Original Article

Shift of HIV/AIDS Deaths to an Older Age and Gender Difference: Inferences Derived from the Vital Statistics of Japan

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SUMMARY: From 1995 to 2000, the mortality rates of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) patients < 54 years of age have declined; however, since 2000, deaths of HIV/AIDS patients aged > 55 have started to increase. Although deaths directly linked to infections have declined since 2005, those related to malignancy, encephalopathy, interstitial pneumonia, wasting syndrome, etc. persisted. In 10 years from 1999–2004 to 2010–2017, the age at death shifted by 5 years towards an older age in the general population and in patients with HIV/AIDS (mainly males), adult T-cell leukemia, or Creutzfeldt-Jakob disease. Among these, HIV/AIDS patients and the general population exhibited an 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. Hence, male HIV/AIDS patients died 22.5 years earlier and female HIV/AIDS patients 15 years earlier than did the general population. A common denominator of HIV/AIDS-related deaths and deaths among the general population could be CD4⁺T cells as these cells are primary targets of HIV, and a decline in naïve CD4⁺T cell count is a hallmark of aging.

INTRODUCTION

We previously reported that the median of the age at death of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) patients was 40–44 years in 1995–1998 and 50–54 years in 2014–2016, hence the survival of HIV/AIDS patients has been extended by 10 years within this 20-year-period. Nonetheless, it is important to note that the life span of the Japanese population has also increased by 10 years (1), which raises the question whether the shift in the age at death of HIV/AIDS patients by 10 years is due to anti-retroviral therapy (ART) or not.

In order to answer this question, we analyzed the age of patients that died due to other diseases, viz., adult T-cell leukemia (ATL) and Creutzfeldt-Jakob disease (CJD). These diseases were chosen because the timing of infection or diagnosis was relatively uniform. ATL is caused by human T-cell leukemia virus type 1 (HTLV-1) that is mostly transmitted maternally (2,3), with 5–10% of virus carriers developing ATL (<https://www.niid.go.jp/niid/ja/kansennohanashi/326-atl.html>) (Japanese); CJD is a prion disease (4) that occurs mostly

sporadic (77% in 2017) in Japan and patients die within a year after diagnosis (<http://www.jichi.ac.jp/dph/prion/cjdresult11.pdf>) (Japanese). We examined direct causes of deaths of HIV/AIDS patients between 1999 and 2017. These studies led to the observation that the mortality of HIV/AIDS patients and that of the general population shares a common feature, a gender effect.

MATERIALS AND METHODS

Data on mortality rates of the general population, HIV/AIDS patients, ATL patients, and CJD patients were derived from Vital Statistics (Vital, Health, and Social Statistics Office, Ministry of Health, Labour and Welfare/MHLW, (<https://www.mhlw.go.jp/toukei/list/81-1.html>)) (Japanese). Data on notification of HIV/AIDS patients were derived from the report of the AIDS Surveillance Committee of the MHLW. In the above statistics, age distribution was represented by 5-year-interval age groups. In order to simplify calculations, the age groups were represented by their medians (e.g., 12.5 years for the 10–15 years age group).

RESULTS

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

In Fig. 1A2, 1B2, and 1C2, the population size of each prefecture ($\times 1,000$) in 2010 is plotted on the

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x-axis and the total number of patients in each prefecture in 1999–2016 for HIV/AIDS and in 1999–2017 for ATL and CJD on the y-axis.

For HIV/AIDS (Fig. 1A2), the slope of the approximation line was 1.34 ($R^2 = 0.756$), indicating that the number of patients per prefecture was proportional to the population size to the power of 1.34. In Fig. 1A3, the population inflow in different age groups is plotted on the y-axis against the population size on 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 steepest slope (1.2) was observed for the sexually most active age group of 20–34 years. Taking the possibility of sexual contact with the immigrant population into account, this slope of 1.2 was similar to the slope of 1.34 determined for HIV/AIDS-related deaths.

For ATL, a disease originally endemic in Kyushu

Fig. 1. Geo-demography of HIV/AIDS (code number "01500" in ICD-10 [2013]) (A), ATL (C91.5) (B), and CJD (A81.0) (C). Fig. 1A1, 1B1, and 1C1: Plot of the number of deaths 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. Fig. 1A2, 1B2, and 1C2: Plot of the total number of the deaths per prefecture in the y-axis against the population size ($\times 1,000$) of the prefectures in the x-axis. Open triangles in panel C2 represent population aged > 65 years. 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 ($\square$); $y = 0.0001X^{1.21}$ ($R^2 = 0.94$) for 20–24 years ($\blacktriangle$); $0.0001X^{1.21}$ ($R^2 = 0.93$) for 25–29 years ($\bullet$); $y = 0.0001X^{1.20}$ ($R^2 = 0.94$) for 30–34 years ($\blacklozenge$); $y = 0.0001X^{1.17}$ ($R^2 = 0.94$) for 35–39 years ($\circ$); $y = 0.0001X^{1.16}$ ($R^2 = 0.95$) for 40–44 years ($\triangle$). An inserted dotted line is to show a plot with 45° slope or with slope 1.

and other Southern prefectures (3,4) (Fig. 1B2), no correlation between the number of patients and the population size was noted ($R^2 = 0.186$); ATL incidence was highest in the Kyushu area (PNs 40–47), Tokyo area (PNs 12–14), Aichi prefecture (PN 23), and Osaka prefecture (PN 27).

The slope determined for CJD (open circles in Fig. 1C2) was 0.81 ($R^2=0.81$). The approximation line was parallel to that in the plot of the population > 65 years

(open triangles in Fig. 1C2), which was expected from the high prevalence of this disease in the elderly (4).

Age distribution of deaths in the general population and in ATL and CJD patients: In Fig. 2A1, 2B1, and 2C1, the cumulative percentage (percentiles) of deaths is plotted against age, which was derived from the plots representing the number of deaths in different age groups (Fig. 2A2, 2B2, and 2C2). The following observations were made: (i) The median of the age of

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.

deaths in the general population shifted to an older age by 5 years for both males and females (males: 70 years in 1999–2000 vs. 75 years in 2011–2017; females: 80 years in 1999–2000 vs. 85 years in 2011–2017). Thus, females in the general population survived males by 10 years. (ii) The median of the age at death of male ATL patients was 65 years in 1999–2004 and 70 years in 2010–2017, while that of female ATL patients was 67.5 years in 1999–2000 and 72.5 years in 2011–2017. (iii) The median of the age at death of male CJD patients was 65 years in 1999–2003 and 70 years in 2011–2017, while that of female CJD patients was 67.5 in 1999–2004 and 72.5 in 2011–2017. Hence, female ATL and CJD patients lived 2.5 years longer than male patients,

a number much smaller than the 10 years observed for the general population and HIV/AIDS patients (see below). (Note: The median of the age at death of the population is a parameter different from the average age of the population, which was 76 and 82 years for males and females, respectively, in 1995 and 81 years and 87 years, respectively, in 2017. See the Abridged Life Table 2017 of the MHLW [<https://www.mhlw.go.jp/toukei/saikin/hw/life/life17/dl/life17-15.pdf>][Japanese] and the Definitions of Several Functions Used in the Life Table [<https://www.mhlw.go.jp/toukei/saikin/hw/life/life09/sankou01.html>] [Japanese]).

In Fig. 3, the annual number of deaths in different age groups is plotted for the general population, ATL

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.

patients, and CJD patients. In all these 3 groups, the annual number of deaths in the oldest age groups (> 80 years for the general population and ATL patients, > 70 years for CJD patients) increased linearly from 1999 on, while the deaths in the other age groups remained similar except for a decreasing trend for the age group of < 59 years of ATL patients, which may be attributable to successful intervention on mother-child transmission of HTLV-1 (<https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou29/>)(Japanese).

Age distribution of deaths of HIV/AIDS patients:

As the age at death of HIV/AIDS patients could be influenced by the age at infection, the age of patients at detection of 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]” are monitored separately; however, for reasons detailed before (1), in the present analysis both entities were combined in the category “HIV/AIDS”). As shown in Fig. 4A1, the median of the

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

detection of HIV/AIDS in males remained at 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. Nonetheless, the age distribution of female HIV/AIDS patients should be taken with caution due to the overall low incidence (see Fig. 4A2).

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

Fig. 4C1 shows the death percentiles of HIV/AIDS

patients for males (open symbols) and females (closed symbols) at different ages. 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 compared to 35 female deaths in 1995–2004 and 516 male deaths compared to 58 female deaths in 2005–2016). Fig. 4C2a and 4C2b show the frequency distributions of male and female deaths, respectively, from which Fig. 4C1 was derived. Although the data on females need to be interpreted with caution, it was found that (i) most of the plots for females (closed symbols, Fig. 4C1) were found on the right of the plots for males (open symbols) and (ii) the plots for males were centrally clustered, while those for females were clustered on the right (Fig. 4C2a and 4C2b). Hence, females were about 5 years older than males at the time

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).

of death in the period of 2005–2010 (compare $\triangle$ and $\blacktriangle$) and 17.5 years older in 2011–2016 (compare $\circ$ and $\bullet$) (Fig. 4C1).

Direct causes of death in HIV/AIDS patients:

In Fig. 5A, the annual numbers of HIV/AIDS patient notifications are plotted by age group. The epidemic was dominated by the age group of 25–34 years until the middle of 2000s, when it was superseded by the age group of 25–44 years. The number of patients in the age group of > 45 years remained relatively low throughout the assessed period.

In Fig. 5B, the annual numbers of HIV/AIDS deaths are plotted by age group. From 1995 to 2000, deaths in the age groups of < 34 years, 35–44 years, and 44–54 years were predominant but gradually subsided. Starting in the mid-2000s, the deaths in the age group of > 65 years increased (see the inserted upward-/right-pointing arrow), a trend similar to that observed for the general population and ATL and CJD patients since 1999 (Fig. 3).

Fig. 5C shows the trend of the direct causes of death in HIV/AIDS patients. Deaths in the category ICD-10 B20 (HIV with complication of infectious diseases) were predominant since 1999 but declined from 2005 on (see the inserted downward-/right-pointing arrow); deaths associated with a malignancy (ICD-10 B21), other defined diseases (ICD-10 B22), such as encephalopathy (ICD-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), or HIV associated with other hematological or immunological pathology (ICD-10 B23.8), remained on a similar level throughout the assessed period (open circles). ICD-10 B24 ($\triangle$ in the graph) represents deaths with unknown cause.

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

DISCUSSION

We previously reported that the median of the age at death of HIV/AIDS patients shifted to an older age by about 10 years in the last 20 odd years. Oddly enough, the same shift was observed in the entire population (1), suggesting that the prolonged survival of HIV/AIDS patients occurred independently of ART. Nonetheless, shortly after the introduction of ART, the deaths of HIV/AIDS patients in the younger age groups (< 34–54 years) declined (Fig. 5B). From late 2000s, the deaths in the age group of > 65 years started to increase (Fig. 5B) and the infection-related deaths started to decline albeit slowly (Fig. 5C). Consequently, since the early 2000s, the overall trend of HIV/AIDS-related deaths became similar to that of the deaths in the general population, ATL patients, and CJD patients in that the majority of the deaths occurred in the older age groups.

We further discovered that HIV/AIDS patients shared a common feature with the general population but not with ATL patients or CJD patients, namely an

obvious gender effect. In 2005–2010 and 2011–2016, the median of the HIV/AIDS-related deaths was 50 and 52.5 years for males and 57.5 and 70 years for females, respectively; hence, females died at an age of 7.5–17.5 years older than males. The median age at death of the general population was 70–75 years for males and 80–85 years for females, thus females lived 10 years longer than males (see box in Fig. 6). In contrast, a gender difference in the age at death of merely 2.5 years was observed for ATL and CJD patients. Thus, HIV/AIDS patients and the general population must have shared a common denominator, which could be CD4⁺T cells. These cells are primary targets of HIV infection and their decline is also a hallmark of aging. [Note: HTLV-1 infects dendritic cells more efficiently than CD4T⁺ cells, i.e., CD4 T⁺ cells are not the major target of HTLV-1 (6)].

An association between an age-related regression of the thymus and a decline in naïve T cell output contributing to the reduction in T cell diversity has been demonstrated 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). In addition, the percentage of naïve T cells and CD8⁺T cells significantly declines with age and the slope of the respective curve was shown to be greater for males than females (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). Moreover, a literature survey indicated a lower risk of death for female HIV/AIDS patients compared to male patients (12). While we recognize that the gender difference in thymic involution could be mediated by multiple pathways (13), we propose a simple model as follows.

In our model (Fig. 6), CD4⁺T cells and other parameters that decline with aging are plotted on the y-axis and the respective age on the x-axis. The plots for females are represented by dotted lines and those for males by solid lines. Plots for females are found on the right of those for males because females died at an older age than males. 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 males than females (10). The place where the straight line crosses the x-coordinate indicates the age at 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 both the HIV/AIDS patient population and the general population. The model explains why HIV-infected older people were identified more as having “AIDS” than as having “HIV infection” (5) and why an older age is a strong predictor of accelerated disease progression after HIV infection (14).

This model raises interesting questions as to (i) T cell diversity before and after HIV infection, i.e., HIV infection may reduce the number of naïve T cells only without changing their diversity, or it may change the

T cell diversity simultaneously; (ii) causes of a gender effect on ATL and CJD deaths, which may involve, such as, genomic instability (15); and (iii) causes of the rightward shift of the age at death observed for the general population, HIV/AIDS patients, ATL patients, and CJD patients as a whole, which appeared gender-independent.

This model may have implications for the HIV/AIDS vaccination strategy. As thymus size is reduced by about 3% per year until middle age (8), at the age of sexual maturity (15–20 years), the thymus size and probably the number of naïve CD4⁺T cells may be reduced to about half of that at birth. Lefebvre and Haynes (16) wrote “understanding how aging impairs CD4⁺T cell functions

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.

is of critical importance to design new immunization and treatment strategies to the elderly population.” For HIV vaccines to be efficient, antigens may have to be administered shortly after birth, and rejuvenation of the immune system appears to be a prerequisite for HIV/AIDS therapy. 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.”

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Conflict of interest None to declare.

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