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Immune Status and Epidemiological Characteristics of Human Immunodeficiency Virus Seroconverters in Korea, 1999−2009

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Abstract

Objectives: The detection of HIV seroconverters increased annually since HIV antigen/antibody testing kits have been available widely in South Korea. This study aimed to identify the epidemiological characteristics of HIV seroconverters and their immune level at HIV diagnosis.

Method: We analyzed the epidemiological and immunological characteristics of 341 HIV seroconverters among 6,008 HIV-diagnosed individuals from 1999 and 2009. The analysis of immune level and epidemiological factors of HIV sero-converters was conducted by using chi-square test on SAS version 9.1.

Results: The seroconverters among newly-identified HIV cases each year increased from 0.5% in 1999 to over 5% or in 2009. The sex ratio of seroconverters was 18:1 (male:female), and 33% were in their 30s, and 28% were in their 20s. Reasons for HIV testing were involvement in voluntary test due to risky behaviors (43%), and health check-up (36%). Discovery of HIV infection occurred primarily in hospitals (84%). Among seroconverters, 55 percent had a CD4 T-cell count of more than 350/μl.

Conclusion: Korean HIV seroconverters tended to be younger at diagnosis, diagnosed during a voluntary test, and their CD4+ T-cell counts at HIV diagnosis were higher than those of non-seroconverters all HIV-infected individuals. This study of HIV seroconverters will be important foundational in future studies on HIV incidence, disease progress, and survival rate.

1. Introduction

In Korea, around 700−900 cases of human immu-nodeficiency virus (HIV) infection are reported recent every year. However, in most cases, it is difficult to identify the time of infection and nearly 70% of the cases are diagnosed in a stage where curative treatment is required [1]. In addition, 99% of HIV infections are

found to have been transmitted through sexual contact. By the end of December 2011, the cumulative number of HIV-infected individuals in Korea reached 8544 and, of that number, 888 were newly identified in 2011 alone, which is an almost 15% increase from 1 year earlier. Although the cumulative number itself is not very large compared to those of other countries, the annual number of new HIV infections has continued to rise [2−4].

According to past studies, 40−90% of recent HIV infections were accompanied by symptoms of acute retroviral syndrome such as fever, fatigue and sore throat. However, retrovirus is hard to detect at that stage with ordinary HIV antibody tests: it is known that only 25% test positive [5]. In the past, the diagnose of early HIV infection mostly depended on clinical observation of patients. More recently, however, HIV antigen tests that allow the diagnosis of HIV infection even in the pre-seroconversion phase and nucleic acid amplification tests (NATs) have become widely available, which made it possible to identify early HIV infection [6]. In the UK, NATs were administered to acute retroviral syndrome patients and HIV risk-groups, which resulted in the diagnosis of early HIV infection [7].

In 2005, diagnostic laboratories in Korea, began NATs on all blood donations, the fourth-generation reagent antigen/antibody tests were adopted in HIV testing laboratories in hospitals, clinics and public health centers [8]. All these led to an increase in the number of HIV cases detected at an early stage of infection. In particular, since there has been a recent increase in the number of patients who are with a negative or indeterminate antibody test but are suspected of HIV infection among samples submitted for testing. It seems that there is a need to study the annual number of seroconverters and the characteristics of and changes in HIV infection patterns among these patients.

Therefore, this study aimed to find out the scale and the trend of HIV seroconverters among HIV-diagnosed individuals in Korea from and analyze their epidemiological characteristics including the reason for HIV testing and immune status at HIV diagnosis.

2. Materials and Methods

2.1. Participants and methods

This study compared and analyzed the epidemiological and immunological characteristics of 6008 Koreans confirmed HIV-positive from 1999 to 2009, of whom 341 were HIV seroconverters. For the purpose of this study, a seroconverter was defined as a person who tested positive for a HIV antigen test or NAT and negative/indeterminate in an antibody western-blottest, but, after a certain period of time, tested positive subsequently. For a doubtful seroconvertor sample, we collected blood again after one weeks to 1 month depending on their HIV antigen/antibody reactions and

HIV testing conducted including western blot and additional CD4 T-cell counts to assess immune status. If a sample tested positive depending on western-blot profile in subsequent testing, the patient was classified as a seroconverter and registered as a HIV-infected individual and subjected to an epidemiological study.

2.2. HIV serology tests and CD4 T-cell counts

HIV antigen/antibody tests were conducted using the particle agglutination assay (SERODIA HIV-1/2; Fugirebio Inc, Tokyo, Japan) for coagulation response testing, Micro-ELISA System Antigen (Vironostika HIV-I Antigen; bioMérieux, Lyon, France), and Micro-ELISA System Antibody (Vironostika HIV Uni-Form II plus O, bioMérieux). Patient samples that tested positive in HIV antigen/antibody tests were subjected to additional HIV western blotting (HIV BLOT 2.2 Western Blot Assay; MP Diagnostics, Geneva, Switzerland) for confirmatory diagnosis of HIV infection. For CD4 T-cell counts, flow cytometry was used.

2.3. Statistical analysis

All HIV-infected individuals and seroconverters were compared on several epidemiological variables: sex, age, transmission route, screening site, marital status, reason for HIV testing and CD4 T-cell counts as an indication of how advanced the disease was. The subjects were divided into six age groups: <20 years; 20−29 years; 30−39 years; 40−49 years; 50−59 years; ≥60 years. Marital status was reported as either "married" or "unmarried", and "married" included "widowed", "separated", and "divorced". Reasons for HIV testing were categorized into four groups: health check-ups, risky behaviors, blood donation, and history of AIDS-related illness. The health check-up group included general check-ups, prenatal examinations, and health check-ups for group home residents. Those who received HIV testing due to suspicion of HIV infection were classified as voluntary subjects. The group that received confirmatory testing due to a history of AIDS-related illnesses included tuberculosis patients and those with clinical symptoms associated with AIDS. After excluding samples with missing values on each variable from frequency calculations, the distribution proportion (%) was calculated. Statistical Analysis Software Version 9.1 was used for frequency analysis and Chi-square tests. The level of significance for all statistical analyses was $p < 0.05$.

3. Results

3.1. Distribution of seroconverters among HIV-infected Koreans by year

From 1999 to 2009, the number of identified HIV infections was 6008. The annual number of newly diagnosed individuals has continued to increase: 189 in

1999; >600 in 2004; and ≥700 in each year since 2006. A total of 341 seroconverters were identified during the 11-year period, accounting for 5.6% of all HIV-infected individuals. Starting with the identification of one seroconverter in 1999, the number of seroconverters found in each year has continued to rise, exceeding 30 in 2003 and reaching 69 in 2006. The percentage of seroconverters among newly-identified HIV cases each year stayed between 0.5% and 1.2% for 3 years from 1999, but later increased to 4% in 2002 and to ≥5% in 2003 and stayed at that level since (Figure 1).

3.2. Epidemiological characteristics of seroconverters in Korea

The epidemiological characteristics of seroconverters are as indicated in Table 1. Compared to HIV non-seroconverters, the proportion of men was higher among seroconverters but there was no statistically significant difference ($p = 0.085$). In a comparison of age distribution, seroconverters showed a higher percentage of those aged <30 years, while, among non-seroconverters, the percentage of those in their 40s was relatively higher, which indicated an age difference between the two groups ($p = 0.001$). As for the route of HIV infection, both for seroconverters and non-seroconverters the dominant route of infection was sexual contact with heterosexual contact being the more likely route of transmission than homosexual contact. There was no significant difference between the two groups as analyzed by transmission route ($p = 0.170$), and the main reason for HIV testing of seroconverters was voluntary test due to risky behaviors (43%). Their discovery of HIV infection occurred primarily in hospitals (84%). And marital status at the time of HIV

Figure 1. Annual trend in HIV-infected individuals and HIV seroconverters from 1999 to 2009. Total = the number of HIV-diagnosed individuals during one year; Seroconverter = the number of HIV seroconverters reported during 1 year.

diagnosis showed no difference between non-seroconverters all HIV-infected individuals and seroconverters ($p = 0.380$).

3.3. Level of CD4 T- cell counts of seroconverters

An analysis of CD4 T-cell count of 231 seroconverers (Table 1), conducted to estimate the stage of disease progression, revealed that the average number of CD4 T-cells was 395×10^6/L and that 55% had a CD4 T-cell count of $>350 \times 10^6$/L. In contrast, only 33% of non-seroconverters showed a CD4 T-cell count of more than 350×10^6/L, which suggests that seroconverters had a higher CD4 T-cell count at HIV diagnosis ($p < 0.001$). Among seroconverters, 13.9% had a CD4 T-cell count $<200 \times 10^6$/L.

4. Discussion

A comparison of epidemiological characteristics showed that Korean HIV seroconverters tended to be younger at diagnosis, detected in hospitals and diagnosed during a voluntary test compared to the general population of HIV-infected individuals. In addition, their CD4 T-cell counts at HIV diagnosis were higher than those of all HIV-infected individuals.

Since the first HIV infection in Korea was reported in 1985, the number of new diagnoses each year has increased to around 100 in 1996 and to >200 in 2000 and thereafter. There now exists a wide spectrum in diagnosis of HIV infection and an increasing number of cases whose HIV infection status is hard to determine [4]. The first case of HIV seroconversion in Korea, reported in 1999, tested positive for antibody in a screening test but did not meet the criteria for a positive diagnosis in confirmatory tests using western blotting. One week later, the case could be confirmed positive for HIV in subsequent testing. Detection of seroconverters increased as antigen/antibody simultaneous testing kits, which are fourth-generation reagents that make detection possible 3 weeks after infection, became widely used for screening tests [6].

In our study, the frequency of detection was high in Korean seroconverters because they often undergo voluntary testing due to suspicion of HIV infection after risky behaviors such as homosexual contacts or sex with unfamiliar partners. They were diagnosed in an early stage of HIV infection, and understanding their characteristics could prove useful in developing effective strategies to enhance the early diagnosis of HIV infection. The findings of the present study emphasize the importance of raising young people's awareness of HIV testing and providing easy access to HIV-related information and HIV testing. However, we have some limitations in this study. The seroconverters could be found lowly, because most of HIV screening sites haven't
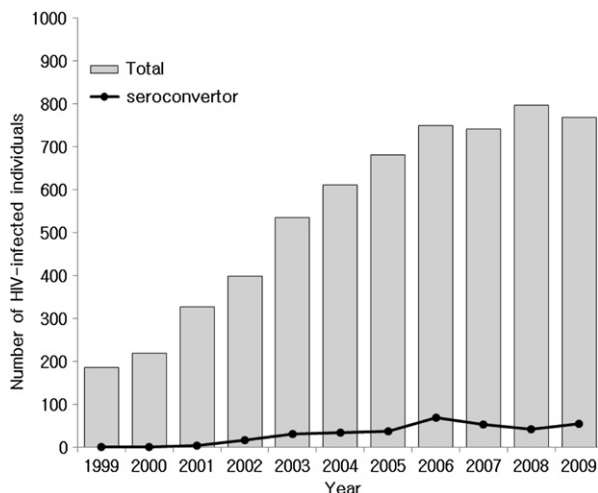
Table 1. Epidemiological characteristics of HIV-infected individuals and HIV seroconverters (1999−2009)

Category	Total HIV-infected individuals (%)	HIV non-seroconverters (%)	HIV seroconverters (%)	p
Total	6008 (100.0)	5667 (100.0)	341 (100.0)	
Gender				0.085
Female	462 (7.7)	444 (7.8)	18 (5.3)	
Male	5546 (92.3)	5223 (92.2)	323 (94.7)	
Age group				0.001
<20	129 (2.1)	117 (2.1)	12 (3.5)	
20−29	1255 (20.9)	1160 (20.5)	95 (27.9)	
30−39	1861 (31.0)	1748 (30.8)	113 (33.1)	
40−49	1471 (24.5)	1409 (24.9)	62 (18.3)	
50−59	855 (14.2)	819 (14.5)	36 (10.6)	
≥60	437 (7.3)	414 (7.3)	23 (6.7)	
Screening site				<0.001
Public health center	1396 (23.2)	1354 (23.9)	42 (12.3)	
Clinic or hospital	4142 (68.9)	3855 (68.0)	287 (84.2)	
Blood center	470 (7.8)	458 (8.1)	12 (3.5)	
Reason for HIV testing[a]				<0.001
Health check-up	2086 (50.2)	1982 (51.3)	104 (35.5)	
Risky behaviors	614 (14.8)	487 (12.6)	127 (43.3)	
Confirmation of disease status	1169 (28.1)	1121 (29.0)	48 (16.4)	
Blood donation	290 (7.0)	276 (7.1)	14 (4.8)	
Transmission route[a]				0.170
Heterosexual intercourse	2900 (58.2)	2742 (58.5)	158 (54.3)	
Homosexual intercourse	2068 (41.5)	1937 (41.3)	131 (45.0)	
Other	14 (0.3)	12 (0.3)	2 (0.7)	
Marital status[a]				0.380
Unmarried	1182 (55.4)	1108 (55.2)	74 (59.2)	
Married	951 (44.6)	900 (44.8)	51 (40.8)	
Initial CD4+ cell count[a]				<0.001
≥500	395 (15.3)	337 (14.4)	58 (25.1)	
350−499	509 (19.7)	440 (18.7)	69 (29.9)	
200−349	762 (29.5)	690 (29.4)	72 (31.2)	
<200	913 (35.4)	881 (37.5)	32 (13.9)	

[a]*These percentage figures were calculated after excluding samples with missing values.*

performed NAT testing except blood centers and there was a different adaptation time of HIV fourth-generation reagents at screening sites.

In Korea, the annual number of HIV infections has increased due to a continuous increase in the number of HIV testing. Current HIV prevalence in the country is nearly 0.01% and follows an unchanging pattern [2,3]. With data from HIV testing, we can estimate the overall HIV prevalence in Korea. However, to understand accurately the current level of HIV transmission or to identify transmission risk groups, we need to estimate HIV incidence. Calculating HIV incidence based on the number of recent infections including seroconverters will contribute to the development of more direct and effective strategies to prevent the spread of HIV. Therefore, there is a clear need for a study of HIV incidence. In 1998, the US Centers for Disease Control developed a plan for a nationwide project called STARHS (serologic testing algorithm for recent HIV seroconversion) for the detection of recent HIV seroconversion in 1998 and has been implementing it both in laboratory settings and on a statistical-surveillance-work basis [9]. The Centers for Disease Control has also developed the detuned assay and BED assay to diagnose recent HIV infections and has performed population-based incidence surveillance using them since 2005 [10].

The natural history of HIV infection in humans is well known and the detection of seroconversion in HIV-affected individuals is of paramount importance for clinical and preventive research. Because early HIV patients have a high viral load and thus are likely to transmit the virus to other individuals, early detection of seroconversion contributes to the reduction of HIV transmission. In addition, the infected individuals can benefit from early treatment and improve their chances of survival as well. In 1994, the CASCADE cohort was created with 2000 seroconverters from 15 countries in Europe including the UK, Australia, and Canada to follow patients from infection, to the onset of AIDS and to death.

The insights from the study are leading the research in HIV-associated factors, treatment effects, changes in viral characteristics over time, immunological and clinical responses, resistance to drugs, etc. [11−13].

Since a few studies related to the time of HIV infection, we could not study about the survival rate after HIV infection, disease progression rate, HIV dynamics over time, etc. Therefore, detection of seroconverters is critical to develop treatment strategies for groups treated with a vaccine or a drug as well as estimating HIV incidence in a region and observing the effects of HIV prevention education and transmission pattern changes in HIV risk groups.

Acknowledgments

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