Original Research Report

Time from Diagnosis to the Initiation of Antiretroviral Therapy among Japanese Infected with HIV

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Background and Objective : Patients unknowingly infected with human immunodeficiency virus (HIV) comprise a strong potential source of transmission. Therefore, minimizing the time that patients spend between infection and diagnosis in the source is important. Obtaining sufficient information about such patients was difficult in Japan due to the small population of individuals who were HIV-infected. Therefore, we tracked such individuals over the course of 8 years.

Subjects and Methods : Of HIV-infected patients registered at Osaka National Hospital, 492 who had been untreated for at least 30 days were enrolled. A Cox proportional hazard regression analysis was performed using the time between the initial diagnosis and the initiation of antiretroviral therapy (ART) as a response variable. The annual rates of decrease of untreated patients with HIV infection were also calculated.

Results : Kaplan-Meier survival curves were drawn for patients with HIV who had average, high or low $CD4^+$ cell (CD4) counts and HIV RNA loads. Risk ratios were $0.994\log_{10}$ for $CD4^+$ T cell count and $1.446\log_{10}$ for HIV RNA. The average time between initial diagnosis and ART initiation was 449.9 days (1.28 years). 1) One-third of individuals who are HIV-positive needed to initiate ART within 1 year of diagnosis, 2) another one-third of patients needed to initiate ART in about 3 years of diagnosis, and 3) the remaining patients progressed slowly.

Conclusion : The study indicated more clear that many individuals with HIV in Japan visit hospital only after their condition progressed nearly to the point of developing acquired immune deficiency syndrome (AIDS). The fact will be helpful for strategy to let more individuals visit the hospital sooner for HIV testing and the therapy.

Key words：acquired immunodeficiency syndrome (AIDS), human immunodeficiency virus (HIV), anti-retroviral therapy (ART), Cox proportional hazard regression analysis, patients unknowingly with HIV

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Introduction

Antiretroviral therapy (ART) is not recommended in patients infected with human immunodeficiency virus (HIV) who demonstrate sufficient cell-mediated immune response[1,2]. However, such patients are a strong potential source of transmission, along with those who are unknowingly infected with HIV. Many campaigns to prevent HIV infection have been developed over the last two decades[3-5]. Basic social support[6] systems have also been provided so that patients unknowingly with HIV are encouraged to visit hospital sooner. Despite these efforts, the number of newly registered patients infected with HIV is increasing[7], and thus the population of potential source of transmission remains substantial.

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Since the potential source of transmission should be reduced, determining the time interval between initial infection and diagnosis is important. The time interval from diagnosis to the initiation of ART has already been performed in a large population of oversea patients infected with HIV[8–11]. These studies calculated a long latency period from initial infection to the development of acquired immune deficiency syndrome (AIDS)[12–15] and established average timelines from diagnosis to the initiation of ART. Based on these results, we could estimate the amount of time patients spend unknowingly infected prior to diagnosis by drawing the time between diagnosis to the initiation of ART from the latency period.

Comparable studies were difficult to perform in Japan because of the small population of individuals infected with HIV. However, such studies are important, as we should minimize the time that patients spend between infection and diagnosis in the source. Therefore, we collected data from Japanese individuals who were HIV-positive over the course of 8 years. Here, we present a timeline from diagnosis to the initiation of ART using a Cox proportional hazard regression model.

Subjects and Methods

In total, 832 patients with HIV were examined at Osaka National Hospital between June 1998 and March 2006. Of these patients, 492 who had been untreated for more than 30 days were enrolled in the study. The period of 30 days that the data should be omitted was set up for the following two reasons. 1) The ART is initiated after opportunistic infection was cured. 2) This is a period necessary to apply for a social support for HIV infection.

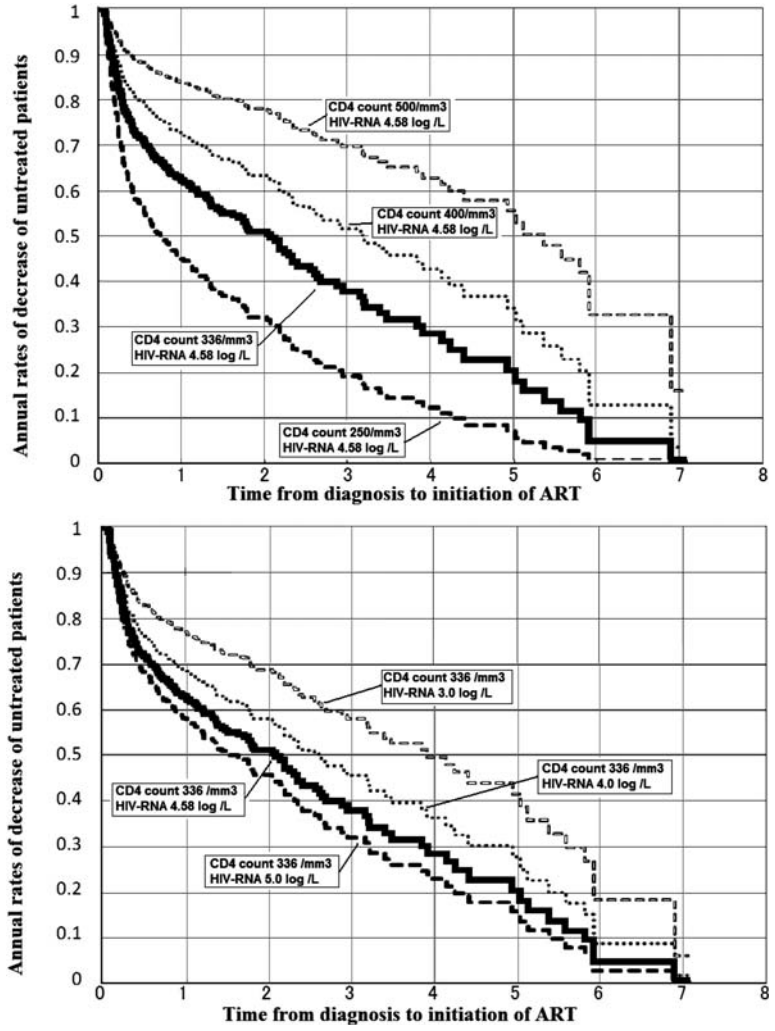

Figure 1 Kaplan-Meier survival curves for various kinds of patients.
The solidlines indicates patients with average $CD4^+$ T cell count and average HIV RNA loads.
The broken lines denote patients with high or low $CD4^+$ T cell counts and HIV RNA loads.

For these reasons, it takes a month to prepare for initiating ART usually. One month is necessary to apply for a certification of dismals. Data pertaining to $CD4^+$ and $CD8^+$ T cell counts, HIV RNA loads (HIV RNA), hemoglobin (Hb), neutrophils (N), lymphocytes (L), monocytes (M), eosinophils (E), basophils (B), platelets (Plt) and age at the patient's first medical test were obtained. The time from diagnosis to the initiation of ART was also obtained. Here, patients were regarded to go to hospital at the same time of being positive for the test.

A Cox proportional hazard regression analysis (PHREG procedure, SAS software) was performed in a stepwise manner using HIV reduction as the endpoint. The response variable was the time from diagnosis to the initiation of ART. The censored variable was the initiation of ART, which we defined as HIV reduction. Explanatory variables were $CD4^+$ and $CD8^+$ T cell counts, HIV-RNA, basic blood parameters, and age.

Kaplan-Meier survival curves were drawn for patients with 250, 336 (average), 400, or 500 $CD4^+$ T cells per mm^3 and an average HIV-RNA (4.58 $\log_{10}$ per mL ; The upper row of Fig. 1). Additional curves were drawn for patients with average $CD4^+$ T cell counts (336 per mm^3) and viral loads of 3.0 $\log_{10}$, 4.0 $\log_{10}$, 4.58 $\log_{10}$ (average), or 5.0 $\log_{10}$ per mL (The lower row of Fig. 1). Annual rates of decrease of ART-untreated patients with average $CD4^+$ T cell counts and HIV RNA loads were calculated for patients who had the times of 0−0.5, 0.5−1, 1−2, 2−3, or 3−6 years from diagnosis to the initiation of ART.

Results

In total, 492 subjects were enrolled in the study (473 : 19, male : female) and the mean patient age was 35.6 ± 10.5 years. Sixteen subjects had hemophilia. All patients were infected with HIV type 1. Average $CD4^+$ and $CD8^+$ T cell counts were 336 ± 224/mm^3 and 861 ± 603/mm^3, respectively. Average blood parameters values were calculated to be 14.2 ± 1.7 g/dL (Hb), 228.4 ± 72.9 × 10^3 per mm^3 (Plt), 3,890 ± 3.820 per mm^3 (N), 1,790 ± 1,370 per mm^3 (L), 449 ± 412 per mm^3 (M), 173 ± 207 per mm^3 (E), and 15 ± 39 per mm^3 (B). The average HIV RNA level was 4.58 ± 0.83 $\log_{10}$ per mL.

The Cox proportional hazard regression analysis had an event and censor count of 267 and 225, respectively (Table 1). Only the $CD4^+$ T cell count and viral load were significant variables in a stepwise manner ($p < 0.0001$). Risk ratios are 0.994 for CD4 count and 1.446 $\log_{10}$ for HIV RNA. A risk ratio of 0.994 means that a patient with a smaller 100 per mm^3 in his/her $CD4^+$ T cell counts has a 1.83 times (0.994^{-100}) higher risk and a risk of 1.446 means that a patient with a greater 1.0 $\log_{10}$ per mL increase in HIV RNA loads has a 1.446 times higher risk. The average time from diagnosis to the initiation of ART was 449.9 days (1.28 years).

Kaplan-Meier survival curves are shown in Fig. 1. The vertical axis displays the proportion of ART-untreated patients and the horizontal axis the time from diagnosis to the initiation of ART. Of the patients with average $CD4^+$ T cell counts and HIV RNA loads, the percentage of ART-untreated patients decreased to blow 40% in 3 years (Fig. 1). The annual rate of decrease of ART-untreated patients with the times of 0−0.5 years was particularly rapid (i.e., 0.56 ; Table 2). The annual rates of decrease of untreated patients with the times of 1−2, 2−3, or 3−6 years were similar, approximately 0.11 per year. If the ART-untreated population maintained such a rate of decrease, untreated patients would be gone in about 9 years as a latency period.

Discussion

We were able to determine statistically relevant curve in the present study, despite a small sample size, and characterized the Japanese population of individuals infected with HIV as follows : 1) one-third of patients

Table 2 Annual rates of decrease of ART-untreated patients with average $CD4^+$ T cell counts and HIV RNA loads

Observed interval (year)	Annual decrease rate
0 to 0.5	0.56/year
0.5 to 1	0.19/year
1 to 2	0.11/year
2 to 3	0.13/year
3 to 6	0.10/year

Table 1 Stepwise Cox proportional hazard regression analysis

Explanatory variable	Estimate	Standard error	Risk ratio	*F*-Value	*p*-Value
CD4 count	−0.00605	0.0005	0.994	151.26	<0.0001
$\log_{10}$ (HIV-RNA)	0.36912	0.0872	1.446	17.92	<0.0001

The survival function $S_i(t)$ is denoted as follows ; $S_i(t) = S_0(t)^{\exp[\omega]}$, where $\omega = -0.00605 \times (CD4_i - CD4_{mean}) + 0.36912 \times (\text{HIV RNA}_i - \text{HIV RNA}_{mean})$ and the survival function $S_i(t)$ for the i th subject with "$CD4_i$" count and $\log_{10}$ (HIV RNA_i) and the survival $S_0(t)$ for the subject with "average CD4 count" and "$\log_{10}$ (average HIV RNA)".

who are diagnosed as HIV-positive need to initiate ART within 1 year of diagnosis, 2) another one-third of patients need to initiate ART within 3 years of diagnosis, and 3) the remaining patients progress slowly.

The rate of decrease of untreated patients within one year of diagnosis, especially 0.5 years, is relatively rapid. This indicates that one-third of patients are diagnosed only after their condition has progressed nearly to the point of developing AIDS. Another one-third of patients also initiate ART within 3 years of diagnosis. Therefore, the number of patients who need to initiate ART during a short time is considerably large.

Next, we considered whether a speed of progression in Japanese at HIV infection is faster than a speed in non-Asian. Moller *et al.* determined survival curves using patient death as the endpoint and presented the number of survivors on 0, 3, 6 and 9 years post-diagnosis. From their report, we calculated the annual rates of decrease of untreated patients in 3−6 years. The annual rates of decrease were between −0.11 and −0.15, depending on the condition of the present study with respect to $CD4^+$ T cell counts and HIV RNA levels, while the rates were between −0.09 and −0.10 in the present study. The rates in Japanese are similar or more moderate. Therefore, speed of progression in Japanese at HIV infection was found to be similar to the one of non-Asian patients. This indicates that the latency period between them is the same. The time of progression from infection with HIV to the onset of AIDS is reported in non-Asian populations as 8−12 years[12–15]. In spite of this long latent period, the average time that patients seek treatment is just 1.28 years. The shortness of the average time indicates that many Japanese with HIV spend a long period of time not knowing that they are infected. This is s considerably serious issue.

We present an overview of HIV infection in the Japanese population (Fig. 2). The first possibility (A) is to prevent HIV transmission, the second (B) is to increase the number of patients visiting hospital sooner, and the third (C) is to initiate ART more quickly. The overview highlights the existence of a large number of patients who are unknowingly infected with HIV (dark gray area), which is a large source of potential HIV transmission. Therefore, actions are necessary to encourage individuals to get tested in order to prevent HIV transmission, diagnose patients who are HIV-positive early, and initiate ART as soon as possible.

Although many such campaigns focusing on action (A) have been already performed, they have been largely unsuccessful. However, we characterized the Japanese population of individuals infected with HIV by determining statistically relevant curve. With respect to action (B)

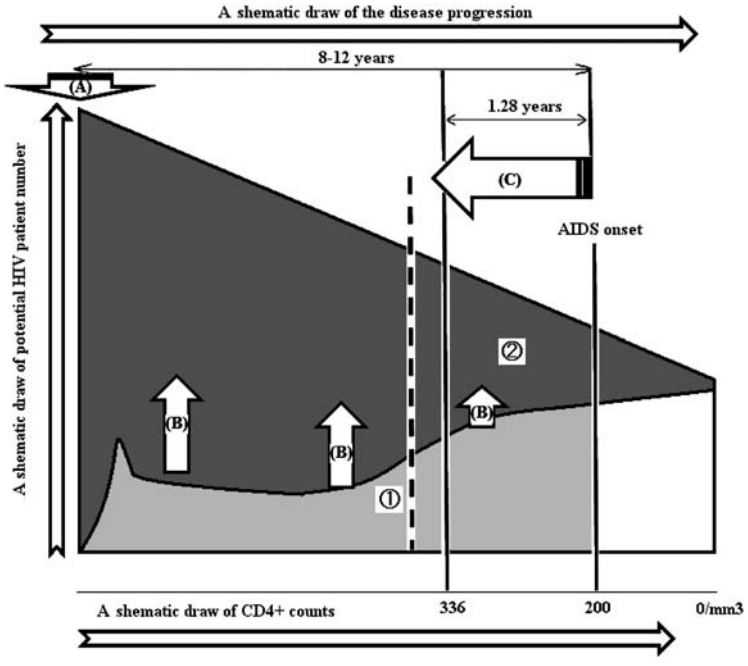

Figure 2 An overview of Japanese patients infected with HIV.
The dark-gray area indicates a high-risk potential HIV transmission source and the light-gray area denotes a low-risk potential source. Ideally, the dark-gray area ① should be equal to the light-gray area ②. (A) The action to prevent HIV transmission, (B) the action to increase the number of patients visiting hospital during the early stages of disease, and (C) the action to initiate ART early.

listed above, the results should help persuade more individuals to visit the hospital sooner for HIV testing. Following recent CD4$^+$ T cell count guidelines[1, 2, 16] for prescribing treatment is a promising step toward starting patients with HIV on ART early. With respect to action (C) listed above, such measures will help reduce the number of potential HIV transmitters. Some studies have already demonstrated that early ART initiation is effective at preventing HIV transmission[17–19]. Furthermore, if ART is initiated early, regardless of CD4$^+$ T cell count, HIV transmission may be reduced even further.

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日本人 HIV 感染症患者における診断から抗 HIV 療法の開始までの時間

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背景と目的：HIV 感染を知らずに過ごす未治療患者は，強力な感染源である。このような患者が感染から初めて病院を受診するまでの時間，受診から治療までの時間を知ることは，この強力な感染源への対策を取るうえで重要である。しかし，これまでは日本人 HIV 感染者のデータ規模は小さいために，これらを知ることができなかった。われわれは 8 年のデータを集積しこれを示した。

被験者と方法：大阪医療センターにおいて 30 日を超える無治療期間を持つ HIV 患者 492 人が研究対象とし，Cox 回帰分析を行った。

結果：解析の結果，CD4 数が 100 少なくなると治療開始のリスクは 1.83 倍に，ウイルス量が 1.0 log 多いと 1.446 倍に上昇した。平均通院期間は 1.28 年しかなかった。患者のうち 1/3 が 1 年以内に治療を開始し，次の 1/3 が 3 年以内に治療を開始していた。残る患者の進行は安定していた。

結論：本研究は，日本におけるどの程度の HIV 感染者が治療前のどの時期に検査を受け，病院を受診するかを明らかにした。かなり多くの患者が感染能力を保持したまま感染を知らずに過ごしていた。これらの結果は，患者により早く検査と治療を受けさせるためにどこに力を注ぐべきかを考えることに役に立つであろう。

キーワード：後天性免疫不全症候群，ヒト免疫不全ウイルス，抗レトロウイルス療法，Cox 比例ハザード回帰分析，自覚なき HIV 感染症患者