HIV/AIDS in Japan: route and age of infection that shaped the epidemics in 1987-2016

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HIV/AIDS in Japan: route and age of infection that shaped the epidemics in 1987-2016

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Running head: Route and age of infection affecting HIV epidemics
Key words: HIV/AIDS, infection route, age of infection; homosexuals vs. heterosexuals, immunological senescence

Summary
In Japan, HIV infection is classified as “HIV” or “AIDS” depending upon whether the infection was detected before or after development of AIDS. For male homosexuals, in the plot of the number of “AIDS” versus the number of “HIV”, the plots fell on a straight line with a slope close to 1. When the number of “HIV” stopped increasing, that of “AIDS” stopped increasing. The number of “HIV” in one region or in one age group was correlated with that of other regions or that of other age groups, respectively. No such correlation was detected for male heterosexuals.

Male homosexuals and females were detected more as “HIV” than male heterosexuals. Detection as “AIDS” increased with age in all the infection categories. Our analysis supported by others suggested that the higher rate of detection as “HIV” among male homosexuals and females than among male heterosexuals was attributable to higher risk of the receptive sexual intercourse, and the higher incidence of “AIDS” among elderlies to immunological senescence.

Introduction
In Japan, patients infected with HIV are notified as “AIDS” if they developed at least one of the index diseases of AIDS; if not, they are notified as “HIV” (http://www.acc.ncgm.go.jp/mhlwinfo/020/surveillance.html). The laboratory finding, such as, “CD4+ T cell count <200 cells/μl or CD4+ T-cell total lymphocytes <14%” (1), is not considered.

We reported that HIV infection was detected more as “HIV” in male homosexuals and females than in male heterosexuals, and more as “HIV” among younger populations than in older populations. We attributed the former to the infection route and the latter to immunological senescence (2). We could not, however, exclude behavioral factors, such as, “older male heterosexuals rarely visit clinics on account of negligence of risk of AIDS”, “they are reluctant in admitting their homosexual behavior”, etc. Similar ethnographic accounts of HIV/AIDS in Japan were compiled by DiStefano (3).
For further clarification, we examined correlation between different parameters, such as, detection as “HIV” or as “AIDS”, infection routes, age of the patients, geographical distribution, etc.

Materials and Methods

The data used were all derived from HIV/AIDS Surveillance Report issued by AIDS Surveillance Committee, Ministry of Health Labour and Welfare (http://api-net.jfap.or.jp/status/2016/16nenpo/16nenpo_menu.html).

Results

Trends of HIV/AIDS in Japan: In Fig. 1A, the annual incidence of patients detected as “HIV” was plotted in the x-axis against that detected as “AIDS” in the y-axis for Japanese male homosexuals (○), Japanese male heterosexuals (●) and Japanese females (△) from 1987 to 2016. It was found:

1. The number of “HIV” increased keeping pace with that of “AIDS” till 1996/1997 for male heterosexuals and till 2006/2007 for male homosexuals. When the number of “HIV” stopped increasing, the number of “AIDS” stopped increasing and the correlation between “HIV” and “AIDS” collapsed. For male heterosexuals, the correlation coefficient (CC) between “HIV” and “AIDS” was 0.85 in 1987-1996 (smaller closed circles) but 0.34 in 1997-2016 (larger closed circles); for male homosexuals, it was 0.98 in 1987-2006 (smaller open circles) but -0.01 in 2007-2016 (largest open circles).

2. When the number of “HIV” and that of “AIDS” was increasing, the slope of the plots of “HIV” vs. “AIDS” was 0.85 for male homosexuals and 1.23 for male heterosexuals, i.e. the slope was around 45° indicating that the pace of increase was the same for “HIV” and “AIDS”. After collapse of the correlation, the plots were clustered where the number stopped increasing.

3. Plots for male heterosexuals were clustered in the upper left of the plots for male homosexuals and females, i.e., the infection was detected more frequently as “AIDS” among male heterosexuals than among male homosexuals and females.

4. Plots for Japanese females were scattered in the close proximity of the approximation line of the plots for male homosexuals, i.e., male homosexuals and females were similar in the pattern of detection of infection with HIV.

The year 1996/1997 was when the annual incidence of male heterosexuals (△ ▲) stopped increasing (gray arrow in Fig. 1B); the number of foreign female “HIV” (□) came down to the level of Japanese female “HIV” (●) (gray arrow in Fig. 1C); among foreign males, incidence of heterosexuals (▲) plateaued and began to be superseded by that of homosexuals (○) (Fig. 1D); and Japanese male heterosexuals infected in Japan started to supersede those infected abroad (Fig. E).

Correlation between “HIV” and “AIDS” in different regions: In Fig. 2A, plotted is annual number of “HIV” in the x-axis against that of “AIDS” in the y-axis for male heterosexuals and male homosexuals for different regions in Japan (female data were not studied on account of the low incidences). The slopes for male homosexuals...
ranged from 0.74~0.75 in Kinki and Tokyo to ~1.328 in Kanto-Koshinetsu, Chugoku-Shikoku-Kyushu and Tokai. The milder slope indicates that the patients were detected more as “HIV”, while the steeper slope indicates that the patients were detected more as “AIDS”. Kinki and Tokyo are rather urban, while Kanto-Koshinetsu etc. are rather rural. The regional variation was, however, difficult to interpret, as the regions were mixtures of urban and rural prefectures. We rather note that the slopes of the regions did not shift much away from 1 (or ~45°). The plots were merged together in Fig. 2B; they were clustered diagonally from the lower left to the upper right. Plots for male heterosexuals (closed symbols) were always on the upper left of those for homosexuals (open symbols).

The above plot patterns suggested that geographical spread of HIV/AIDS in Japan was uniform and synchronous. For further confirmation, annual incidence of “HIV” among male homosexuals in one region was plotted in the x-axis against that of those in other regions. Plots of Hokkaido-Tohoku-Hokuriku against the other regions are shown in Fig. 3C. The CCs obtained through such plots are tabulated; for male homosexuals; incidences of “HIV” were inter-correlated (CC>0.7) in all the region pairs (Table in Fig. 3A1). Among male heterosexuals, the incidences of “HIV” in prefectures were generally uncorrelated with possible exception of Kinki vs. Chugoku-Shikoku-Kyushu (CC=0.708) (Table in Fig. 3B). As correlation between “HIV” and “AIDS” among male homosexuals collapsed in the middle of 1997-2016 (Fig. 1A), the 1997-2016 data were split into 1997-2006 and 2007-2016 data and analyzed. The correlation between the regions collapsed too in 2006/2007 (compare tables in Fig. 3-A2 and Fig. 3-A3).

In Fig. 3D the number of “HIV” (upper panel) or “AIDS” (lower panel) was plotted in the y-axis against population size of prefectures in the x-axis. The number of the patients y could be expressed as a function of the population size x with an equation y = Cx^s, where C is a constant. The slope s was ~1.5 from 1997 till 2016 both for “HIV” and “AIDS”. The population size dependency of HIV/AIDS epidemics was thus not affected by the epidemiological transitions in 1996/1997 or 2005/2006 (See (4) for plots before 1997).

Correlation between incidence in one age group and that in another: The data added for 5-year time span, 1997-2001, 2002-2006, 2007-2011 and 2012-2016 were used. Here, we examined whether increase or decrease of incidence in one age group was correlated with that in another age group. Positive correlation will emerge when two age groups share the same epidemiological platform. Fig. 4A shows the plot of “HIV” in age group <19 years in the x-axis against “HIV” in other age groups in the y-axis for male homosexuals. All the plots run in parallel. The plot for 20-29 years was on the top followed by that of the other age groups in the order of increase of age, which was as if young homosexuals were attracted to homosexuals of nearer age. CCs tabulated for all the combinations of age groups were all >0.7 suggesting that there was no age barrier among male homosexuals.

HIV incidences in one age group of females were plotted in the x-axis against those of male heterosexuals in various ages in the y-axis. The incidences of the pair of 30-39 year females with 50-59 year males (CC = 0.786) and pairs of 40-49 year females with 20-29 year males (CC = 0.912) and with >60 year males (CC=0.828) were inter-
correlated (Figs. 4B and 4D); these age pairs may be pairs of preference. There was no other pairs inter-correlated (Fig. 4D). Females >60 years were disregarded in this analysis on account of the low incidence (6~14 per the 5-year time span).

Relation between the age of the patients and detection as “HIV” or as “AIDS”: The 5-year time span data, 1997-2001, 2002-2006, 2007-2011 and 2012-2016, were again used. The plot of “AIDS” in the y-axis against that of “HIV” in the x-axis showed:

1. Plots for younger people were on the right and those for older people on the left (Figs. 5A); typically for male homosexuals, the plots running parallel shifted leftward with the advance of age (Fig. 5A1); ratio of “AIDS” relative to “HIV” was calculated from the approximation lines and plotted in the y-axis against age in the x-axis (see an insert on the right side of Fig. 5-A1); the ratio linearly increased from 0.05 in < 29 years to 1.05 in 50-59 years. The same trend was observed for male heterosexuals and females.

2. The plots for females were clustered in the close vicinity of the extrapolated approximation line of male homosexuals (Fig. 5-A4), suggesting that females and male homosexuals constituted one epidemiological group and male heterosexuals another.

In Fig. 5B, the ratio of “AIDS” to “HIV” (AIDS/HIV) was plotted against the age of the patients from 1987 to 2016. With advance of age, the ratio continued rising in male heterosexuals (●), while the ratio stopped increasing around in 40-50 years in male homosexuals (O) and in females (□) as reported previously (2). Thus, the above pattern remained unchanged from the start of the HIV/AIDS epidemic till 2016.

Fig. 5C shows the plot of number of patients detected as “HIV” (open symbols) or as “AIDS” (closed symbols) in the y-axis against age of the patients in the x-axis. Among male heterosexuals (Fig. 5-C1), the peak of “HIV” (△) was 30-39 years and that of “AIDS” 40-49 years. For male homosexuals (Fig. 5-C2) and females (Fig.5-C3), the peak age of “HIV” (open symbols) and that of “AIDS” (closed symbols) were overlapping and shifted towards left (20-29/30-39 years).

Discussion

We previously reported that HIV infection was detected more frequently as “HIV” in male homosexuals and females than in male heterosexuals; we attributed it to severer symptoms of the acute HIV infection (AHI) associated with the receptive sexual intercourse (2). Actually, higher probability of progression to AIDS was correlated with shorter incubation and longer duration of AHI (5) that will increase the chance of detection as “HIV. According to Health in Men cohort in Sydney in 2001-2004, per-contact probability of infection for receptive sexual intercourse was 1.43% if ejaculation occurred inside the rectum but only 0.11% for insertive sexual intercourse if he was circumcised (6); and for 100 sexual intercourses per year, cumulative probability of transmission was estimatedly 0.0022 for female-to-male, 0.0043 for male-to-female and 0.043 for male to male transmission (7).

We also reported that HIV infection was detected more as “AIDS” among elders than among young people (2), which we attributed to the age-related change in immune response. Actually, Belanger et al (8) reported that among 393 patients
including 262 male homosexuals, progression from category B (similar to “HIV” in Japan) to category C (similar to “AIDS” in Japan) was longer for 37-46 years than for ≥47 years. According to Phillips et al (9), among hemophiliacs, the relative risk of developing AIDS by any given time after seroconversion was 1.45 for each 10 year increase in age. Similar age-related risk was reported by others (10-11). Similarity between immunologic alterations in HIV infected individuals and those associated with aging in HIV-free elderly was indicated (12).

One intriguing observation was the high correlation of annual incidence of “HIV” and that of “AIDS” among male homosexuals. As it was expected that detection as “HIV” preceded detection as “AIDS”, we plotted annual incidence of “HIV” against annual incidence of “AIDS” in one year later, two years later, etc. (+ frameshift) or in one year before, two years before, etc. (- frameshift) (Figs. 6A and 6B) and the CC between “HIV” and “AIDS” was calculated (called “lag analysis”). The CCs thus obtained were plotted in the y-axis against number of + or - frameshifts in the x-axis (Fig. 6C). For male homosexuals, the peak CC was obtained with the frameshift +0 (○). As the peak was rather flat for 2001-2016/1997-2012 (plot pair B-B’), similar plots were done for 1989-1998/1990-1999 when HIV/AIDS incidence was increasing (plot pair A-A’) (△). Again the peak was at the frameshift +0. It indicated that most HIV infection was detected either as “HIV” or as “AIDS” within a short period after infection.

Actually, in a community-based screening in the United States, among 90 participants, 77% of them experienced acute retroviral syndrome (ARS) associated with AHI (13), and in a study by Grupo Argentino de Séroconversión (14), among the cohort of those diagnosed during primary infection, 74% presented with acute retroviral syndrome (ARS). As for incubation period, according to Swiss and Australian cohort study (5), the time between infection and the patients’ visit to clinics was 21.5 days (5-70 days) and its duration was 15.5 days (3-67 days). Probably most HIV infections among male homosexuals are detected as “HIV” or as “AIDS” shortly after infection. The synchronized homogeneous geographical spread (Fig. 2) being taken into account, their HIV epidemic was like an epidemic of the acute infection.

The situation was different for male heterosexuals, whose insertive sexual intercourse was less risky (6-7). The AHI could be unnoticed and the infection could be detected only after development of “AIDS” as late as 10 years later (15).

In Fig. 6D plotted are the total number of “AIDS” together with that of “HIV” till 2016 against age of the patients, which gives a good perspective on the current HIV/AIDS epidemic in Japan, i.e.,:

- HIV infections among homosexuals and females are indistinguishably similar but they are entirely different from HIV infections in male heterosexuals.
- The peak of the incidence was in 25-29/30-39 years for all the categories.
- On the left side of the peak (<29 years), most infection was detected as “HIV” irrespective of the infection route. On the right side of the graph, i.e., age group >29 years, there was a big difference between male homosexuals/females and male heterosexuals.
- In male homosexuals and females, the area of “HIV” shrunk with age, but the belt of “AIDS” extending to the right remained of the same width, which was
explained by decrease of homosexual population with age and relative increased detection as “AIDS” owing to immunological senescence.

- In male heterosexuals, the area on the right side of the peak was much fatter both for “HIV” and “AIDS”. As for the fat area of “HIV”, the “fatness” was probably brought about by severer AHI symptoms in old ages due to immunological senescence. The fat area of “AIDS” could be attributable to two factors: one, the immunological senescence that will increase not only detection as “HIV” but also as “AIDS” (portion below the dotted line); second, people infected young whose infection was not detected due to mild or absent AHI symptoms develop AIDS after long incubation (portion above the dotted line).

Final question is the number of the HIV-infected population in Japan. The findings presented in this report suggest that total number of HIV/AIDS in Japan was not very far from sum total of “HIV” and “AIDS”, i.e., 23,055 (15,839 “HIV” plus 7,218 “AIDS” reported till 2016). The uncertainty comes largely from male heterosexuals infected when young who have not developed AIDS yet, which is a “reserve army” of the portion above the dotted line in Fig. 6-D1; additional uncertainty comes from number of the HIV-infected people deceased (the annual deaths from 2012 to 2016 were 50, 45, 45, 52 and 132 reported in respective years to the National Statistics). We previously estimated that the number of HIV/AIDS in Japan was about 4-5 times higher than the reported number based on the assumption that the latency of detection as “AIDS” was 10 years and detection as “HIV” at 5 years post infection (16). The estimation was surely an overestimation.

Conflict of Interest: None to declare.

References
8. Belanger F, Meyer L, Carre N et al. Influence of age at infection on human immunodeficiency virus disease progression to different clinical endpoints: the


Figure Legends

Fig. 1: Epidemiological trends of HIV/AIDS in Japan in 1987-2016. A: Number of “HIV” in the x-axis vs. number of “AIDS” in the y-axis, B: Annual incidence of Japanese male heterosexuals or homosexuals; C: Annual incidence of “HIV” among Japanese and non-Japanese females; D: Annual incidence of “HIV” among non-Japanese male heterosexuals and homosexuals; E: Ratio of infection in Japan to that abroad (Japan/abroad) among Japanese male heterosexuals.

Fig. 2: Plot of number of “HIV” (x-axis) against number of “AIDS” (y-axis) for different regions (A) and plots merged (B). C: the location of the regions.

Fig. 3: Correlation between annual incidence of “HIV” in one region to “HIV” in another for male homosexuals in 1997-2016 (A1), in 1997-2006 (A2) and in 2007-2016 (A3) and among male heterosexuals in 1997-2016 (B). C: Plot of Hokkaido-Tohoku-Hokuriku (x-axis) to other regions (y-axis). D: Plot of “HIV” (upper panel) or “AIDS” (lower panel) in the y-axis against population size of prefectures in 2010 (x1,000) in the x-axis.

Fig. 4: Correlation between one age group to other age groups with respect to incidence of “HIV”. A: “HIV” in age group <19 years in the x-axis against “HIV” in other age groups in the y-axis for male homosexuals. B: “HIV” in females in age group <19 years or 40-49 years in the x-axis against HIV among male heterosexuals in different age groups in the y-axis. C: CCs between “HIV” incidences among different age groups in male homosexuals. D: CCs between “HIV” in females and “HIV” in male heterosexual in different age groups.

Fig. 5: Plot of “HIV” vs. “AIDS” for different age groups. A1: male homosexuals
accompanied by a graph showing ratio “AIDS”/“HIV” in different age groups (y for x=1 in equations, y=0.05x^{1.11} for <29 years; y=0.33x^{0.98} for 30-39 years; y=0.81x^{0.91} for 40-49 years; y=1.05x^{0.94} for 50-59 years; and y=0.35x^{1.18} for >60 years); A2: male heterosexuals; A3: females; A4: A1-A3 merged. B: “AIDS”/“HIV” in different age groups since 1987. C: Frequency of detection as “HIV” (open symbols) or as “AIDS” (closed symbols) in different age groups among male heterosexuals (C1), male homosexuals (C2) and females (C3).

Fig. 6: Lag analysis. A: Annual incidence of “HIV” was paired with that of “AIDS” in coming years (frame +) or with past years (frame -). “HIV”-“AIDS” whose CC was calculated are boxed. B: Annual incidence of “HIV” plotted against “AIDS shifted forward (frame +) or backward (frame -)”. C: Plot of CC in the y-axis against frames + or – in the x-axis. D: Total number of the patients detected as “HIV” or as “AIDS” in 1985-2016 (y-axis) plotted against age groups (x-axis) for male heterosexuals (D1), male homosexuals (D2) and females (D3).
A: Japanese males and females

B: Japanese males
○: male homosexuals detected as “HIV”
●: male homosexuals detected as “AIDS”
△: male heterosexuals detected as “HIV”
▲: male heterosexuals detected as “AIDS”

C: Females:
○: Japanese; □: non-Japanese

D: Non-Japanese males
▲: heterosexuals; ○: homosexuals

E: Ratio of infection in Japan to abroad (Japan/abroad) among Japanese male heterosexuals

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Fig. 1
Fig. 2
A: Correlation between HIV in one region to HIV in another region among male homosexuals

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B: Correlation between HIV in one region to HIV in another region among male heterosexuals

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C: Plot of Hokkaido-Tohoku-Hokuriku (x-axis) vs. other regions (y-axis) for shaded part of panel A1

D: Plot of “HIV” or “AIDS” per prefecture in the y-axis vs. population size of prefectures (x1000) in the x-axis
A: Male homosexuals in age group <19 years (x-axis) against those in other age groups (y-axis) (data corresponding to the shaded part in Table 1C)

B: Male heterosexuals in different age groups
Females 30-39 years vs. Females 40-49 years

C: Correlation between HIV incidences in different age groups among male homosexuals (1997-2016)

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D: Correlation of HIV incidences in male heterosexuals (column) vs. females (raw) in different age groups (1997-2016)

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A: Number of “HIV” (x-axis) vs. number of “AIDS” (y-axis) for 1997-2001, 2002-2006, 2007-2011 and 2012-2016 periods

A1: Male homosexuals

Fraction of “AIDS” in different age groups

A2: Male heterosexuals

A3: Females

A4: Male homosexuals, male heterosexuals and females merged

B: Detection as “AIDS” relative to “HIV” in different age groups

C1: Male Heterosexuals

C2: Male Homosexuals

C3: Females
### Table for lag analysis

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**Fig. 6**

- **A**
  - **Table for lag analysis**
  - **Male homosexuals**
  - **Female homosexuals**

- **B**
  - **Graph showing correlation coefficients**
  - **Y = 0.3822x**
  - **R² = 0.9501**

- **C**
  - **Graph showing number of HIV and AIDS per age group (1985-2016)**
  - **D1: Male heterosexuals**
  - **D2: Male homosexuals**
  - **D3: Females**

- **D**
  - **Graph showing number of “HIV” and “AIDS” per age group (1985-2016)**
  - **D1: Male heterosexuals**
  - **D2: Male homosexuals**
  - **D3: Females**

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**Accepted Manuscript**