

Epidemiology and Clinical Features of HIV Infection/ AIDS in Korea

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HIV infection/AIDS shows characteristic epidemiological and clinical patterns according to the region, country, and race. The epidemiological and clinical patterns of HIV infection/AIDS in Korea was investigated by retrospectively analyzing the medical records of 176 HIV-infected persons who visited two major referral hospitals of AIDS in Korea from 1985 to April 2000. The most common transmission route was heterosexual contact (52.3%), followed by homosexual contact (23.9%). Among the opportunistic diseases, candidiasis was the most prevalent (21.6%), followed by *Pneumocystis carinii* pneumonia (15.9%), tuberculosis (12.5%), and CMV infection (9.1%). The most common initial AIDS-defining opportunistic disease was tuberculosis (33.3%). The most common causes of death were tuberculosis (25.7%) and *Pneumocystis carinii* pneumonia (25.7%). This study describes the epidemiological and clinical patterns of HIV infection/AIDS in Korea, which not only enables us to accurately understand HIV infection/AIDS in this country, but eventually to aid in establishing effective preventive measures and treatment guidelines in Korea.

Key Words: HIV, HIV infection, AIDS, Korea, epidemiology, clinical feature

INTRODUCTION

After the discovery of acquired immune defi-

ciency syndrome (AIDS) in 1981, human immunodeficiency virus (HIV) infection has spread quickly and has become the most serious health problem for mankind. The number of those infected with HIV has now reached nearly 40 million world-wide.¹ The clinical patterns of HIV infection and the opportunistic diseases due to immune suppression vary and show different characteristics, according to the transmission mode, risk factor, living environment, and treatment. Since opportunistic diseases are related to microorganisms invading from the outside in addition to endogenous microorganisms within the infected person, the types and frequencies of opportunistic diseases differ according to the region, country, race, and environment.²⁻⁵

After the first case of HIV infection was reported in Korea in 1985,⁶ the number of those infected with HIV has steadily risen and reached 1,280 as of December 2000. Korea is significantly different from the United States, Europe, Africa, and Southeast Asia in terms of region, race, cultural background, and living environment, and therefore, those infected with HIV and patients with AIDS in Korea may show different patterns from the other regions in terms of transmission factors, clinical progress, the pattern of opportunistic diseases, and causes of death.

Thus, a descriptive study of the epidemiological and clinical features of HIV infection/AIDS in Korea was done to accurately understand HIV infection/AIDS in this country, in the hope to contribute in the establishment of effective preventive measures and treatment guidelines in

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Korea in the future.

MATERIALS AND METHODS

Subjects

The subjects were those who visited Severance Hospital, Yonsei University College of Medicine, and Pusan National University Hospital from 1985, when the first case of HIV infection was reported in Korea, to April 2000. Retrospective analysis was performed using the medical records of 176 HIV-infected persons (118 from Severance Hospital and 58 from Pusan National University Hospital) for whom clinical observation and laboratory findings were available. In Korea, zidovudine was available since 1991, didanosine in 1996, and other antiretroviral drugs, including lamivudine and indinavir since 1997. Patients with AIDS or AIDS-related symptoms and subjects of CD4⁺ T cell counts <500/mm³ were treated with zidovudine. Of the 176 subjects, 54 were on zidovudine, 48 were on didanosine, and 67 were on highly active antiretroviral therapy.

Methods

At the time of the first visit, the medical records provided information on sex, age, transmission route, reasons for testing, past history of diseases, state of the disease, and the presence or absence of opportunistic diseases. Laboratory findings included the results of VDRL, FTA-ABS, hepatitis viral markers (HbsAg, anti-HBV, Anti-HCV), cytomegalovirus (CMV) IgM & IgG, and toxoplasma IgM & IgG, etc. In addition, CD4⁺ cell count and percentage, β_2 -Microglobulin (MG), HIV RNA level, HIV p24 Ag, and the results of delayed type hypersensitivity skin testing were also included. However, HIV RNA PCR was performed only at Severance Hospital from October, 1997. These patients were followed up every month to evaluate the disease state and the presence of opportunistic diseases. T-cell subsets and HIV RNA PCR were performed every 3 months.

Delayed type hypersensitivity skin testing was performed using a multi-CMI skin test antigen, and β_2 MG was measured by EIA (Roche, Indiana

Polis, USA). The number of CD4⁺ lymphocytes were calculated by multiplying the number of lymphocytes measured using an automatic cell counter by the percentage of CD4⁺ antigen positive cells using monoclonal antibody (Becton Dickinson, New Jersey, USA). HIV RNA was measured using RT-PCR (Roche, Indiana Polis, USA), and p24 Ag was measured by ELISA (Organon Teknika, Boxtel, Netherlands).

AIDS was defined in those cases positive by Western blot and with an AIDS defining disease. AIDS defining diseases were determined using the criteria established by the Centers for Disease Control & Prevention (CDC) in USA in 1993.⁷

RESULTS

Epidemiological characteristics

Among a total of 176 HIV-infected persons, 156 (88.6%) were males and 20 (11.4%) were females, with the male:female ratio of 7.8:1. As for age distribution at the time of the initial diagnosis of HIV infection, 1 patient (0.6%) was diagnosed in the teens; 44 (25.0%) in their 20's; 78 (44.3%) in their 30's; 35 (19.9%) in their 40's; and 18 (10.2%) were older than 50 years of age. The average age of these patients was 35.9 ± 9.3 years.

In terms of the transmission route, a large proportion of cases were infected through heterosexual contact, 92 patients (52.3%), followed by homosexual contact, 42 (23.9%), transfusion or blood products, 4 (2.3%), intravenous drug injection, 2 (1.1%), and other routes, 36 (20.5%).

At the time of the first visit, 75 patients (42.6%) showed asymptomatic HIV infection, 29 (16.5%) had HIV infection with symptoms other than the AIDS defining diseases, and 72 (40.9%) had AIDS (Table 1).

In terms of the initial reason for testing HIV, 59 patients (33.5%) visited the hospital due to symptoms. Other reasons were through regular physical check-up, 24 (13.6%), through regular check-up of sex workers, 16 (9.1%), through contact with infected spouse, 11 (6.3%), through screening test for blood donation, 10 (5.7%), through an anonymous test, 8 (4.5%), and etc.

Table 1. Characteristics of 176 HIV-infected Persons at Presentation

Demographic characteristics	No. of cases (%)
Sex	
Male	156 (88.6%)
Female	20 (11.4%)
M : F	7.8 : 1
Age	
Mean	35.9 ± 9.3 years
< 14 yr	1 (0.6%)
15 - 24 yr	44 (25.0%)
25 - 34 yr	78 (44.3%)
35 - 44 yr	35 (19.9%)
> 45 yr	18 (10.2%)
Route of transmission	
Heterosexual contact	92 (52.3%)
Homosexual contact	42 (23.9%)
Transfusion/blood products	4 (2.3%)
IV drug use	2 (1.1%)
Undetermined	36 (20.5%)
State of HIV infection	
Asymptomatic HIV infection	75 (42.6%)
Symptomatic HIV infection	29 (16.5%)
AIDS	72 (40.9%)
Immunologic & virologic status	Mean value
CD4+ lymphocyte count (n=167)	252/mm ³
CD4+ lymphocyte % (n=167)	14.80%
HIV RNA (n=72)	226,035 copies/mm ³
β ₂ MG (n=118)	3.1 mg/L
Laboratory findings	Positive rate (%)
HBs Ag (n=114)	8.8
Anti-HCV Ab (n=64)	3.1
VDRL (n=99)	11.1
FTA-ABS (n=76)	17.1
CMV-IgM (n=51)	12
Toxoplasma IgM (n=29)	0
Anergy in Multi-CMI skin test (n=41)	98

HCV, hepatitis C virus; CMV, cytomegalovirus; MG, microglobulin; CMI, cell-mediated immunity.

Clinical characteristics

At the time of first visit, the average CD4+ cell

count and percent were 252/mm³ and 14.8% (conducted in 167 patients), and the average HIV RNA titer was 226,035 copies/mm³ (conducted in 72 patients). Average β₂MG was 3.1 mg/L (conducted in 118 patients), and 98% showed anergy on the multi-CMI skin test (conducted in 41 patients) (Table 1).

Of 176 HIV-infected persons, 232 cases of opportunistic diseases developed in 121 patients (52.2%). The average age at the time of diagnosis of the opportunistic disease was 39.7 ± 9.3 years, and this was an average of 19.9 months after the diagnosis of HIV infection. The average CD4+ cell count at the time of the diagnosis of opportunistic disease was 140/mm³, the average β₂MG 3.6 mg/L, and the average HIV RNA 347,403 copies/mm³.

In terms of the frequency of opportunistic diseases, candidiasis (50 cases, 21.6%) was the most prevalent followed by *Pneumocystis carinii* pneumonia (37 cases, 15.9%), oral hairy leukoplakia (30 cases, 12.9%), tuberculosis (29 cases, 12.5%), CMV infection (21 cases, 9.1%), HIV wasting syndrome (15 cases, 6.5%), HIV encephalopathy (9 cases, 3.9%), and herpes zoster (9 cases, 3.9%). Malignant lymphoma was present in 3 patients (1.3%), Kaposi's sarcoma, 2 (0.9%), cervical carcinoma, 1 (0.4%) (Table 2). The average period from the time of initial diagnosis of HIV infection to the time of development of opportunistic disease was as follows: candidiasis developed in an average of 27.6 ± 28.9 months, *P. carinii* pneumonia in 22.4 ± 24.7 months, tuberculosis in 18.7 ± 30.6 months, and CMV infection in 33.6 ± 26.5 months. The average CD4+ cell count at the time of the diagnosis of opportunistic disease was 71/mm³ in candidiasis, 63/mm³ in *P. carinii* pneumonia, 142/mm³ in tuberculosis, 32/mm³ in CMV infection, 51/mm³ in atypical mycobacterium infection, and 46/mm³ in malignant lymphoma (Table 2).

Among the 317 opportunistic diseases, 150 were AIDS-defining diseases accounting for 47.3%. Among the AIDS-defining diseases, *P. carinii* pneumonia was the most prevalent (37 patients, 24.7%), followed by tuberculosis (29 patients, 19.3%), CMV infection (21 patients, 14.0%), HIV wasting syndrome (15 patients, 10.0%), esophageal candidiasis (14 patients, 9.3%), and HIV encephalopathy (9 patients, 6.0%) (Table 3).

Table 2. Opportunistic Diseases of 121 HIV-infected Persons (n=232 cases)

Opportunistic diseases	No. of cases (%)	Mean CD4+ Cell count (/mm ³)	Mean HIV RNA (copies/mm ³)	Mean β_2 MG (mg/L)
Candidiasis	50 (21.6)	71	338,474	3.6
Oral	36 (15.5)	77	415,274	3.5
Esophageal	14 (6.1)	57	141,000	3.7
PCP	37 (15.9)	63	281,967	3.2
Oral hairy leukoplakia	30 (12.9)	206	236,295	3.2
Tuberculosis	29 (12.5)	142	817,012	3.7
Pulmonary	18 (7.8)	162	833,158	3.1
Extrapulmonary	11 (4.7)	89	807,786	5.1
CMV infection	21 (9.1)	32	204,093	4.1
Retinitis	15 (6.5)	28	-	3.7
Other infections*	6 (2.6)	37	204,093	4.4
HIV wasting syndrome	15 (6.5)	67	139,890	3.9
HIV encephalopathy	9 (3.9)	80	798,552	3.8
Herpes zoster	9 (3.9)	247	46,191	3.1
Peripheral neuropathy	8 (3.4)	79	24,701	4.1
Atypical mycobacterial infection	6 (2.6)	51	182,630	4.7
Cryptococcal meningitis	4 (1.7)	88	-	2.2
HSV, chronic ulcer	3 (1.3)	80	144,364	3.4
Toxoplasmosis, brain	3 (1.3)	21	-	4.9
Malignant lymphoma	3 (1.3)	46	1,422	5.4
Kaposi's sarcoma	2 (0.9)	198	541,913	3.7
PML	2 (0.9)	183	254,297	3.7
Cervical cancer	1 (0.4)	266	17,742	3.4

PCP, *Pneumocystis carinii* pneumonia; CMV, cytomegalovirus; HSV, herpes simplex virus; PML, progressive multifocal leukoencephalopathy.

*lung, esophagus, stomach, & colon infections.

-not done.

The first AIDS defining disease in AIDS patients was tuberculosis in 25 patients (33.3%), followed by *P. carinii* pneumonia in 17 patients (22.6%), esophageal candidiasis in 14 patients (18.7%), CMV infection in 5 patients (6.6%), and HIV wasting syndrome in 4 patients (5.3%) (Table 4).

Among a total of 176 HIV-infected persons, 35 patients (19.9%) died. The most prevalent causes of death were tuberculosis and *P. carinii* pneumonia, each caused 9 deaths (25.7%), followed by bacterial pneumonia in 7 (20.0%), HIV encephalopathy in 3 (8.5%), cryptococcal meningitis in 2 (5.7%), and malignant lymphoma in 2 (5.7%) (Table 5).

DISCUSSION

The main transmission routes of HIV infection are through sexual contact, syringes, blood products, and vertical transmission. In the US, the main transmission route is homosexual contact (47%), followed by intravenous drug injection (25%) and heterosexual contact (10%), and eighty six percent of infected children under the age of 13 have HIV-infected mothers.⁸ In Germany, the main transmission route is also through homosexual contact (64.6%), followed by intravenous drug injection (14.9%) and heterosexual contact (8.8%).⁹ Intravenous drug injection is the main

Table 3. AIDS-defining Opportunistic Diseases in 75 AIDS Patients (n=150 cases)

Opportunistic diseases	No. of cases (%)	Mean CD4+ cell count (/mm ³)	Mean HIV RNA (copies/mm ³)	Mean β_2 MG (mg/L)
PCP	37 (24.7)	63	281,967	3.2
Tuberculosis	29 (19.3)	142	817,012	3.7
Pulmonary	18 (12.0)	162	833,158	3.1
Extrapulmonary	11 (7.3)	89	807,786	5.1
CMV infection	21 (14.0)	32	204,093	4.1
Retinitis	15 (10.0)	28	-	3.7
Other infections*	6 (4.0)	37	204,093	4.4
HIV wasting syndrome	15 (10.0)	67	139,890	3.9
Esophageal candidiasis	14 (9.3)	57	141,000	3.7
HIV encephalopathy	9 (6.0)	80	798,552	3.8
Atypical mycobacterial infection	6 (4.0)	51	182,630	4.7
Cryptococcal meningitis	4 (2.7)	88	-	2.2
HSV, chronic ulcer	3 (2.0)	80	144,364	3.4
Toxoplasmosis, brain	3 (2.0)	21	-	4.9
Malignant lymphoma	3 (2.0)	46	1,422	5.4
Kaposi's sarcoma	2 (1.3)	198	541,913	3.7
PML	2 (1.3)	183	254,297	3.7
Cervical cancer	1 (0.7)	266	17,742	3.4

PCP, *Pneumocystis carinii* pneumonia; CMV, cytomegalovirus; HSV, herpes simplex virus; PML, progressive multifocal leukoencephalopathy.

*lung, esophagus, stomach, & colon infections.

-not done.

Table 4. Initial AIDS-defining Opportunistic Diseases in 75 AIDS Patients (n=75 cases)

Opportunistic diseases	No. of cases (%)
Tuberculosis	25 (33.3)
Pulmonary	17 (22.7)
Extrapulmonary	8 (10.6)
PCP	17 (22.7)
Esophageal candidiasis	14 (18.7)
CMV infection	5 (6.6)
Retinitis	3 (4.0)
Enterocolitis	2 (2.6)
HIV wasting syndrome	4 (5.3)
Atypical mycobacterial infection	2 (2.6)
HIV encephalopathy	2 (2.6)
Cryptococcal meningitis	2 (2.6)
Malignant lymphoma	1 (1.3)
Kaposi's sarcoma	1 (1.3)
HSV, chronic ulcer	1 (1.3)

PCP, *Pneumocystis carinii* pneumonia; CMV, cytomegalovirus; HSV, herpes simplex virus.

Table 5. Causes of Death in 35 Expired HIV-infected Persons (n=35 cases)

Cause of death	No. of cases (%)
Tuberculosis	9 (25.7)
Pulmonary	6 (17.1)
Extrapulmonary	3 (8.6)
PCP	9 (25.7)
Bacterial pneumonia	7 (20.0)
HIV encephalopathy	3 (8.5)
Cryptococcal meningitis	2 (5.7)
Malignant lymphoma	2 (5.7)
Sepsis	1 (2.9)
Toxoplasmosis, brain	1 (2.9)
Myocardial infarction	1 (2.9)

PCP, *Pneumocystis carinii* pneumonia.

transmission route in Eastern Europe.¹⁰ Unlike Europe and America, the main transmission route in Southeast Asia and Africa is through heterosexual contact and intravenous drug injection. In Thailand, for example, heterosexual contact (81.2%) is the main route, followed by intravenous drug injection (5.3%) and vertical transmission (5.1%).¹¹⁻¹³ The main transmission route is heterosexual contact in southern Africa, whereas heterosexual contact and intravenous drug injection are the main routes in northern and central regions of Africa. In Africa, the percentage of pregnant women has reached up to 40% in certain regions, which is a high risk for vertical transmission.¹⁰ In Korea, we determined that heterosexual contact was the most frequent route, and that homosexual contact was also a major contributor accounting for approximately one third of all sexual contacts. No official reports of infection due to intravenous drug injection has been issued in Korea, however, two cases were confirmed in the present study. We speculate that transmission among intravenous drug abusers is rare in Korea because Korean intravenous drug abusers can easily purchase syringes in pharmacies, and the population of drug abusers is relatively low in Korea compared to the Western countries and other Asian countries.

At the time of the first visit, 40.9% of the patients were diagnosed as AIDS and their immunity was significantly suppressed with an average CD4+ cell count of 252/mm³. Despite the trend of a decreasing frequency of opportunistic infections and AIDS due to the development of anti-HIV drugs⁸ in the US and Europe, the percentage of those diagnosed as AIDS at the initial visit in the Korean population is still high, which indicates that there is lack of early diagnosis and delay in the treatment of HIV-infected persons in Korea.

Opportunistic infections are due to microorganisms invading from the outside and endogenous microorganisms within the infected person, which differ depending on the environment and the race. A study in the US in 1999 reported that the most prevalent opportunistic disease was *P. carinii* pneumonia (53.0%), and this was followed by atypical mycobacterium infection (30.0%), esophageal candidiasis (24.4%), Kaposi's

sarcoma (22.6%), HIV wasting syndrome (20.8%), and CMV retinitis (20.6%).¹⁴ In the northern European countries, the major opportunistic diseases are *P. carinii* pneumonia, in the mid-European countries, Kaposi's sarcoma and toxoplasmosis, in southeastern European countries, CMV retinitis, and in southwestern European countries, extrapulmonary tuberculosis.¹⁵ Tuberculosis (31 - 61%) is the most frequent opportunistic disease in Thailand, India, and other Southeast Asian countries, followed by cryptococcal meningitis (14 - 38%), candidiasis (11 - 35%), and *P. carinii* pneumonia (13 - 33%). In particular, the endemic fungal infection, penicilliosis, is especially frequent in Thailand (4 - 25%).^{5,12,14} The major opportunistic diseases in Africa are tuberculosis, followed by bacterial pneumonia, cryptococcal meningitis, isosporiasis, CMV infection, and sepsis due to nontyphoidal *Salmonella* spp. In Zaire, for example, the most frequent opportunistic disease is tuberculosis (41%), followed by bacterial pneumonia (34%), cryptococcal infection (19%), Kaposi's sarcoma (16%), CMV infection (13%), and nonspecific enteritis (13%).^{4,16,17} This Korean study shows that the most frequent opportunistic disease is candidiasis, followed by *P. carinii* pneumonia, oral hairy leukoplakia, tuberculosis, CMV infection, and HIV wasting syndrome. Another study of the Korean population by Oh et al.¹⁸ reported that the most frequent opportunistic disease in Korea was candidiasis, followed by tuberculosis, herpes zoster, *P. carinii* pneumonia, and CMV infection. Thus, in Korea, tuberculosis, which is a frequent opportunistic disease in the underdeveloped and developing countries, such as Africa, south and Southeast Asia, and *P. carinii* pneumonia and candidiasis, which are frequent opportunistic diseases in the advanced countries in Europe and the US, are both highly prevalent.

Candidiasis, which was the most prevalent opportunistic disease determined in Koreans, increases in prevalence with time and disease progression in HIV-infected persons reaching up to 30 - 94%. There is a high possibility of developing AIDS with the development of oral candidiasis.^{19,20} We found 36 cases (15.5%) of oral candidiasis and 14 cases (6.1%) of esophageal candidiasis. Esophageal candidiasis was the third common initial AIDS-defining opportunistic disease.

The average CD4+ cell count was 77/mm³ at the time of the diagnosis of oral candidiasis, and 57/mm³ at the time of the diagnosis of esophageal candidiasis, which was slightly lower than the average of 79/mm³ at the time of the diagnosis of AIDS-defining disease.

The most prevalent AIDS-defining disease in Koreans was *P. carinii* pneumonia, which was more prevalent than tuberculosis. The average CD4+ cell count with *P. carinii* pneumonia development was 63/mm³, and the average HIV RNA titer was 281,967 copies/mm³, indicating that this disease developed after profound immune deterioration. Although *P. carinii* pneumonia is the most prevalent opportunistic disease in the US, with an incidence of more than 50%, this incidence has decreased in recent years due to a combination of preventive measures and anti-HIV treatment.²¹ Our study results showed that except for only 1 patient, in all the patients who developed *P. carinii* pneumonia, they were not diagnosed as HIV and were accordingly not on *P. carinii* prophylaxis. So this disease occurred mainly in those who did not maintain appropriate preventive measures and anti-HIV treatment.

Tuberculosis developed in 29 cases in our study; pulmonary tuberculosis in 18 cases (7.8%) and extrapulmonary tuberculosis in 11 cases (4.7%). In this study, tuberculosis was the most common initial AIDS-defining opportunistic disease. The average CD4+ cell count was 142/mm³, and the average HIV RNA titer was 817,012 copies/mm³ at the time of the diagnosis of tuberculosis. Prophylactic treatments for tuberculosis were not given. Bacille Calmette-Guerin (BCG) vaccine has been recommended in Korea for universal childhood immunization since 1960. Among those patients who developed tuberculosis, 34% had a past history of tuberculosis. Moreover, among the total of 176 patients studied, 24 patients had a past history of tuberculosis, among which 10 patients (42%) re-activated tuberculosis after HIV infection.

Atypical mycobacterial infection developed in 6 patients (2.6%), of which 4 showed pulmonary invasion and 2 extrapulmonary invasion. The average CD4+ cell count on the diagnosis of atypical mycobacterial infection was 51/mm³. Thus, caution is needed for the development of atypical

mycobacterial infection in patients with severely low immune function.

CMV infection was found in 21 patients (9.1%), and was diagnosed at a relatively late stage compared to the other AIDS-defining diseases. A study in the US reported invasion of the retina in about 90%, followed by colon, stomach, and esophagus.²² Our study showed that retinitis was the most common CMV infection found in 15 patients (71.4%), followed by invasion of the lung, esophagus, stomach, and colon.

Cryptococcal meningitis and toxoplasmosis, which are reported to be common in HIV-infected persons in the Western countries, Southeast Asia, and Africa, were rare among Korean HIV-infected persons. This may be related to the low incidence of cryptococcal infection and toxoplasmosis in Korea. Also, malignancies such as malignant lymphoma and Kaposi's sarcoma, were rare.

Opportunistic diseases, which are not AIDS-defining diseases, also differ according to the region, country, and race. The incidence of chronic candidiasis of the oral cavity or reproductive system is very high (35.2%) in Thailand and Southeast Asia.¹² Sepsis (18 - 26%) and nonspecific enteritis (5 - 15%) are also reported to occur frequently in Africa.⁴ Our study showed that the prevalences of oral candidiasis, oral hairy leukoplakia were high, and that the prevalences of herpes zoster and peripheral neuropathy were also relatively high.

P. carinii pneumonia is the most common cause of death in the US, and 26.1% of AIDS patients died from this disease in 1995, but this decreased to 8.5% in 1998. Deaths due to other causes than PCP, including pneumonia, malignant tumors, renal failure, and hepatic failure, are now increasing in the US.²³ In Africa, pneumonia and sepsis are the prevalent causes of death, and the mortality rate of infants younger than 1 year of age has increased from 10% in 1992 to 52% in 1996; the main causes being pneumonia and enteritis.²⁴ Our study found that 19.9% of those infected with HIV died, and that the main causes were tuberculosis, *P. carinii* pneumonia, and bacterial pneumonia.

This descriptive study characterizes the epidemiological and clinical patterns of HIV infection/AIDS in Korea to accurately understand HIV

infection/AIDS in this country, in the hope to contribute in the establishment of effective preventive measures and treatment guidelines in Korea in the future.

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