Original Article

Analysis of HIV/AIDS Epidemiology in Japan from 1985–2011—Infection Detection Pattern for Male Homosexuals Different from That for Male Heterosexuals but Similar to That for Females

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SUMMARY: This article reviews Japanese HIV/AIDS surveillance data from 1985 to 2011. It revealed that heterosexual males are more prone to be detected as “AIDS cases,” whereas male homosexuals and females are more prone to be detected as “HIV cases,” irrespective of the gender, age, infection route, residential area, and nationality. The probability of being detected as an “AIDS case” increased with advanced age, irrespective of the gender and infection route. Interpretation of the data requires further information on the clinical latency of AIDS that could differ depending on differences in infection routes, gender, age, nature of the acute-phase syndrome and factors enhancing it, e.g., route and dose of infection, and mucosal immunity involved in sexually transmitted HIV/AIDS infection and the influence of age and gender on it.

INTRODUCTION

HIV/AIDS is classified as a category V infectious disease under the Infectious Disease Control Law in Japan. Doctors must notify all cases of HIV/AIDS within 7 days after diagnosis using the format provided (1). Surveillance of HIV/AIDS began in 1984 and covers HIV infections through routes other than blood transfusion or blood-derived products (2). It has been conducted in compliance with the AIDS Prevention Law from 1989 to March 1999 and in compliance with the Infectious Disease Control Law since April 1999 till date (3). The present analysis used the data derived from the annual report of the National AIDS Surveillance Committee for year 2012 released by the Specific Disease Control Division, the Ministry of Health, Labour and Welfare (4). Since 2007, approximately 1,500 HIV/AIDS cases have been reported annually (3).

It is important to note that, in the Japanese reporting system, if the infection is detected before the development of AIDS, the patient is notified as an “HIV case” and if the infection is discovered after development of AIDS, the patient is notified as an “AIDS case.” (The indicator diseases of AIDS are listed in http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou11/01-05-07.html [Japanese].) Once notified as an “HIV case,” the patient continues to be counted as an “HIV case” even if he/she may later develop AIDS. Therefore, whether a case is “HIV” or “AIDS” is determined by the stage of infection at the time of detection of the infection.

MATERIALS AND METHODS

The data used for the present analysis were derived from “AIDS Surveillance Committee, Ministry of Health, Labour and Welfare Japan: Annual Report of HIV/AIDS Trends” (http://api-net.jfap.or.jp/status/2013/13nenpo/tenpo_menu.htm [Japanese]). All the analysis was conducted by using Microsoft Excel 2010.

RESULTS

Fig. 1 shows a plot of the cumulative number of patients detected as “HIV cases” in the horizontal axis and the cumulative number of patients detected as “AIDS cases” in the vertical axis for the time span from 1985 to 2011. The plots closest to the origin of the coordinates correspond to the year 1985 and those furthest from the origin correspond to the year 2011. Thus, a coordinate point (xi, yi) indicates that from 1985 until year i, there were total xi individuals detected as “HIV cases” and yi individuals detected as “AIDS cases” in total. It should be noted here that the slope of the plots in Fig. 1 is equivalent to the ratio of detected “AIDS cases” to detected “HIV cases.” This type of plot is called the “AIDS-HIV plot” below, and the ratio of detected “AIDS cases” to detected “HIV cases” is called the “AIDS-HIV ratio.” The “AIDS-HIV ratio” was 0.79 in male heterosexuals, while it was 0.28 in male homosexuals and 0.32 in females (panel A). Thus, infections detected as “AIDS cases” were approximately 2.4–2.8-fold (0.79 divided by 0.28 or 0.32) more frequent in male heterosexuals than in male homosexuals or females.

Panel B shows the AIDS-HIV plot of non-Japanese infected individuals in Japan. The AIDS-HIV ratio was 0.73 in male heterosexuals, 0.3 in male homosexuals, and 0.51 in females. Thus, the tendency was similar in Japanese and non-Japanese populations.

Throughout this article, the plot of cumulative numbers was used because (i) the current HIV/AIDS epidemic is a single continuing epidemic, (ii) under the
Fig. 1. AIDS-HIV plots for Japanese and non-Japanese HIV patients in Japan (1985–2011). Panel A: Japanese male heterosexuals (closed circles), Japanese male homosexuals (open circles), and Japanese female (closed triangles) (The data from 1987 to 2009 was published previously (1)). Panel B: Non-Japanese male heterosexuals (closed circles), non-Japanese male homosexuals (open circles), and non-Japanese female (closed triangles). Horizontal axis; cumulative number of patients detected as HIV case, Vertical axis; cumulative number of patients detected as AIDS case. The slopes of the plots (equivalent to ratio of detection as “AIDS cases” to detection as “HIV cases”) are shown beside corresponding plots. Plots closest to the origin are for year 1985 and the furthest for year 2011.

Japanese surveillance system, a patient is counted only once and never twice, (iii) the statistic precision which depends on the data volume, increases as time passes, and (iv) the plot of cumulative numbers allows monitoring of epidemic trends and gives an overall picture of an epidemic.

“In panel B in Fig. 1, the plot of non-Japanese females deflected upward from the straight line in 1994–1998. This is probably related to the sharp increase in non-Japanese female “HIV cases” registered from 1991 to 1994, with a conspicuous peak in 1992 (see Fig. 4 in http://api-net.jfap.or.jp/status/2012/12 nenpo/h24gaiyo.pdf). If a large number of apparently healthy HIV-infected people is introduced into a country at a given time, the number of “HIV cases” will increase disproportionately in the absence of an increase in “AIDS cases.” Hence, the observed upward deflection probably reflects the resumption of the “normal course” of accumulation of “HIV” and “AIDS.” This indicated that the influx of HIV-infected immigrants may distort the “normal course” of the HIV-AIDS plot. However, as shown in Fig. 1, except for the above case of the non-Japanese females, the plots maintained linearity from 1985 to 2011.

Fig. 2 shows the trends of the place of HIV infection from 1985 to 2011. For Japanese males and females in the period of 1985–1990, the patients acquired infection in Japan and abroad at nearly equal frequencies (see the left-most plots in panels A and B); from 1991 to 1996, however, the place of infection largely shifted to Japan (see the right-side plots in panels A and B). For non-Japanese individuals, in the early phase (1985–1996), many of the “HIV cases” had acquired infection before coming to Japan (see plots ○ and △ in panel C); however, since 2002, infection in Japan became predominant. A similar tendency was observed for “AIDS cases” (see panel D). As the plots in Fig. 1 maintained linearity overtime, it can be inferred that the
Fig. 2. Probable place of infection, either in Japan or abroad. Panel A; Japanese “HIV cases,” Panel B; Japanese “AIDS cases,” Panel C; Non-Japanese “HIV cases” (in this panel, the data for HIV non-Japanese female in 1997–2001 should be disregarded as place of infection unknown occupied 53% of the cases). Panel D; Non-Japanese “AIDS cases.” Explanations under the graphs; “HIV Japanese male in Japan” below the graphs, for example, means “HIV cases” with Japanese nationality, male, infected in Japan. Explanation of symbols; ●; males infected in Japan, ○; males infected abroad, ▲; females infected in Japan, △; females infected abroad. Vertical axis; % total of cases classified according to the probable place of infection, in Japan (closed symbols), abroad (open symbols) or unknown (not shown) during the period indicated in the horizontal axis; HIV non-Japanese the plots in panel C. Horizontal axis; time intervals, 1985–1990, 1991–1996, 1997–2001, 2002–2006, and 2007–2011 from the left to the right.

AIDS-HIV plot remains unaffected by the place of acquisition of HIV infection.

Fig. 3 shows AIDS-HIV plots for 7 prefectural areas and Tokyo Metropolis. While the slopes were variable from block to block, the plots for male heterosexuals were always steeper than those for male homosexuals and females; the AIDS-HIV ratio was 0.63–1.41 for heterosexuals, 0.23–0.44 for homosexuals, and 0.2–0.48 for females (figures for individual regions are tabulated in columns of “slope of AIDS-HIV plot” in the upper panel of Table 1). Thus, HIV infection was more frequently detected as “AIDS cases” in male heterosexuals than in male homosexuals and females, irrespective of the areas.

Fig. 4 shows AIDS-HIV plots for different age groups of male heterosexuals (top panel), male homosexuals (middle panel), and females (bottom panel). In all 3 groups, the slope became steeper with advancing age, i.e., as patients became older, the rate of detection of “AIDS cases” increased (see the right-side figure, which plots the AIDS/HIV ratio in the vertical axis as a function of age groups in the horizontal axis).

While the AIDS/HIV ratio continued to rise until 55 years and 50 years in male heterosexuals and male homosexuals, respectively, it ceased increase around the age 40 years in females. The plots for male heterosexual groups were always above the plots for male homosexuals and females, i.e., in the same age group, the AIDS/HIV ratio was always higher for heterosexuals than for homosexuals or females, except in the age group of < 24 years in which the AIDS-HIV ratio was uniformly low.

The above observations can be summarized as follows: (i) The rate of detection of “AIDS cases” was much higher for male heterosexuals than for male homosexuals and females. Between male homosexuals and females, there was no significant difference in this regard. The above tendency was shared by Japanese and non-Japanese populations. (ii) With a few exceptions, the plots were always precisely following straight lines, i.e., in each of the sexual preference groups, age groups, or geographic groups, the ratio of detected “AIDS cases” to detected “HIV cases” was constant from 1985 to 2011. This implies that the ratio of those detected as
Fig. 3. AIDS-HIV plots for Japanese HIV-infected patients in Japan by prefectural blocks (1985–2011). Closed circles; male heterosexuals, open circles; male homosexuals, open triangles; females. Horizontal axis; cumulative number of patients detected as “HIV cases,” Vertical axis; cumulative number of patients detected as AIDS case. The slopes of the plots are found near the corresponding plots. Tokyo is excluded from the plots for Kanto-Koshinetsu.

“HIV/AIDS Detection vs. Infection Route and Age

``AIDS cases'' to those detected as “HIV cases” was more or less fixed for each group. (iii) In all age groups, the AIDS-HIV ratio was higher in heterosexuals than in homosexuals and females. The AIDS-HIV ratio increased with advancing age, e.g., in male heterosexuals, it was 0.03 for those patients <19 years, 0.10 for those aged 20–24 years, 0.28 for those aged 25–29 years, 0.38 for those aged 30–34 years, 0.80 for those aged 35–39 years, 0.92 for those aged 40–44 years, 1.14 for those aged 45–49 years, 1.39 for those aged 50–54 years, and 1.47 for those aged ≥55 years. (iv) Among the different prefectural areas, though the AIDS-HIV plots were variable, the AIDS-HIV ratio was always higher for male heterosexuals than for male homosexuals and females. Taking into account the fact that the AIDS-HIV ratio was higher for male heterosexuals than for male homosexuals and females and the fact that the ratio increased with advancing age, the variation in the AIDS-HIV plot among prefectural areas could be attributable to regional variation in the age distribution and infection routes. The steeper slope for homosexuals in Hokkaido and Kanto-Koshinetsu is indicative of a relative dominance of older homosexuals, while the gentle slope for homosexuals, for instance, that in Kinki and Tokyo, is indicative of a relative dominance of young homosexuals. (However, this could not be confirmed with the current database because it does not give regional information on the prevalence of infection routes.)

DISCUSSION

In short, the data could be summarized as follows:

Heterosexual males are more prone to be detected as “AIDS cases,” whereas male homosexuals and females are more prone to be detected as “HIV cases.” The probability of being detected as an “AIDS case” increased with advancing age, irrespective of the infection route.

The data raised the following questions: Why is the detection rate of “AIDS cases” in male heterosexuals higher than that among male homosexuals and females? Why does the detection rate of “AIDS cases” increase with age, irrespective of the infection route?

Factors potentially involved in a higher detection rate of “HIV cases” among male homosexuals: The first question is equivalent to “why is the detection rate of “HIV cases” among male homosexuals and females
higher than that in male heterosexuals?” Two hypotheses were put forward: one is motivational and the other is biological (5). The former hypothesis assumes that homosexuals and females are more motivated to visit HIV/AIDS clinics being more conscious of the HIV risk than heterosexual males; thus, their visits to clinics before the development of AIDS will be more frequent than those of heterosexuals. The second hypothesis assumes a higher viral load in male homosexuals and females than in male heterosexuals during the HIV exposure and assumes more severe acute symptoms in the former groups, prompting clinical consultation.

The motivation hypothesis cannot be formally excluded because the motivation does not appear in the statistics. However, the data presented in this article do not appear to corroborate it because the higher detection rate of “HIV cases” among homosexuals was observed not only in different geographic areas but also in different age groups. In addition, the same trend was observed among non-Japanese individuals, to whom access to the Japanese health care system may not be so easy. It is difficult to imagine that all male homosexuals and females with such diverse backgrounds were equally more concerned about their HIV risk, visiting clinics at earlier stages of infection.

The alternative hypothesis is as follows: Homosexuals and females have receptive roles during sexual intercourse, exposing the vaginal or rectal mucosa to a large amount of seminal fluid ejaculated by HIV-infected males; thus, females and homosexuals will be exposed to a larger amount of virus for a longer time, which may cause higher plasma virus loads, resulting in more severe acute syndromes. More severe symptoms will prompt male homosexuals and females to visit clinics in the early phase of infection. In fact, a study in Kenya showed that acute symptoms, including fever, vomiting, headache, fatigue, arthralgia, myalgia, sore throat, skin rash, and/or being too sick to work, were associated with an increase in the virus load of 0.4 log 10 copies/ml (6) during the acute phase.

Factors potentially involved in the increase in the detection of “AIDS cases” with advancing age: It has been documented that AIDS develops usually after approximately 10 years of incubation (7). If so, it is expected that the epidemic of “AIDS cases” lags behind that of “HIV cases” by approximately 10 years, and patients detected as “AIDS cases” will consequently be older than those detected as “HIV cases.” We call this line of reasoning the “10-year lag hypothesis” here. It should be noted that the “10-year lag hypothesis” is tenable only when the 10-year clinical latency is an established fact. However, establishing the period of
### Table 1. Summary table of slopes (AIDS-HIV ratios)

| Region           | Age Incidence/100,000 population | Slope of AIDS-HIV plot | Slope ratio |
|------------------|----------------------------------|------------------------|-------------|
|                  | < 40 yr | AIDS | HIV | AIDS/HIV | Hetero | Homo | Female | Homo/Homo | Female/Female |
| Hokkaido–Tohoku | 0.4    | 2.1  | 2.9 | 0.72     | 0.84   | 0.44 | 0.48   | 0.53       | 0.57         |
| Kanto–Koshinetsu | 0.44   | 5.7  | 9.3 | 0.61     | 1.0    | 0.47 | 0.39   | 0.47       | 0.39         |
| Tokyo            | 0.46   | 12.6 | 39.3| 0.32     | 0.58   | 0.23 | 0.2    | 0.4        | 0.34         |
| Tokai            | 0.45   | 4.8  | 8.9 | 0.54     | 0.82   | 0.37 | 0.36   | 0.45       | 0.44         |
| Hokuriku         | 0.42   | 2.2  | 3.9 | 0.56     | 0.62   | 0.32 | 0.3    | 0.48       | 0.45         |
| Kinki            | 0.39   | 4.3  | 11.1| 0.39     | 1.41   | 0.23 | 0.26   | 0.16       | 0.18         |
| Chugoku–Shikoku  | 0.41   | 2.1  | 3.9 | 0.54     | 0.63   | 0.35 | 0.36   | 0.56       | 0.57         |
| Kyushu           | 0.43   | 2.6  | 4.5 | 0.58     | 0.98   | 0.34 | 0.29   | 0.35       | 0.3          |

### Lower panel; Tabulation of data in Fig. 3. Slopes (AIDS-HIV ratio) of AIDS-HIV plots for male heterosexuals, male homosexuals, and females according to age group.

| Age (yr) | Male heterosexual | Male homosexual | Female |
|----------|-------------------|-----------------|--------|
| ≤ 19     | 0.03              | 0.01            | 0.04   |
| 20–24    | 0.1               | 0.07            | 0.1    |
| 25–29    | 0.28              | 0.13            | 0.21   |
| 30–34    | 0.38              | 0.23            | 0.3    |
| 35–39    | 0.8               | 0.34            | 0.48   |
| 40–44    | 0.92              | 0.4             | 0.54   |
| 45–49    | 1.14              | 0.57            | 0.52   |
| ≥ 50     | 1.39              | 0.86            | 0.49   |
|          | 1.47              | 0.79            | 0.56   |

Clinical latency is very difficult because, except for infection through blood or blood-derived products, the time of infection typically cannot be determined as a result of a history of multiple sexual encounters and a generally obscure patient memory. Nevertheless, information on the clinical latency period is crucial for interpreting the presented data.

Although the argument is too simplistic, we can expect that if the clinical latency of 10 years is the rule, the epidemic curve of detected “AIDS cases” will lag behind that of detected “HIV cases” by 10 years. If the 10-year lag exists, the chance of detecting the lag in the Japanese data is high (i) because the AIDS-HIV ratio was constant (Fig. 1) and (ii) because the HIV/AIDS surveillance in Japan began at the earliest phase of the epidemic (there were only 6 reports in 1985, 5 in 1986, and 14 in 1987 [17 Japanese and 8 non-Japanese]. The constant AIDS-HIV ratio predicts that if the “10-year lag hypothesis” is correct, the epidemic of “HIV cases” is expected to reflect that of “AIDS cases” 10 years later. Fig. 5 shows the time course of the cumulative number of patients detected as “HIV cases” or as “AIDS cases.” For females, the epidemiological curve of “AIDS cases” was shifted to the right by approximately 10 years as the “10-year lag hypothesis” predicts (panel C-1). However, the same pattern was observed for non-Japanese females, who may not necessarily stay in Japan for longer than 10 years (panel C-2). For Japanese male populations, no clear time lag was discernible. For heterosexuals, initially, there was a 2-year interval between detected “HIV cases” and detected “AIDS cases,” which gradually merged together; for homosexuals, detected “HIV cases” and detected “AIDS cases” were seen to overlap initially; however, they gradually diverged over time. The same observations were reflected in the non-Japanese population.

Although it is difficult to identify a consistent explanation, the nearly overlapping plots of “AIDS cases” and “HIV cases” for male heterosexuals and homosexuals may indicate that clinical latency may not be as long as 10 years in most male HIV/AIDS cases in Japan. In fact, as reported previously (8), “the period of latency varies in length from as little as 1 to 2 years to more than 15 years, though the onset of AIDS is rare in less than 3 years, except in children.” For females, the data may indicate that the clinical latency is as long as 10 years; however, to the author’s knowledge, a difference in the latency between males and female has not been reported till date. In the face of data that cannot be interpreted consistently, it may be necessary to contemplate a mechanism other than the “10-year lag” hypothesis.

One possible candidate hypothesis is as follows: Mucosal immunity, including neutralizing IgA, is involved in the defense against HIV (9) and immunity, including mucosal immunity, decreases with age (10–12). In that case, AIDS may develop earlier as the age advances, and the detection rate of “AIDS cases” relative...
to that of “HIV cases” will consequently increase with age. Another possible candidate hypothesis, which is not necessarily incompatible with the former, takes into account how the acute clinical symptoms are generated. The acute symptoms could very well be a result of an inflammatory defense reaction, which may decline with aging. If so, it is possible that the reaction is stronger among young people than among older people. It is interesting to note that the detection rate of “AIDS cases” increased until the age of 50 years, eventually reaching a plateau there (Fig. 4). In females, the detection rate of “AIDS cases” ceased to increase around the age of 40 years. If age-associated immunological decline is responsible for the increasing rate of detected “AIDS cases,” the related immunological change is expected to begin early in life, such as thymus involution (http://en.wikipedia.org/wiki/Thymus).

The present author notes that most of the above arguments are conjectural and based on assumptions, the validity of which is to be verified by clinical data. The following information will be crucial in understanding the phenomenon presented: (i) the clinical latency of AIDS that may be variable according to the infection route, sex, and age. (ii) the nature of the acute-phase syndrome and factors that enhance it, such as route of infection and exposure dose. (iii) mucosal immunity
involved in sexually transmitted HIV/AIDS infection and the influence of aging and gender on it.

In conclusion, the present observations remind us of the currently limited understanding of the pathophysiology of the host response that immediately follows HIV infection and the lifelong evolution of the immune system of humans.

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Conflict of interest  None to declare.

REFERENCES
1. Reporting form of Acquired Immunodeficiency Syndrome (including HIV infections) Available at <http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou11/pdf/01-05-07.pdf>, downloaded on January 21, 2014. Japanese.
2. National Institute of Infectious Diseases and Tuberculosis and Infectious Diseases Control Division, Ministry of Health, Labour and Welfare. AIDS/HIV Surveillance in Japan 1985–1997. Infect Agents Surveillance Rep. 1998;19:72’-3’.
3. National Institute of Infectious Diseases and Tuberculosis and Infectious Diseases Control Division, Ministry of Health, Labour and Welfare. HIV/AIDS in Japan, 2012. Infect Agents Surveillance Rep. 2013;34:251’-2’.
4. Specific Disease Control Division, the Ministry of Health, Labour and Welfare. Annual report of the National AIDS Surveillance Committee for year 2012. Available at <http://api-net.jfap.or.jp/status/2013/13nenpo/nenpo_menu.htm>. Accessed February 18, 2015. Japanese.
5. Yoshikura H. HIV Epidemic in Japan: different detection patterns between male homosexuals and male heterosexuals. Jpn J Infect Dis. 2011;64:349-50.
6. Lavreys L, Baeten JM, Overbaugh J, et al. Virus load during primary human immunodeficiency virus (HIV) type 1 infection is related to the severity of acute HIV illness in Kenyan women. Clin Infect Dis. 2002;77:81.
7. Fauci, AS, Clifford Lane H. Human Immunodeficiency Virus (HIV). In: Braunwald E, Fauci AS, Kasper DL, editors. Harrison’s Principles of Internal Medicine. 15th ed. Columbus, OH: McGraw-Hill; 2001. p.1852-1913.
8. Hunt RM. Human immunodeficiency virus and AIDS; the course of the disease, Microbiology and Immunology On-line. Available at <http://www.microbiologybook.org/lecture/hiv3.htm>. Accessed February 18, 2015.
9. Hur EM, Patel SN, Shimizu S, et al. Inhibitory effect of HIV-specific neutralizing IgA on mucosal transmission of HIV in humanized mice. Blood. 2012;120:4571-82.
10. Arranz E, O’Mahony S, Barton JR, et al. Immunosenescence and mucosal immunity: significant effects of old age on secretory IgA concentrations and intraepithelial lymphocyte counts. Gut. 1992;33:882-6.
11. Schmucker DL, Heyworth MF, Owen RL, et al. Impact of aging on gastrointestinal mucosal immunity. Dig Dis Sci. 1996;41:1183-93.
12. Schmucker DL, Owen RL, Outenreath R, et al. Basis for the age-related decline in intestinal mucosal immunity. Clin Dev Immunol. 2003;10:167-72.