.go.jp/niid/ja/kansennohanashi/326-atl.html); CJD was a prion disease (4), mostly sporadic (77% in 2017) in Japan, and patients died within a year after diagnosis (http://www.jichi.ac.jp/dph/prion/cjdrresult11.pdf). We then examined direct causes of deaths of HIV/AIDS patients from 1999
to 2017. These studies led us to observation that death of HIV/AIDS patients and that of the general population shared a common feature, which was gender effect.

Materials and Methods

The data on deaths of the general population, HIV/AIDS, ATL patients and CJD patients were derived from Vital Statistics (Vital, Health and Social Statistics Office, MHLW, https://www.mhlw.go.jp/toukei/list/81-1.html). The data on notification of HIV/AIDS patients were derived from the report of AIDS Surveillance Committee, MHLW. In the above statistics, the age distribution was represented by 5-year interval age groups. In this article, for simplifying calculations, the age groups were represented by their median of the ages, for example, 12.5 years for age group 10-15 years.

Results

Geo-demography of HIV/AIDS, ATL and CJD: Prefectures were numbered from North to South (Fig. 1D). In Figs. 1A1, 1B1 and 1C1, prefecture number (PN) is plotted in the x-axis and the number of the deaths per prefecture in 1999-2004 (open circles) and in 2011-2017 (closed circles) in the y-axis. Plot pattern of HIV/AIDS (Fig. 1A1), ATL (Fig. 1B1) and CJD (Fig. 1C1) remained almost unchanged between 1999-2004 and 2011-2017.

In Figs. 1A2, 1B2 and 1C2, population sizes of prefectures (x1,000) in 2010 are plotted in the x-axis and the total number of patients in prefectures in 1999-2016 for HIV/AIDS and in 1999-2017 for ATL and CJD in the y-axis.

For HIV/AIDS (Fig. 1A2), the slope of the approximation line was 1.34 (R²=0.756), indicating that the number of patients per prefecture was proportional to the population size to the power of 1.34. In Fig. 1A3, plotted are number of inflow population in different age groups in the y-axis against population size in the x-axis; the slopes were 1.10, 1.21, 1.21, 1.21 1.16 and 1.16 for immigrants aged, 15-19, 20-24, 25-29, 30-34, 35-39 and 40-44 years, respectively; the slope was steepest, 1.2, for sexually most active age group 20-34 years. Possibility of sexual contacts among immigrant population being taken into account, the slope 1.2 was not far from the slope of HIV/AIDS deaths 1.34.

For ATL which was originally found as a disease endemic to Kyushu and other Southern prefectures (3, 4) (Fig. 1B2), there was no correlation between the number of the patients and the population size (R²=0.186); its incidence was highest in Kyushu area (PNs 40-47), Tokyo area (PNs 12-14), Aichi prefecture (PN 23) and Osaka prefecture (PN 27).

For CJD (open circles in Fig. 1C2), the slope was 0.81 (R²=0.81). The approximation line ran in parallel to the plot of the population >65 years (open triangles in Fig. 1C2), which was expected from its high prevalence among elderlies (4).

Age distribution of deaths in general population, ATL and CJD: In Figs. 2A1, 2B1 and 2C1 plotted are cumulative percentage (percentiles) of deaths against age, which were derived from plots of the number of the deaths in different age groups (Fig. 2A2, 2B2 and 2C2). It was found: (i) the median of the ages of the deaths of the general population shifted to older age by 5 years both for males and females; the median of
the ages of deaths for males was 70 years in 1999-2000 and 75 years in 2011-2017; that for females was 80 years in 1999-2000 and 85 years in 2011-2017. Thus, in the general population, the median of the ages of the deaths of females was 10 years older than that of males; (ii) the median of the ages of the deaths of male ATL patients was 65 years in 1999-2004 and 70 years in 2010-2017, while that for female ATL patients was 67.5 years in 1999-2000 and 72.5 years in 2011-2017, (iii) the median of the ages of the deaths of male CJD patients was 65 years in 1999-2003 and 70 years in 2011-2017, while that for female CJD patients was 67.5 in 1999-2004 and 72.5 in 2011-2017. Both for ATL and CJD, the ages of the deaths of the female patients was 2.5 years higher than those of males; it was far smaller than 10 years observed for general population and HIV/AIDS (see below). [Note: the median of the deaths of the population is a parameter different from the average age of the population, which was 76 and 82 years respectively for males and females in 1995 and 81 years and 87 years respectively in 2017: see Ministry of Health Labour and Welfare’s Abridged Life Table 2017 (https://www.mhlw.go.jp/toukei/saikin/hw/life/life17/df/life17-15.pdf) and Definitions of Several Functions Used in the Life Table (https://www.mhlw.go.jp/toukei/saikin/hw/life/life09/sankou01.html).]

In Fig. 3, plotted are the annual number of the deaths in different ages for general population, ATL patients and CJD patients. In all these three groups, annual deaths of the oldest age groups (>80 years for general population and ATL patients; >70 years for CJD patients) increased lineally from 1999 on; the deaths of the other age groups remained in similar level except for ATL that showed decreasing trend for age groups <59 years. The decreasing trend of ATL in age group <59 years may be attributable to successful intervention on mother-child transmission of HTLV-1 (https://www.mhlw.go.jp/bunya/kenkou/kekakku-kansenshou29/).

Age distribution of deaths of HIV/AIDS patients: As the age of the HIV/AIDS deaths could be influenced by the age of infection, age distribution as HIV or AIDS was examined. [Note: in the AIDS surveillance in Japan, detection as “HIV (before development of AIDS)” and detection as “AIDS (after development of AIDS)” were monitored separately; however, on account reasons detailed before (1), in the present analysis they were added together to make a category “HIV/AIDS”.] As shown in Fig. 4A1, the median of the detection of HIV/AIDS among males remained around 32.5 ~ 35 years from 1995-2002 to 2011-2017 (open symbols); for females, the median was 30 years in 1995-2010 and 37.5 years in 2011-2017. Here, age distribution of female HIV/AIDS patients should be taken with caution on count of their low incidence (see Fig. 4A2).

Fig. 4B1 shows the percentile deaths at different ages of the HIV/AIDS patients of the both sexes, which was derived from the plot of the number of the deaths in different age groups (Fig. 4B2). The median of the ages of the deaths of the HIV/AIDS patients was 42.5 years in 1995-1998 and 52.5 years in 2011-2016; the median of the ages of the deaths shifted rightward by 10 years from 1995-1998 to 2011-2016 and by 5 years from 1999-2004 to 2011-2016.

Fig. 4C1 shows the percentiles of deaths at different ages among HIV/AIDS patients for males (open symbols) and for females (closed symbols). The plots for males were almost identical to those for both sexes (Fig. 4B1), because the HIV/AIDS deaths were
overrepresented by males (627 male deaths in contrast to 35 female deaths in 1995-2004; and 516 male deaths in contrast to 58 female deaths in 2005-2016). Fig. 4C2a and Fig. 4C2b respectively show frequency distributions of male and female deaths, from which derived was Fig. 4C1. Though the female data need to be interpreted with caution, it was found that: (i) as shown in Fig. 4C1, most of the plots for females (closed symbols) were found on the right of the plots for males (open symbols) and (ii) as shown in Fig. 4C2a and 4C2b, the plots for the males were centrally clustered, while those for females were clustered on the right side. At face value, compared with males, females died older by about 5 years in 2005-2010 (compare △ and ○) and by 17.5 years in 2011-2016 (compare ○ and ●) (Fig. 4C1).

Direct causes of the deaths of the HIV/AIDS patients: In Fig. 5A, plotted are the annual number of HIV/AIDS patients notified, which were classified according to the age groups. The epidemic was dominated by the age group 25-34 years till late 2000s, when they were caught up by the age group 35-44 years. The patients in the age group >45 years remained in relatively low level from the start of the epidemic till 2016.

In Fig. 5B, plotted are the annual number of HIV/AIDS deaths classified according to age groups. From 1995 to 2000, the deaths of the age groups <34 years, 35-44 years and 44-54 years were dominant, which subsided gradually. From mid-2000s, the deaths of the age group >65 years started increasing (see the inserted upward right directing arrow), which trend was similar to what was observed for general population, ATL and CJD since 1999 (Fig. 3).

Fig. 5C shows the trend of the direct causes of the deaths among the HIV/AIDS patients. Causes of the deaths belonging to ICD-10 B20 (HIV with complication of infectious diseases) were dominant from 1999 on but on decline from 2005 (see the inserted downward right directing arrow); the deaths associated with the malignancy (ICD-10 B21), other defined diseases (ICD-10B22), such as encephalopathy (B22.0), lymphatic interstitial pneumonia (ICD-10 B22.1), wasting syndrome (ICD-10 B22.2), etc., and HIV/AIDS with other complications, such as, acute HIV-1 infection (ICD-10 B23.0), persistent systemic lymphadenopathy (ICD-10 B23.1), HIV associated with other hematological or immunological pathology (ICD-10 B23.8), remained in the similar level throughout (open circles). ICD-10 B24 (△) in the graph was the death due to unknown reasons.

Fig. 5D shows the percentile age distribution of the deaths due to direct causes, either ICD-10 B20 (infectious diseases) or ICD-10 B21-23 (non-infectious diseases). For the both, the median of the ages of the deaths shifted towards older ages by about 5 years from 1999-2007 to 2008-2017.

**DISCUSSION**

We previously reported that the median of the ages of the deaths of HIV/AIDS patients became older by about 10 years in the past twenty odd years. Oddly enough, the median of the ages of the deaths of the entire population too became older by about 10 years (1). It was as if the anti-retroviral therapy (ART) had nothing to do with the prolonged survival of the HIV/AIDS patients. We found, however, that shortly after its
introduction, the deaths of HIV/AIDS patients in younger age groups (<34-54 years) actually declined. The decline of young deaths was reflected in the plots of cumulative frequency distribution of the deaths. The deaths in the age group <45 years (□) in 1999-2004 decreased to the level of that in 2005-2010 (Δ) (Fig. 4B1) and the plot pattern resembled plots for deaths due to non-infectious diseases, B21-B23, (o) (Fig. 5D1). The trend, however, soon stopped in 1999, when the deaths of the age group >65 years started increasing (Fig. 5B). The infection-related deaths started declining in 2005 though slowly (Fig. 5C). Consequently, from early 2000s on, the overall trend of HIV/AIDS deaths became quite similar to that of the deaths in general population, ATL patients and CJD patients in that the majority of the deaths was occupied by aged people.

We found, however, that HIV/AIDS shared a common feature with the general population but not with ATL or CJD. It was the clear gender effect. In 2005-2010 and 2011-2016 respectively, the median of the HIV/AIDS deaths was 50 and 52.5 years for males and 57.5 and 70 years for females; females died older by 7.5-17.5 years than males. The median of the deaths of the general population was 70-75 years for males and 80-85 years for females the latter dying older by 10 years (see box in Fig. 6). The gender difference of deaths due to ATL or CJD was only by 2.5 years. Thus, HIV/AIDS patients and the general population must have shared a common denominator. It could be CD4+T cells, because they were primary targets of HIV infection and the decline of naïve CD4+T cells was hallmark of senescence. [Note: HTLV-1 infects dendritic cells more efficiently than CD4+T cells, i.e., CD4 T cells are not the major target of HTLV-1 (6).]

Age-related regression of the thymus was associated with a decline in naïve T cell output contributing to the reduction in T cell diversity in older individuals (7); “the decline in the number of recent thymic emigrants in the blood with increasing age was gender-linked providing females with a higher number of recent thymic emigrants for longer periods of life (8); in animals, “thymii of female mice at 9 months of age contained double the number of CD4+CD8 compared with male mice (9); with age, percentage of naïve T cells and CD8+T cells significantly declined and the slope of the curve was greater for men than for women (10); the defect in CD4 T cell function is caused by multiple factors some of which are associated with an increased post-thymic age of the cells in older individuals (11); surveyed literatures indicated lower risk of death among females than in males among HIV/AIDS patients (12). While recognizing that the gender difference in thymic involution could be mediated by multiple pathways (13), we propose a simple model as below.

In the model (Fig. 6), CD4+T cell and other parameters that degrade with aging is plotted in the y-axis and the age in the x-axis. The plots for females are represented by dotted lines and those for males by solid lines. Plots for females are on the right of those for males because females died older. The slope is less steep for females than for males, because the decline in the percentage of naïve CD4+T cells and CD8+T cells was greater for men than women (10). The x-coordinate where the straight line crosses is the age of death. As HIV infection kills CD4+T cells, the rightward descending straight lines labelled “general population” are brought down to the levels labelled “HIV/AIDS”, and then surviving naïve T cells decline continuously with age. Thus, males
die younger than females in the HIV/AIDS patients as in the general population. The model explains why HIV-infected older people were detected more as “AIDS” than as “HIV” (5) or why older age is a strong predictor of accelerated HIV disease progression (14).

This model raises interesting questions as to (i) T cell diversity before and after HIV infection, i.e., HIV infection may reduce just number of naive T cells without changing their diversity or may change the T cell diversity simultaneously; (ii) causes of gender effect on ATL and CJD deaths, which may involve, such as, genomic instability (15); and (iii) cause of the rightward shift of age of deaths observed for general population, HIV/AIDS, ATL and CJD, which appeared gender-independent.

This model may have an implication on HIV/AIDS vaccine strategy. As thymus size is reduced by about 3% per year until middle age (8), at the age of the sexual maturity (15-20 years), the thymus size and probably the number of naive CD4+T cells may be reduced to about a half of the birth size. Lefebvre and Haynes (16) wrote “understanding how aging impairs CD4+T cell functions is of critical importance to design new immunization and treatment strategies to the elderly population”. As HIV vaccines to work, antigens may have to be administered shortly after birth. For therapy of HIV/AIDS, rejuvenation of immune system is prerequisite. Dorshkind and Swain (17) already noted that “at least for T cells, rejuvenation of thymus leads to production of new naïve T cells that function as well as young cells and better than those from the aged”.

Conflict of interest: none to declare.

Acknowledgement

The author thanks Ms. Kaori Nakayama, Ministry of Health, Labor and Welfare International Classification Information Management Office, for her advice in using Vital Statistics.

References
7. Aw D, Palmer DB. The origin and implication of thymic involution. Aging Dis.

Figure legend

Fig. 1: Geo-demography of HIV/AIDS (code number “01500” in ICD-10(2013)) (A), ATL (C91.5) (B), and CJD (A81.0) (C). Figs.1A1, 1B1, and 1C1: Plot of the number of patients per prefecture in the y-axis versus the prefecture number starting from Hokkaido in the North to Okinawa in the South (see Fig. 1D) in the x-axis. Figs. 1A2, 1B2 and 1C2: Plot of the total number of the patents per prefecture in the y-axis against the population size (x1000) of the prefectures in the x axis. Fig. 1A3: The number of inflow population in the y-axis against the number of the resident population in the x-axis. Approximations of the plots were: y=0.0002X^{1.10} (R^2=0.86) for 15-19 years (□); y=0.0001 X^{1.21} (R^2=0.94) for 20-24 years (▲); 0.0001X^{1.21} (R^2=0.93) for 25-29 years (●); y=0.0001X^{1.20} (R^2=0.94) for 30-34 years (◆); y=0.0001X^{1.17} (R^2=0.94) for 35-39 years (○); y=0.0001X^{1.16} (R^2=0.95) for 40-44 years (△). An inserted dotted line is to show a plot with 45° slope or with slope 1.

Fig. 2: Percentile age distribution (A1-C1) and the frequency distribution (A2-C2) of ages of the deaths for entire population (A1-A2), ATL (B1-B2) and CJD (C1-C2). Males
are represented by open symbols and females by closed symbols.

Fig. 3: Trends of the deaths in the entire population, ATL patients and CJD patients, classified according to the age groups. The number of the deaths is plotted in the y-axis and the year in the x-axis.

Fig. 4: Percentile (A1, B1 and C1) and frequency distribution (A2, B2 and C2) of the ages of the detection of HIV/AIDS (A1 and A2) and deaths (B1, B2, C1 and C2a, C2b).

Fig. 5: HIV/AIDS deaths classified according to age groups and direct causes of the death. A: Number of HIV/AIDS patients notified annually; B: Number of deaths of HIV/AIDS patients notified annually classified by age groups; C: Number of deaths of HIV/AIDS patients notified annually classified according to direct causes of the deaths; D: Age distribution of HIV/AIDS deaths due to different direct causes, percentile distribution on the left (D1) and number of notification per age groups on the right (D2).

Fig. 6: Model proposed for explaining gender difference of ages of deaths and summary table of medians of ages of deaths. In the main graph depicting the model, plots for males are represented by solid lines and those for females by dotted lines. Plots for HIV/AIDS are represented by downward right directing lines and those for ATL and CJD by vertical downward arrows.
Fig. 1
Fig. 2
Fig. 3
Fig. 4
A: Number of HIV/AIDS patients notified annually in 1987-2016

B: Number of deaths of HIV/AIDS patients notified annually in 1995-2016 classified by age group

C: Number of deaths of HIV/AIDS patients notified annually in 1995-2016 classified by direct causes of the deaths

D: Age distribution of HIV/AIDS deaths due to different direct causes

Fig. 5
Fig. 6

<table>
<thead>
<tr>
<th>Populations</th>
<th>sex</th>
<th>1999-2004</th>
<th>2010-2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population</td>
<td>male</td>
<td>70</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>female</td>
<td>80</td>
<td>85</td>
</tr>
<tr>
<td>ATL</td>
<td>male</td>
<td>65</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>female</td>
<td>67.5</td>
<td>72.5</td>
</tr>
<tr>
<td>CJD</td>
<td>male</td>
<td>65</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>female</td>
<td>67.5</td>
<td>72.5</td>
</tr>
<tr>
<td></td>
<td>male</td>
<td>50</td>
<td>52.5</td>
</tr>
<tr>
<td></td>
<td>female</td>
<td>57.5</td>
<td>70</td>
</tr>
</tbody>
</table>

All dying older (by 5 years from 1999-2003 to 2011-2017)