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Epidemiology of Human Immunodeficiency Virus infection in Republic of Korea

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서울대학교 보건대학원
보건학과 역학전공
이 은 영

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ABSTRACT

Epidemiology of Human Immunodeficiency Virus infection in Republic of Korea

Lee Eunyoung

Dept. of Public Health, Epidemiology

Graduate School of Public Health

Seoul National University

Introduction and Objective

Human immunodeficiency virus (HIV) infection is a sexually-transmissible chronic infection, the occurrence of which has increased continuously in Korea. Each step of the diagnosis, engagement in antiretroviral therapy (ART), and care maintenance is necessary to control an HIV infection. However, epidemiological data on the achievement of these steps are not well-established in Korea. This study was conducted to investigate the epidemiology of HIV infection in Korea, using nationwide claims data from the Korean National Health Insurance database. The objectives are as follows:

(1) To identify the number of annual HIV infections and their epidemiological characteristics in Korea through an analysis of the national claims data and evaluate the usefulness of these data for an epidemiological study of HIV infection in Korea.

(2) To identify medication adherence for ART among those diagnosed with HIV in Korea and determine risk factors for suboptimal adherence via the medication possession ratio (MPR).

(3) To identify the percentage of HIV-syphilis coinfection in Korea and risk factors for HIV-syphilis coinfection by using national claims data.

Methods

(1) Using the National Health Institute database, we established two surveillance systems to yield the prevalence and incidence of HIV infection in Korea from 2007 to 2015. We then compared these results to those reported in the Korea Centers for Disease Control and Prevention (KCDC) registry, based on positive laboratory tests.

(2) We estimated ART adherence among incident HIV-infected individuals and investigated factors affecting low medication adherence using the national health insurance claims data from 2007 to 2016. The MPR was used to measure medication adherence and risk factors for suboptimal adherence were identified by multivariable logistic regression analysis.

(3) This study was retrospective in nature, using the claims database of the NHI system from 2008 to 2016. The clinical characteristics of people living with HIV with or without syphilis coinfection were analyzed. People with HIV and syphilis coinfection

were divided into two groups based on an MPR cutoff of 95%: an optimal ART adherence group and a suboptimal ART adherence group.

Results

(1) The number of patients who visited hospitals recorded in the KCDC registry differed by about 10%. However, age and sex trends by year were comparable to the number of existing and newly diagnosed cases reported by the KCDC. In particular, the claims data provided a more accurate estimate of the number of patients with a CD4-positive T cell count of less than 200/mm^3, while much of those data were missing in the KCDC registry.

(2) Of the 8,501 newly diagnosed HIV-infected individuals identified during 2009-2016 with at least one ART prescription, 5,981 (70.4%) patients had adequate adherence to ART (defined as MPR ≥ 95%). Women (odds ratio [OR] 1.6), age under 20 and same or over 50 compared to 30–39 (OR 1.6, 1.4), a history of malignancy (OR 1.6), lower socioeconomic status (OR 1.2), not visiting a tertiary-level hospital (OR 1.2), and being diagnosed in the earlier years (OR for 2009 3.7-2015 1.7) were found to be risk factors for lower adherence.

(3) Of the 9,393 people living with HIV, 4,536 (48.3%) were diagnosed with a syphilis coinfection. Optimal adherence to ART was independently associated with a syphilis coinfection (OR 1.18; 95% confidence interval 1.08–1.30; P=0.001). Male gender, having a bacterial or protozoan sexually transmitted disease, and having a genital

herpes viral infection were also identified as risk factors for an HIV-syphilis coinfection. An HIV-syphilis coinfection was still associated with an optimal adherence >95% to ART even after the definition of syphilis infection has been limited since the diagnosis of HIV infection.

Conclusions

(1) The first study found that the claims data are valuable in estimating the epidemiology of people living with HIV/acquired immunodeficiency syndrome visiting the hospital. The KCDC registry reports the total number of people living with HIV and the claims data shows their hospital visits. A combination of the two databases can be used as a tool to connect diagnosed people living with HIV to the treatment they require. We suggest building a matched HIV surveillance system linking the claims data and the nationwide registry built by the government.

(2) The results from the second study indicate that health authorities should take modifiable and unmodifiable barriers into consideration, in order to establish a sustainable monitoring system at the national level and to improve adherence.

(3) The results from the third study suggest that the occurrence of unsafe sex is independent of medication adherence. Although HIV is unlikely to be transmitted when the viral load is controlled, consistent use of condoms is needed to prevent a syphilis infection.

Key words : HIV, AIDS, Claims analysis, Medication adherence, Syphilis, Republic of Korea

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CHAPTER 1.

INTRODUCTION

1-1. HIV infection and Acquired Immune Deficiency Syndrome

In 1985, the first human immunodeficiency virus (HIV) infection was detected in a Korean individual who stayed abroad. Since then, the number of HIV-infected people has gradually increased in Korea, with approximately 1,000 newly infected people being diagnosed annually. A total of 12,320 people living with HIV infection (PLHIV) were reported by the end of 2017, and the actual number of undiagnosed PLHIV is expected to be higher. (1)

HIV destroys the immune system, leading to Acquired immune deficiency syndrome (AIDS). AIDS is a condition where various complications such as infectious diseases or malignant tumors may arise due to reduced immunity caused by an HIV infection. The duration of progression from initial infection to AIDS varies from patient to patient. In general, the higher the basal HIV RNA, or the lower the number of basal CD4-positive T cells , hastens the progression to AIDS. This progression takes an average of 10 years without treatment. (2) Without treatment, the average survival rate is 38-40 months for a CD4-positive T cell count of less than 200/mm^3 and 12–18 months for a count less than 50/mm^3. Therefore, early detection and initiation of treatment are important as it can prevent the development of opportunistic infections and various non-AIDS-defining illnesses due to an immunocompromised status.

Symptom onset may occur at any time after an HIV infection but is usually indicated by a decrease in the CD4-positive T-cell count. Symptoms generally appear due to bacterial infections that would ordinarily not occur in an immunocompetentstatus. These infections are called opportunistic infections, and specific opportunistic infections are used to diagnose AIDS by classifying AIDS-defining illnesses as a characteristic that occurs in PLHIV at an

advanced stage of disease. AIDS-defining illnesses presented by the Centers for Disease Control and Prevention are as follows (3):

- Bacterial infections, multiple or recurrent
- Candidiasis of bronchi, trachea, or lungs
- Candidiasis of esophagus
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV relatedΔ
- Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 month's duration)
- Kaposi sarcoma
- Lymphoma, Burkitt (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- Mycobacterium avium complex (MAC) or Mycobacterium kansasii, disseminated or extrapulmonary
- Mycobacterium tuberculosis of any site, pulmonary, disseminated, or extrapulmonary
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- Pneumocystis jirovecii pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent
- Toxoplasmosis of brain, onset at age >1 month
- Wasting syndrome attributed to HIV

AIDS is diagnosed based on immune status through CD4-positive T-cell count and AIDS-defining illness as follows (AIDS in grey color):

Table 1. A 1993 revised classification system for HIV infection and expanded AIDS surveillance case definition for adolescents and adults

CD4+ T Cell Categories	Clinical Categories		
	A Asymptomatic, Acute (primary) HIV or PGL	B Symptomatic, Not A or C Condition	C AIDS-Indicator Conditions
1. ≥500/㎕	A1	B1	C1
2. 200 ~ 499/㎕	A2	B2	C2
3.<200/㎕	A3	B3	C3

* The shaded areas indicate the expanded AIDS surveillance case definition.
PGL; progressive generalized lymphadenopathy.
MMWR 42 (No. RR-17), December 18, 1992.

1-2. Development of antiretroviral agents and prolongation of life expectancy of PLHIV

Antiretroviral agents were developed to ensure effective suppression of HIV , convenience with fewer pills and fewer adverse reactions. With the development of antiretroviral agents, the life expectancy of PLHIV has significantly increased. PLHIV under antiretroviral therapy (ART) not only have a longer life expectancy but also live healthier lives owing to reduction in the risk of opportunistic infections. PLHIV in the United States and Canada who were diagnosed in their 20s were predicted to survive until their early 70s. (4) Therefore, there is a need for the management of chronic diseases such as cardiovascular diseases and aging-related diseases, in addition to the ongoing continuous ART.

For ideal clinical benefit, PLHIV should receive continuous ART. The process of diagnosis, linkage to care, starting ART, and achieving HIV suppression through the maintenance of ART is called the treatment cascade. The Joint United Nations Programme on

HIV/AIDS (UNAIDS) aims to diagnose more than 90% of PLHIV, initiate ART in more than 90% of diagnosed PLHIV, and achieve HIV suppression in more than 90% of PLHIV on ART (the 90-90-90 target). (5)

1-3. HIV infection and co-infection with other sexually transmitted diseases

The Undetectable = Untransmittable (U = U) initiative led to a medical-scientific basis that influenced behavioral and social science to remove the fear or guilt from human immunodeficiency virus (HIV) infection. (6) However, the percentage of concomitant sexually transmitted diseases (STDs) infection in people living with HIV varies. A systematic review reported that the median seroprevalence of HIV-syphilis coinfection was 15.7%, but among men in the US who have sex with men, it was 64.3–90.0%. (7) Condomless sex is not totally discouraged after achieving undetectable HIV load, but the prevalence of STDs in the group is unknown. Before suggesting condomless sexual relationships among people living with controlled HIV, it is reasonable to identify the current status of unsafe sex and then develop a policy.

1-4. National health insurance system of Korea and HIV infection

Korea has a single-payer national health insurance plan. All medical utilisation within the National Health Institute (NHI) is monitored for reimbursement, and all use of healthcare with the purpose of treating a medical condition is reimbursed in various proportions. The NHI claims database contains retrospective cohort data on basic information on the patients' sociodemographic characteristics and visits to medical institutions as well as precise

information on their diagnoses, prescriptions or diagnostic procedures and the characteristics of the medical clinics they visited. Since the National Health Insurance Service (NHIS) covers all antiretroviral therapy agents and follow up tests necessary for HIV infection treatment, all the medication prescriptions and treatment process can be detected from claims data. The NHIS database can be used as a nationwide cohort without an independent cohort program for the HIV treatment cascade.

1-5. Study Objectives

This study was conducted to investigate the epidemiology of HIV infection in Korea using nationwide claims data from the Korean NHI database. The objectives are as follows:

First, identify the number of annual HIV infections and their epidemiological characteristics in Korea through an analysis of the national claims data and evaluate the usefulness of the claims data for an epidemiological study of HIV infection in Korea.

Second, identify medication adherence among PLHIV on ART in Korea and risk factors for suboptimal adherence via the medication possession ratio (MPR).

Third, identify the percentage of HIV-syphilis coinfection in Korea and risk factors for HIV-syphilis coinfection by using the national claims data.

The investigation of the epidemiology of the HIV infection treatment cascade in Korea might provide guidance for future epidemiological research and establish evidence for efficient infection control policies.

CHAPTER 2.

Usefulness of the Korean National Health Insurance database in establishing surveillance systems of treatment cascade for HIV infection

2-1. Introduction

The number of people newly infected with the HIV has declined since 1997 according to UNAIDS. (8) However, that in the Republic of Korea has been increasing steadily and the number of PLHIV has reached approximately 10,000. (9) It is important to gain a better understanding of the HIV epidemiology more accurately and take action accordingly to control HIV infection. Specifically, in order to achieve the 90-90-90 targets, (10) it is necessary to identify and manage the number of PLHIV and that of PLHIV visiting hospitals, which can be optimized through communication between the government and medical centers.

The KCDC has played a central role in the registration, treatment and management of PLHIV. (11) However, the surveillance system for the HIV treatment cascade has not been effectively managed after HIV detection, confirmation and registration. On the other hand, the Korean Government has adopted a single universal mandatory health insurance plan, the NHIS, which covers almost the entire Korean population. The NHIS has accumulated nationwide medical records related to medical cost since 2002. In 2011, there were 1.3 billion medical claims from the entire Korean population. We believe these two databases could complement each other. It is possible to identify PLHIV at the government level, manage them in hospitals, and give information back to the government based on claims data. In this study, we proposed the potential use of the NHIS database as a surveillance tool for the HIV treatment cascade.

2-2. Materials and Methods

Study design

In this cross-sectional study, we screened for HIV infection from nationwide claims data from 2007 to 2015, and analyzed all of the subjects' medical facility visits. The results were compared to the KCDC reports, including reports of registered PLHIV, new PLHIV registered annually, and those of PLHIV with CD4-positive T-cell counts less than 200/mm^3. In Korea, all positive HIV Ag/Ab screening test results are reported to the KCDC. The confirmation test is carried out by the western blot method at the KCDC or local government-run laboratories networked to the KCDC. If HIV infection is confirmed, the regional public health officer interviews PLHIV individually to collect information including the CD4+ T-cell count. As the KCDC report is regarded as the authorized source of national surveillance data on HIV infection, we attempted to compare the NHIS claims database and the KCDC registration database.

Database

The NHIS consists of two components: the National Health Insurance (NHI), which currently covers 97% of the total population of 50 million, and the National Medical Aid, which covers the remaining 3%. The suitability of reimbursement of all the medical claims including prescriptions submitted by individual health care providers is reviewed by the government agency. (12) In such a process, a database of national health care utilization is formed with data such as age, sex, health care provider characteristics, diagnoses using International Classification of Diseases and Related Health Problems 10^{th} revision (ICD-10) codes, procedures or operations, drug prescriptions, type of insurance, and medical care costs. We obtained information from the NHIS database for the period January 01, 2007 to

December 31, 2015. We collected data on the patients' age, sex, HIV and acquired immune deficiency syndrome (AIDS)-related diagnoses by ICD-10 codes (main diagnosis and up to 40 sub-diagnoses), date of hospital visit and medication prescriptions (generic name, dose, date of prescription), laboratory test (HIV Ag/Ab screening test [enzyme-linked immunosorbent assay], HIV RNA quantification, HIV drug resistance mutation sequencing, T-cell subset), and date of assessment.

Definitions

Diagnosis of HIV infection

The data were screened for HIV-related diagnoses (Table 2-1). For all screened subjects with HIV-related diagnoses, we excluded those who were expected to have HIV-related diagnoses for post-exposure prophylaxis prescription. An HIV-exposed person was defined as one who received antiretroviral therapy (ART) prescription on the same day of an HIV screening test without any of the following subsequent HIV-specific tests, which are performed in almost all PLHIV: 1) T-cell subset, or 2) HIV drug resistance mutation sequencing (Table 2-2, 2-3). Subjects who had undergone 3 or more screening tests at the outpatient clinic of the same medical facility within 24 months without the above subsequent tests, were also regarded as post-exposure prophylaxis cases and were excluded. Subjects younger than 10 years were excluded because there are few cases of vertical transmission in Korea.

Diagnosis of AIDS

Among PLHIV, we defined AIDS if a patient met one of the following conditions: 1) AIDS-defining illness diagnostic codes, 2) prophylactic dosage of oral trimethoprim-

sulfamethoxazole or oral dapsone prescription for pneumocystis pneumonia prevention as these medications are recommended for all HIV patients with CD4-positive T-cell counts less than 200/mm^3. (13)

Initial hospital visits of HIV-infected people

We collected data on confirmed PLHIV from 2007 to 2015, and then counted newly-diagnosed PLHIV from their first visit to any medical facility, after excluding the existing PLHIV in the initial two years (2007 and 2008). Therefore, we assumed that PLHIV who visited medical facilities with an HIV-related diagnosis after an absence for 2 years of the same kind of visit were newly-diagnosed PLHIV.

Statistical analysis

We counted the PLHIV during the study period of 2007–2015. Initial hospital visits of PLHIV were counted from 2009 to 2015 after a window period of 2 years. AIDS patients and those newly diagnosed with AIDS were also calculated in the same way. All statistical analyses were performed using the statistical software SAS Enterprise Guide, version 6.1 (SAS Institute, Inc., Cary, NC, USA).

Table 2-1. ICD-10 code for human immunodeficiency virus infection/acquired immunodeficiency syndrome (AIDS) diagnosis

Human immunodeficiency virus infection		
1	B20-B24	Human immunodeficiency virus [HIV] disease
2	Z21	Asymptomatic human immunodeficiency virus [HIV] infection status
3	O98.7	Human immunodeficiency virus [HIV] disease complicating pregnancy, childbirth and the puerperium
AIDS-defining illness		
1	B37.1	Pulmonary candidiasis
2	C53	Malignant neoplasm of cervix uteri
3	B38	Coccidioidomycosis
4	B45	Cryptococcosis
5	B25	Cytomegaloviral disease
	B20.2	HIV disease resulting in cytomegaloviral disease
6	B22.0	HIV disease resulting in encephalopathy
7	B00.7	Disseminated herpesviral disease
8	B39	Histoplasmosis
9	A07.3	Isosporiasis
10	C46	Kaposi′s sarcoma
	B21.0	HIV disease resulting in Kaposi′s sarcoma
11	J84.10	Lymphoid interstitial pneumonia
	B22.1	HIV disease resulting in lymphoid interstitial pneumonitis
12	C83.7	Burkitt lymphoma
	B21.1	HIV disease resulting in Burkitt lymphoma
13	B21.2	HIV disease resulting in other types of non-Hodgkin lymphoma
	C85	Other and unspecified types of non-Hodgkin lymphoma
14	A31	Infection due to other mycobacteria
	B20.0	HIV disease resulting in mycobacterial infection
15	A15-A19	Tuberculosis

16	B59	Pneumocystosis
	B20.6	HIV disease resulting in *Pneumocystis jirovecii* pneumonia
17	A81.2	Progressive multifocal leukoencephalopathy
18	A02.1	Salmonella sepsis
19	A58.2	Toxoplasma meningoencephalitis
20	M62.5	Muscle wasting and atrophy, NEC
21	B22.2	HIV disease resulting in wasting syndrome

Table 2-2. List of antiretroviral agents and prophylactic antibiotics for HIV infection with CD4+ T cell less than 200/mm^3

Antiretroviral agents	
NRTI	Abacavir
	Didanosine
	Emtricitabine
	Lamivudine
	Stavudine
	Tenofovir
	Zidovudine
NNRTI	Efavirenz
	Nevirapine
	Etravirine
PI	Atazanavir
	Darunavir
	Indinavir
	Lopinavir
	Nelfinavir
	Ritonavir
	Saquinavir
FI	Enfuvirtide
CCR5 inhibitor	Maraviroc
INSTI	Raltegravir
	Elvitegravir
	Dolutegravir
Prophylactic antibiotics for HIV infection with CD4+ T cell under 200/mm^3	
Trimethoprim/Sulfamethoxazole	
Dapsone	

Table 2-3. List of laboratory tests to diagnosis human immunodeficiency virus infection

Laboratory tests
HIV Ag/Ab
HIV Ag
HIV Ab
Western blot
Drug resistance mutation
HIV RNA Quantification
RT-PCR Quantification
bDNA Assay
T cell subset

2-3. Results

Comparability between the NHI database and KCDC registry

Out of the national population of 50 million, a total of 31,253 subjects who visited medical clinics 447,285 times from 2007 to 2015 were screened using HIV-related diagnostic codes (Fig. 2-1). Among them, 579 who were regarded as having post-exposure statuses were excluded. We also excluded 14,542 who did not undergo specific testing for HIV and 51 younger than 10 years. To confirm excluded cases, we checked prescriptions for ART and did not find any ART prescriptions among them. After applying the above exclusion criteria, a total of 19,821 were excluded. Thus, a total of 11,381 PLHIV with 416,595 medical facility visits were considered during the study period.

Of the 11,381 PLHIV, there were 10,324 men (90.7%), and 5,243 AIDS patients (46.1%) (Table 2-4). With respect to age, PLHIV in the 30–39 year age group were most frequent at 3,128 (27.4%). PLHIV who visited tertiary hospitals were most frequent at 8,686 (76.3%) with respect to the type of medical facilities. With respect to the geographical location of the medical facilities, 5,727 (50.3%) visited medical facilities in Seoul (the capital city) and 3,116 (27.4%) visited facilities in 6 other metropolitan cities. Regarding insurance type, 10,090 (88.7%) were covered by the NHI and 1,287 (11.3%) were covered by the National Medical Aid. Compared to the KCDC reports, the number of surviving Korean PLHIV in 2015 was 10,502, and the cumulative number of Korean PLHIV in the same year was 13,909. (11)

The number of hospital visits increased steadily from 3,367 in 2007 to 9,544 in 2015 (Fig. 2-2, Table 2-5). The proportion of hospital visits in 2010 according to the NHI claims data was 84.8% of the KCDC registry (hospital visit 5,333 *vs.* KCDC 6,292) and increased annually to 90.9% (hospital visit 9,544 *vs.* KCDC 10,502) in 2015. The ratio of men to

women was similar to that reported by the KCDC. The number of AIDS patients who visited hospitals was more than 1,000 in 2007 alone (n=1,185); thereafter, it decreased from 549 in 2008 to 459 in 2015.

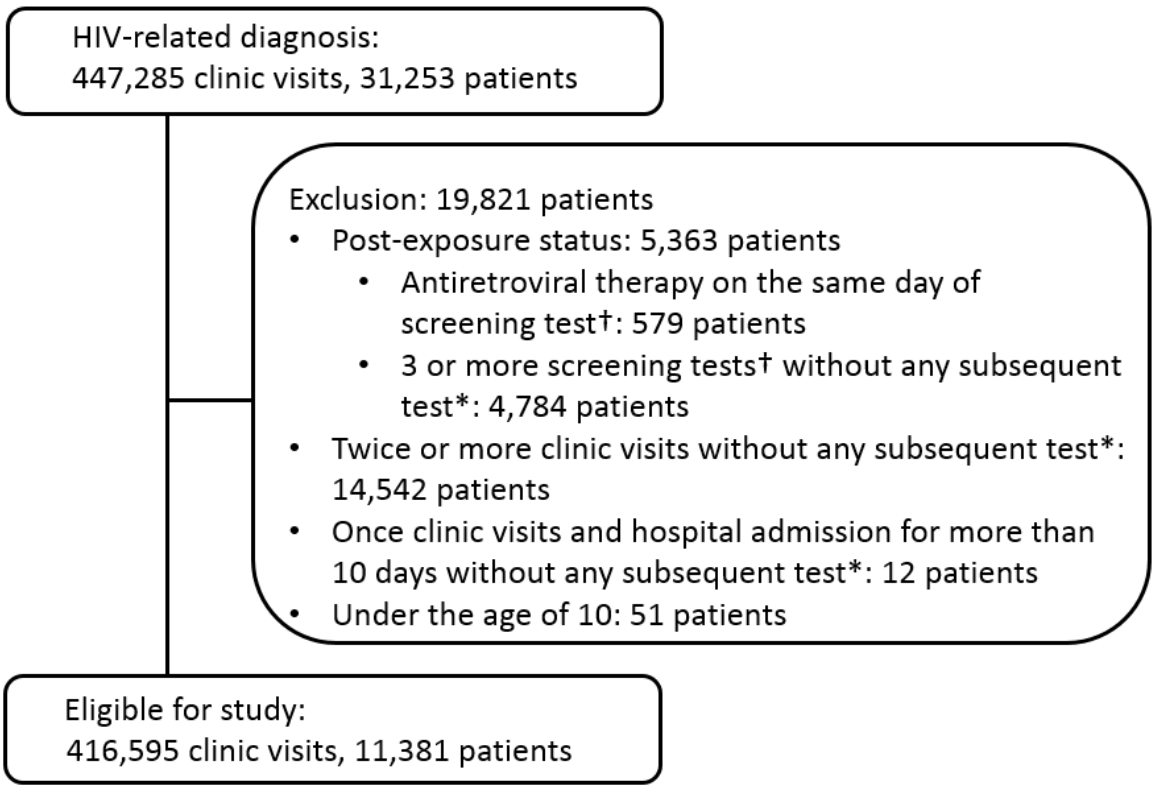


Figure 2-1. Flow chart of study design

HIV, Human immunodeficiency virus

†HIV Ag, Ab or Ag/Ab

*T cell subset or drug resistance mutation

Table 2-4. Clinical characteristics of hospital visiting people living with HIV in Korea

	HIV 2007-2015	AIDS 2007-2015	KCDC 2015 Survival Korean status	KCDC 2015 Cumulative Korean status
Total	11,381	5,243	10,502	13,909
Gender				
Men	10,324 (90.7)	4,822 (92.0)	9,735 (92.7)	12,604 (90.6)
Women	1,057 (9.3)	421 (8.0)	767 (7.3)	1,305 (10.4)
Age				
10-19	331 (2.9)	56 (1.1)	66 (0.6)	-
20-29	2,434 (21.3)	690 (13.2)	1,692 (16.1)	-
30-39	3,128 (27.4)	1,478 (28.2)	2,291 (21.8)	-
40-49	2,886 (25.2)	1,573 (30.0)	2,934 (27.9)	-
over 50	2,602 (22.8)	1,446 (27.6)	3,519 (33.5)	-
Type of medical facility				
Teaching hospital	8,686 (76.3)	4,045 (77.2)	-	-
General hospital	2,576 (22.6)	1,178 (22.5)	-	-
Primary care hospital	40 (0.4)	14 (0.1)	-	-
Public health center	22 (0.2)	4 (0.1)	-	-
Nursing home	2 (0.0)	2 (0.0)	-	-
Region of medical institution				
Seoul*	5,727 (50.3)	2,414 (46.0)	-	-
Metropolitan cities	3,116 (27.4)	1,554 (29.7)	-	-
Rural	2,538 (22.3)	1,275 (24.3)	-	-
Health Insurance status				
NHI	10,090 (88.7)	4,431 (84.5)	-	-
NMA	1,287 (11.3)	809 (15.4)	-	-
Veterans hospital	4 (0.0)	3 (0.1)	-	-

*Seoul, capital city, HIV, human immunodeficiency virus, AIDS, acquired immune deficiency syndrome, KCDC, Korea Centers for Disease Control and Prevention, NHI, the National Health Insurance, NMA, the National Medical Aid. The value denotes the subject number (%).

Table 2-5. Annual hospital visit of people living with HIV/AIDS in Korea by age

	HIV						AIDS						KCDC (Korean HIV patients)					
	Total	**10-19**	**20-29**	**30-39**	**40-49**	**50 +**	**Total**	**10-19**	**20-29**	**30-39**	**40-49**	**50 +**	**Total**	**0-19**	**20-29**	**30-39**	**40-49**	**50 +**
2007	3,367 (W*=319)	35 (1.0)	452 (13.4)	1,070 (31.8)	1,001 (29.7)	809 (24.0)	1,185 (F=97)	11 (0.9)	127 (10.7)	366 (30.9)	374 (31.6)	303 (25.6)	-	-	-	-	-	-
2008	4,019 (W=377)	37 (1.0)	519 (12.9)	1,200 (29.9)	1,244 (31.0)	1,019 (25.4)	549 (F=37)	3 (0.5)	78 (14.2)	157 (28.6)	182 (33.2)	129 (23.5)	-	-	-	-	-	-
2009	4,616 (W=423)	41 (0.9)	591 (12.8)	1,307 (28.3)	1,440 (31.2)	1,237 (26.8)	514 (F=44)	4 (0.8)	61 (11.9)	146 (28.4)	158 (30.7)	145 (28.2)	-	-	-	-	-	-
2010	5,333 (W=468)	56 (1.1)	653 (12.2)	1,460 (27.4)	1,674 (31.4)	1,490 (27.9)	497 (F=38)	4 (0.8)	56 (11.3)	148 (29.8)	153 (30.8)	136 (27.4)	6,292	-	-	-	-	-
2011	6,102 (W=532)	61 (1.0)	770 (12.6)	1,616 (26.5)	1,867 (30.6)	1,788 (29.3)	512 (F=41)	4 (0.8)	65 (12.7)	141 (27.5)	152 (29.7)	150 (29.3)	7,030 (F=569)	-	-	-	-	-
2012	6,831 (W=588)	60 (0.9)	898 (13.1)	1,731 (25.3)	2,050 (30.0)	2,092 (30.6)	480 (F=32)	8 (1.7)	68 (14.2)	120 (25.0)	131 (27.3)	153 (31.9)	7,788 (F=624)	57 (0.7)	1,077 (13.8)	2,006 (25.8)	2,285 (29.3)	2,363 (30.3)
2013	7,705 (W=661)	95 (1.2)	1,075 (14.0)	1,906 (24.7)	2,219 (28.8)	2,425 (31.5)	506 (F=48)	8 (1.6)	84 (16.6)	134 (26.5)	140 (27.7)	140 (27.7)	8,662 (F=684)	72 (0.8)	1,260 (14.5)	2,115 (24.4)	2,504 (28.9)	2,711 (31.3)
2014	8,746 (W=734	96 (1.1)	1,322 (15.1)	2,080 (23.8)	2,459 (28.1)	2,789 (31.9)	545 (F=46)	10 (1.8)	78 (14.3)	140 (25.7)	153 (28.1)	164 (30.1)	9,615 (F=730)	70 (0.7)	1,484 (15.4)	2,210 (23.0)	2,738 (28.5)	3,113 (32.4)

	)																
2015	9,544 (W=782)	90 (0.9)	1,523 (16.0)	2,157 (22.6)	2,652 (27.8)	3,122 (32.7)	459 (F=38)	4 (0.9)	73 (15.9)	126 (27.5)	130 (28.3)	126 (27.5)	10,502 (F=767)	66 (0.6)	1,692 (16.1)	2,291 (21.8)	2,934 (27.9)	3,519 (33.5)

*W = number of women, HIV, human immunodeficiency virus, AIDS, acquired immune deficiency syndrome, KCDC, Korea Centers for Disease Control and Prevention

The value denotes the subject number (%) unless otherwise indicated.

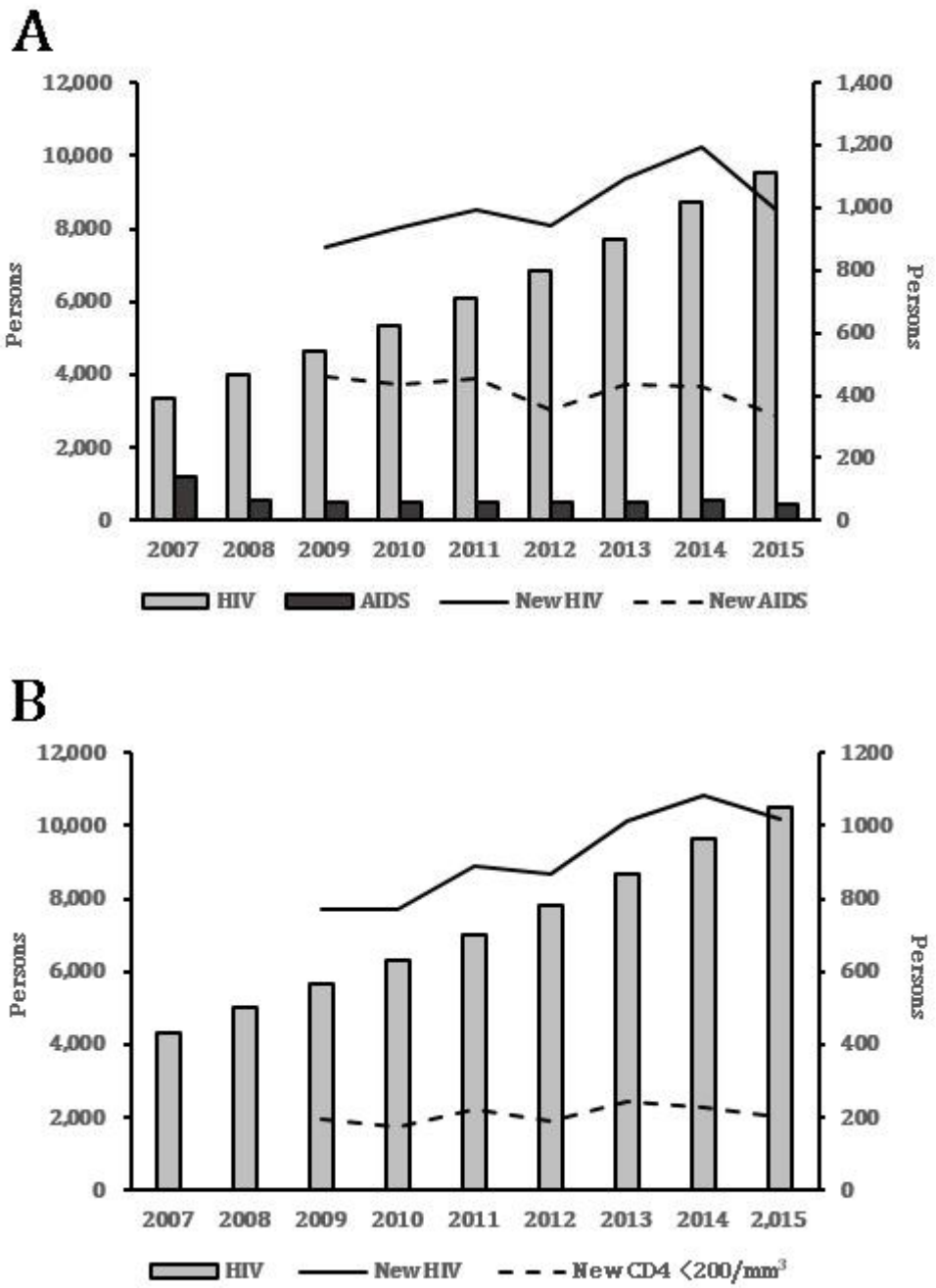


Figure 2-2. Annual hospital visits of HIV/AIDS patients in Korea. The number of hospital visits among HIV-infected people increased steadily during 2007-2015, and that of AIDS patients decreased during the study period (bar) (A). After excluding the existing patients in the first 2 years, we counted new patients at medical facilities. The number of newly diagnosed HIV-infected patients and that of newly diagnosed AIDS patients showed a similar trend with existing patients (line). The trends of HIV- infected patients were observed in the KCDC data (B). Data on survival among AIDS patients were not available. The annual trends of existing HIV-infected patients and newly-diagnosed HIV-infection were similar to those in the hospital visit records. The number of HIV- infected patients with

CD4-positive T-cell counts less than 200/mm3 was smaller than that of AIDS patients in the claims data.

Current status of PLHIV/AIDS in the Republic of Korea

PLHIV were most prevalent in the 30–39 year age group at 1,070 (31.8%) in 2007 (Table 2-5). However, after 2008, the proportion of PLHIV in the 30–39 year age group decreased while and the proportion of PLHIV in the 20–29, 40–49 and over 50 year age groups increased in both directions. The increasing trend of younger and older age groups was also observed in the KCDC data.

The number and percentage of AIDS patients with hospital visits decreased from 1,185 (35.2% of HIV-infected people) in 2007 to 459 (4.8% of HIV-infected people) in 2015. Patients in the 30–39 and 40–49 year age groups were in the majority in 2007 at 366 (30.9%) and 374 (31.6%), respectively, and comprised major age groups during the study period. However, the proportion of patients in the 20–29 year age group increased from 10.7% (127 patients) in 2007 to 15.9% (73 patients) in 2015.

Current status of incident PLHIV /AIDS in the Republic of Korea

After excluding the existing PLHIV in the first two years, we estimated the yearly incidence of PLHIV and AIDS based on hospital visits among patients visiting medical facilities. The number of new PLHIV was 873 in 2009 and increased annually to 995 in 2015 (Table 2-6). The number of newly-diagnosed PLHIV who visited the hospital was comparable to that reported by the KCDC. With respect to age, the proportion of younger PLHIV in the 20–29 year age group increased from 18.2% (159 patients) in 2009 to 32.8% (327 patients) in 2015. The proportion of young PLHIV in the 10–19 year age group also increased from 2.4% (21 patients) in 2009 to 4.5% (45 patients) in 2015. The increasing proportion of young PLHIV was also observed in the KCDC reports.

The number of newly-diagnosed AIDS patients was 460 (52.7% of PLHIV) in 2009 and decreased annually to 337 (33.9% of PLHIV) in 2015. Among newly-diagnosed AIDS patients, the number and proportion of patients with CD4-positive T-cell counts less than 200/mm^3 on the basis of pneumocystis pneumonia prophylaxis also decreased in 2015 compared to that in 2009 (Fig. 2-3A). The KCDC also assessed CD4-positive T-cell counts in newly-reported PLHIV by individual contact to patients via phone call or personal interview. There were missing data regarding CD4-positive T-cell counts in a significant number of patients (Fig. 2-3B).

Table 2-6. Annual initial hospital visit of people living with HIV/AIDS in Korea by age

	HIV						AIDS						HIV KCDC*					
	Total	**10-19**	**20-29**	**30-39**	**40-49**	**50 +**	**Total (% of HIV)**	**10-19**	**20-29**	**30-39**	**40-49**	**50 +**	**Total**	**0-19**	**20-29**	**30-39**	**40-49**	**50 +**
2009	873 (W**=90)	21 (2.4)	159 (18.2)	247 (28.3)	238 (27.3)	208 (23.8)	460 (52.7)	4 (0.9)	62 (13.5)	140 (30.4)	127 (27.6)	127 (27.6)	839 (W=80)	27 (3.5)	160 (20.8)	199 (25.9)	184 (24.0)	198 (25.8)
2010	938 (W=80)	29 (3.1)	173 (18.4)	255 (27.2)	264 (28.1)	217 (23.1)	438 (46.7)	4 (0.9)	52 (11.9)	136 (31.1)	130 (29.7)	116 (26.5)	837 (W=75)	29 (3.8)	150 (19.4)	208 (26.9)	183 (23.7)	203 (26.3)
2011	995 (W=99)	35 (3.5)	213 (21.4)	261 (26.2)	240 (24.1)	246 (24.7)	452 (45.4)	4 (0.9)	56 (12.4)	121 (26.8)	136 (30.1)	135 (29.9)	959 (W=82)	40 (4.2)	230 (24.0)	221 (23.0)	237 (24.7)	231 (24.1)
2012	942 (W=85)	35 (3.7)	247 (26.2)	227 (24.1)	212 (22.5)	221 (23.5)	353 (37.5)	7 (2.0)	62 (17.6)	83 (23.5)	90 (25.5)	111 (31.4)	953 (W=89)	34 (3.6)	286 (30.0)	241 (25.3)	175 (18.4)	217 (22.8)
2013	1,095 (W=105)	54 (4.9)	312 (28.5)	268 (24.5)	235 (21.5)	226 (20.6)	433 (39.5)	8 (1.8)	76 (17.6)	110 (25.4)	119 (27.5)	120 (27.7)	1,114 (W=98)	53 (4.8)	320 (28.7)	268 (24.1)	241 (21.6)	232 (20.8)
2014	1,195 (W=103)	52 (4.4)	362 (30.3)	274 (22.9)	241 (20.2)	266 (22.3)	426 (35.7)	11 (2.6)	69 (16.2)	101 (23.7)	117 (27.5)	128 (30.0)	1,191 (W=91)	43 (3.6)	367 (30.8)	282 (23.7)	229 (19.2)	270 (22.7)
2015	995 (W=81)	45 (4.5)	327 (32.8)	242 (24.3)	190 (19.1)	191 (19.2)	337 (33.9)	4 (1.2)	59 (17.5)	92 (27.3)	89 (26.4)	93 (27.6)	1,152 (W=72)	42 (3.6)	383 (33.2)	278 (24.1)	217 (18.8)	232 (20.1)

*2009, 2010 data are Korean statistics excluding foreigners, **W= number of women, HIV, human immunodeficiency virus, AIDS, acquired immune deficiency syndrome, KCDC, Korea Centers for Disease Control and Prevention, The value denotes the subject number (%) unless otherwise indicated.

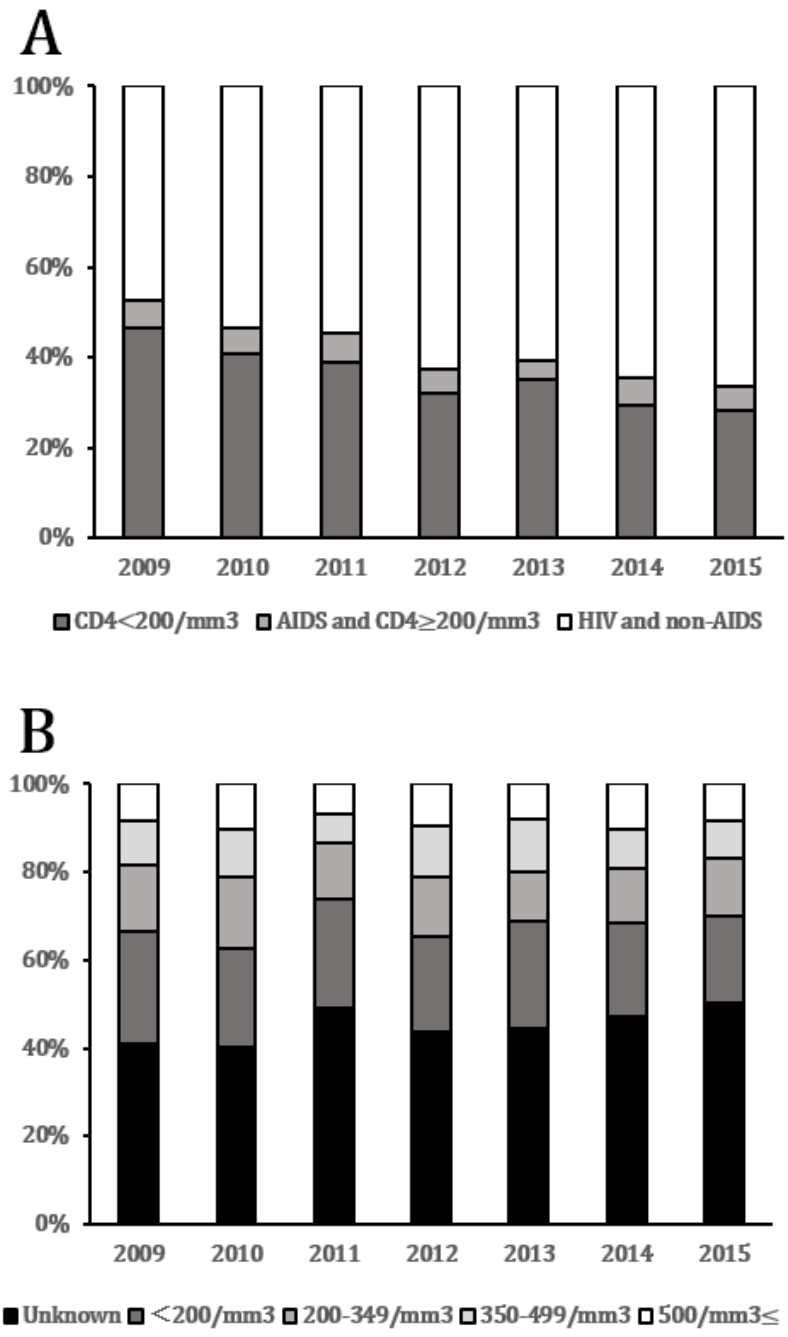


Figure 2-3. Classification of HIV-infected patients by CD4-positive T-cell counts during the annual initial hospital visits compared to KCDC data. The number and proportion of HIV-infected patients with CD4-positive T-cell counts less than 200/mm3 among patients who visited the hospital decreased (A). In the KCDC report, the CD4-positive T-cell counts were unknown in a significant number of patients (B).

2-4. Discussion

Using nationwide claims database, this study compared the two databases, NHI and KCDC. It showed that most of the PLHIV visited hospitals and also elucidate their epidemiological characteristics including age and sex distribution. Moreover, important epidemiological characteristics of CD4-positive T-cell counts that were not appropriately identified in the KCDC reports were revealed in the claims data.

Compared with claims data and the KCDC annual report since 2010, the number of PLHIV who visited hospitals gradually increased from 84.8% in 2010 to 90.9% in 2015. Regarding incident PLHIV, almost all of those diagnosed between 2009 and 2014 visited the hospital. These results indicate that the proportion of PLHIV receiving ART after the diagnosis of HIV infection has increased to close to the 90-90-90 targets. However, the proportion of PLHIV diagnosed in 2015 who were identified in the claims data were as low as 86.4% (995/1,152) of those reported by the KCDC. We estimate that this finding arose because the year 2015 was the last year of the study period. We believe that a delay could occur more than a few months until PLHIV visit the hospital after diagnosis. The strong stigma against HIV infection in Korea might be a barrier to hospital visit. (14) We defined AIDS patients among PLHIV using prophylactic antibiotic prescriptions and AIDS-defining diseases. The proportion of AIDS patients among PLHIV was 35.2% (1,185/3,367) in 2007, and gradually decreased to 4.8% (459/9,544) in 2015. We estimate that generalization of early treatment contributed to a reduction in the proportion of AIDS patients.

This study revealed that national level claims data could be used to monitor hospital visits or patient retention among PLHIV. The KCDC manages a national surveillance system

based on positive laboratory test results. The number of patients diagnosed with HIV infection in public health centers or hospitals has been monitored by the KCDC since 1998.(15) However, HIV testing can be done anonymously, and even if it is not done anonymously, identification of individuals is regulated and undisclosed by the KCDC. Therefore, it is impossible to track individual PLHIV. Thus, we cannot estimate the proportion of patients under retention in care and undergoing ART by the KCDC registry. In Korea, all costs of HIV-related treatment are supported by the government and the NHI system to improve adherence – 10% of individual medical costs of PLHIV is reimbursed by the government and the remaining 90% is covered by the NHI. Considering the high cost of HIV treatment, the number of PLHIV not covered by the NHI claim data would be negligible. Thus, the claims database could be an important source to investigate the HIV epidemiology. Furthermore, it is possible to detect PLHIV who do not visit hospitals on a regular basis with claims data. With this information, the government can plan a program to manage and track PLHIV who are lost to follow up (Fig. 2-4). This algorithm can be achieved when the NHIS and the KCDC establish a linked system to share roles and functions. It is very important to identify medical adherence to ART for HIV infection management. As we previously reported, using claims data also has the advantage of being able to identify ART adherence. (16) Therefore, if PLHIV are properly linked using the algorithm, patients who did not visit the hospital after registry enrollment are expected to receive appropriate treatment.

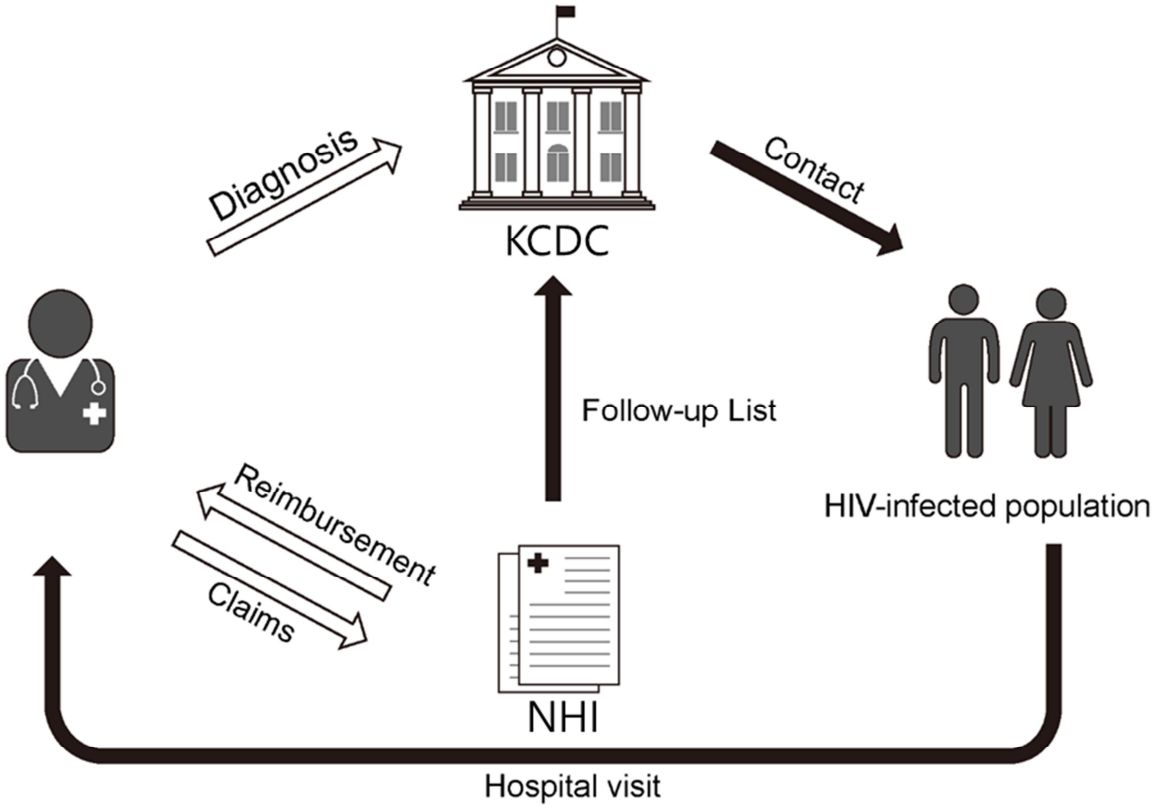


Figure 2-4. Suggestion of an HIV infection management system constructed by linking the NHIS and KCDC databases. In the current system, hospitals report new cases of HIV infection based on positive laboratory tests to the KCDC and request reimbursement from the NHIS (white arrows). After analyzing the clinic visit statuses of HIV-infected individuals, information is sent to the KCDC who in turn contact the population lost to follow-up (black arrows). Person with a stethoscope: Hospital, Documents: NHIS, Building with a flag: Government, Standing people: HIV-infected population

To assess HIV epidemiology, it is necessary to set up a surveillance system or establish a separate cohort which requires a huge investment in human resources and budget. (17-21) In comparison, a surveillance system using claims data has an advantage in that some valuable epidemiological information can be obtained using existing data with little or no additional manpower and cost. (22, 23) Moreover, claims data can provide various epidemiological information, including the detection of changes in the region of hospitals used by patients over time, treatment adherence to prescribed drugs, economic status using the type of health insurance, and cost of treatment. (24-28) These epidemiological data might even be more accurate than those obtained using individual surveys.

We also found that claims data were also useful for identifying important indicators related to HIV epidemiology, which are not present in the KCDC registry. For example, although the KCDC confirmed the CD4-positive T-cell counts in newly-diagnosed PLHIV, the CD4-positive T-cell count results were unavailable in a significant number of PLHIV, which was 50.4% in 2015. (11, 29) In the present study, we could estimate the proportion of patients with CD4-positive T-cell counts less than 200/mm^3 among newly-diagnosed PLHIV based on prescriptions for pneumocystis pneumonia prophylaxis. It was determined that some of PLHIV who were reported to have unknown CD4-positive T-cell counts were identified in this study.

This study has some limitations. First, we excluded PLHIV who visited the hospital for two years to define newly diagnosed PLHIV and there was no previous study to refer to. We tried to determine the window periods of 1 year, 2 years, and 3 years since 2007 and confirmed that there was no difference in estimating incidental PLHIV after 2010 when the existing PLHIV were excluded for 2 years and 3 years. Nonetheless, existing PLHIV who had not visited hospitals for three years or longer might be presumed to be newly diagnosed. Second,

there is not much research on claims data for PLHIV, and according to our knowledge, there was no previous study using the operational definition of AIDS. There is a methodological limitation in that we did not directly confirm actual CD4 T-cell counts and some AIDS patients may not be included in our operational definition. However, based on the generalization of prophylactic antibiotics in patients with CD4-positive T-cell counts less than 200/mm^3 and the results of the majority of patients visiting specialized tertiary hospitals, it is presumed that this possibility did not have a significant impact on the analysis. Third, claims data includes all patients covered by Korean NHI. There are about 10% of foreigners in PLHIV and it is not clear how many foreigners were included in this claims data.

In conclusion, claims data are valuable in estimating HIV/AIDS epidemiology, and we suggest building a matched surveillance system that manages PLHIV by linking hospital claims data and nationwide registry built by the government.

CHAPTER 3.

Adherence to antiretroviral therapy and factors affecting low medication adherence among incident HIV-infected individuals during 2009–2016: A nationwide study

3-1. Introduction

The global target of UNAIDS to combat HIV infection by 2020 is summarized as the 90-90-90 target. (30, 31) Since the innovative study by Granich in 2009, it has been recommended to initiate ART as soon as an individual is diagnosed with an HIV infection, and early treatment is considered as the top priority in HIV management by clinicians. (32) A recent mathematical modelling study reported that interventions for HIV infection will impact the basic reproduction number and HIV incidence if they target HIV patients who are not yet undergoing ART rather than those who are already undergoing ART. (33)

An adherence to ART of 95% is required as an appropriate level to achieve maximal viral suppression (34-36) and lower the rate of opportunistic infections. (37) Non-adherence is related to the development of ART resistance, (38) progression to AIDS, (39) and death. (40) However, in clinical practice, the maintenance of optimal ART adherence is challenging. A meta-analysis of 84 studies estimated that only 62% of HIV patients achieved optimal adherence (of > 90%). (41) Despite complete government funding of the medical service fees relevant to HIV (including ART) in Korea, there are limited data on medication adherence at the national level. In a setting in which patients have very low barriers to treatment, there may be risk factors for low ART adherence that have not been previously reported. In a former Korean study, continuity of care was assessed by analysing the consistency of hospital visits in 3- month intervals using a hospital-based HIV cohort of 247 patients who started ART between 2002 and 2008. (42) However, whether an individual is being treated with ART, and the continuity of medications are more valuable and direct indices than the number of clinic visits. Therefore, this study aimed to elucidate the ART adherence of incident HIV-infected individuals and to investigate factors affecting low medication adherence in Korea.

3-2. Materials and Methods

Study population

Of the nationwide NHI cohort of 50 million individuals, 40,338 individuals received an HIV infection diagnosis (ICD-10 codes B20-24) at least once during 2007-2016 (Fig. 3-1). Among these, 12,318 individuals had at least one ART prescription during the same period and among these ART receivers, 377 never went through any of the HIV follow-up tests of the following: HIV RNA quantification test, T cell subset analysis, HIV drug resistance mutation sequencing. Among these 377 individuals, 345 individuals who were expected to have received ART for post-exposure prophylaxis (PEP), pre-exposure prophylaxis (PrEP) or other preventive care were excluded. In specific, there were three categories of these excluded individuals. First, those who received HIV screening test after ART prescription were excluded since this implies that HIV infection was not confirmed after former ART prescription. Second, if there were primary diagnosis code of the following together with ART prescription, ART were expected to have been prescribed for other purpose: contact with or exposure to HIV, occupational exposure to risk factor, sexually transmitted diseases such as syphilis, major injury with bleeding, or open wound. Third, those who received only one ART product or two nucleoside analogue reverse transcriptase inhibitor (NRTI)s were likely to have received ART for other purpose than HIV infection treatment considering the number of ART products. The day of first ART prescription was regarded as the day of initial diagnosis of HIV infection, as well as the index date of cohort recruitment for adherence assessment. In order to select only incident HIV-infected individuals for follow-up of ART prescription, we excluded those who had ART prescription before 2009 and recruited only those who had first ART prescription after two years of window period, resulting in 8,501

final study population of incident HIV-infected individuals during 2009-2016.

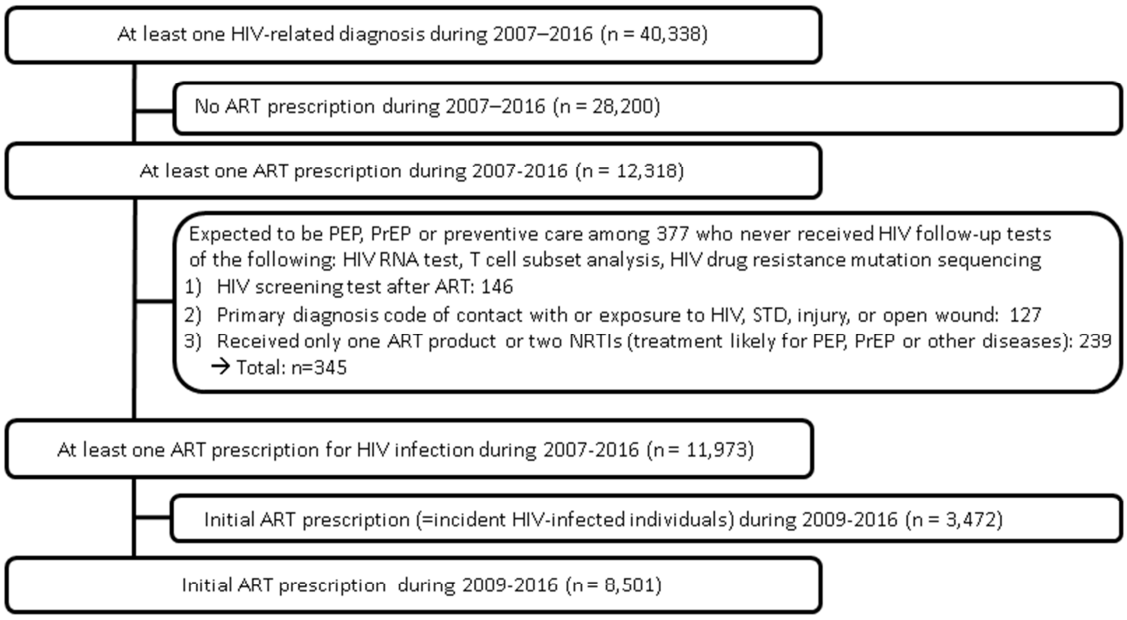


Figure 3-1. Flow chart of study population

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; PEP, post-exposure prophylaxis; PrEP, pre-exposure prophylaxis; STD, sexually transmitted disease; NRTIs, nucleoside analogue reverse transcriptase inhibitors

Definitions

The characteristics of the study population was accessed only from the database before the time of initial ART, which was used as the time of initial HIV infection diagnosis and cohort index date. Therefore, the risk factors evaluated in this analysis could overcome reverse causation. For example in case of comorbidity, the existence of certain comorbid condition was searched within the records of one's many clinic visits only before the day of initial visit for ART. The time of the initial ART prescription, a substitute for initial HIV diagnosis, was used to determine age, health insurance status (used as a proxy for socioeconomic status), and region/type of the visited hospital. A person with AIDS was defined as an individual who received at least one diagnosis of an AIDS-defining illness as defined by CDC. (43) Individuals who were prescribed with prophylactic dosage of trimethoprin/sulfamethoxazole or dapsone for the prevention of pneumocystis pneumonia were defined as 'Requiring prophylactic antibiotics', which could indicate CD4+ T cell counts <200 cells/mm3. As infectious diseases specialists in tertiary teaching hospitals mainly treat HIV-infected patients in Korea, the types of hospitals were categorized as designated tertiary hospital *vs.* others. Among tertiary hospitals, the government entitles hospitals with high proportion of severe patients as designated tertiary hospital every 3 years. When grouping hospitals by their region, we defined metropolitan cities as cities designated as such by the government which is a large part a classification by its' economic size including the capital city. In the comparisons of the clinical characteristics of HIV patients by MPR group, we analysed the frequency of visits to the emergency department and that of hospital admissions (any kind of visit or admission regardless of HIV infection). Hypertension included only primary hypertension, not secondary, and hypertensive diseases such as heart or renal disease (ICD-10 codes I10–13). Malignancy included all kinds of

neoplasm including malignant or benign ones (ICD-10 codes C00–D48), and viral hepatitis included all viral hepatitis including acute or chronic hepatitis B or C. Psychiatric disorders included all mental or behavioural conditions such as dementia, mood disorders including depression, and unspecified mental disorders (ICD-10 codes F00–99). In our analysis of risk factors for suboptimal adherence, we adjusted for the number of all prescribed medications including medication for conditions other than the HIV infection: We divided this number by the number of months of observation to reflect the total duration of observation. Medications included only reimbursed medications (excluded over-the-counter medications).

Adherence measurements

The MPR is a method of measuring medical adherence using prescription records during a certain period, and has been reported as a measure of adherence that is associated with short-term viral response. (44) The MPR was calculated as the sum of the days of treatment supplied for all ART prescriptions filled, from the first round of ART until the last day of 2016, divided by the number of days during that same time period. We used the MPR instead of the proportion of days covered as HIV patients generally receive various different ART agents at single visit, covering the same period at each visit, which was also confirmed from the database. Moreover, as the intake of each ART agent could not be checked individually, it was not possible to use information of each agent within multiple drug regimens.

As we recruited incident HIV-infected individuals, we assumed that they were all on their first line of ART. During the study period, the first regimen recommended by the clinicians included two NRTI backbones plus one of the following: protease inhibitors, non-

nucleoside analogue reverse transcriptase inhibitors, or integrase strand transfer inhibitors, as recommended by international guidelines. (45) For the NRTI backbone, the preferred agents in the guideline were tenofovir/emtricitabine and abacavir/lamivudine.

The start of observation period was the first ART fill date, and the end was one of the two cases: until the last refill date for those who never returned to care after loss to follow-up , or the last day of 2016 for those who were still under follow-up. Since we were unable to differentiate between regular clinic visits with long gaps and infrequent visits with shorter gaps before or after a loss to follow-up using the MPR, the pattern of long term follow-up loss was analysed, which was defined as no medical clinic visit for ART for same or more than a year. Instead of applying various indices such as retention or loss to follow-up to measure the patterns of clinic visits, as used in a previous study, (46) we utilized a single measurement, the MPR, to analyse adherence for the following reasons. First, the proportion of long term follow-up loss was less than 6% and second, among these patients, the majority had the gap in the middle of care, not in the end. Last, among several methods of describing adherence such as retention to care or persistence, the proportion of days with ART treatment was considered as the most important factor for the management of HIV-infected individuals and of being of the highest interest for clinicians by the authors.

Statistical analysis

Analysis of variance (ANOVA) was used to compare the means of the four MPR groups (≥95%, 80–95%, 50–80%, and <50%). For continuous variables, post-hoc analysis was conducted with the Tukey method, with a p value 0.001 considered significant, to test difference between the ≥95% MPR group and the other groups. The Chi-Square test was used

to test the statistical significance of the differences between the groups. We applied Mantel-Haenszel Chi-Square test to assess trends in the four MPR groups; moreover, a pairwise comparison was performed between the ≥95% MPR group and the remaining 3 groups. ORs for suboptimal adherence (MPR <95%) were calculated using a multivariable logistic regression model with a stepwise option of an entry limitation with a *p* value of 0.05. To consider different lengths of observation periods and changes in treatment guidelines or available regimens on the market, the year of diagnosis was included as an adjusting variable. The final model was verified as adequate and the concordance statistic estimate (c) was 0.685 with a concordance of 68%. SAS Enterprise Guide, version 6.1 (SAS Institute, Inc., Cary, NC, USA) was used for all analyses.

Ethics statement

The institutional review board of the Seoul National University Boramae Medical Centre (IRB No. 07 - 2017 - 8 / 052) approved this study. The board waived informed consent due to the use of an existing secondary database.

3-3. Results

General characteristics of the study population

The annual number of HIV-infected individuals recruited from NHI cohort data using ART prescriptions was comparable to the actual number reported in the annual HIV incidence report of the KCDC. In Korea, public and private clinics mandatorily report all HIV-infected individuals to the KCDC.

The study population consisted of 8,501 HIV-infected individuals during 2009–2016 (Fig. 1). We identified 5,981 (70.4%), 798 (9.4%), 654 (7.7%), and 1,068(12.6%) individuals in the four MPR groups (≥95%, 80–95%, 50–80%, and <50%), respectively (Table 3-1). Men accounted for 92% of the study population. In both cases of AIDS-defining illness and requiring prophylactic antibiotics, we observed the highest proportion of individuals in the MPR <50% group with statistically significant trend of increase as adherence gets worse. Most patients (93%) were insured through the NHI, with the remaining 7% being covered by the National Medical Aid (NMA) (p <.0001). In case of the year of diagnosis, the proportion of patients with adequate adherence of MPR ≥95% increased continuously from 2009 to 2016 with statistically significant trend (p <.0001). When long term follow-up loss was defined as no record of a clinic visit for ART prescription for same or more than a year, 223 (20.9%) belonged in MPR<50% group while 16 (0.3%) were in MPR ≥95% group (p <.0001).

Table 3-1. Characteristics of newly diagnosed human immunodeficiency virus-infected individuals by medication possession ratio, 2009–2016

	Total (n=8,501)	≥95% (n=5,981)	80-95% (n=798)	50-80% (n=654)	<50% (n=1,068)	*p* value[a]
Gender						
Men	7,824 (92.0)	5,560 (93.0)	734 (92.0)	595 (91.0)	935 (87.5)	<.0001
Women	677 (8.0)	421 (7.0)	64 (8.0)	59 (9.0)	133 (12.5)	
Age						
10-19	225 (2.6)	143 (2.4)	29 (3.6)	23 (3.5)	30 (2.8)	<.0001
20-29	2,135 (25.1)	1,548 (25.9)	198 (24.8)	192 (29.4)	197 (18.4)	
30-39	2,202 (25.9)	1,579 (26.4)	212 (26.6)	161 (24.6)	250 (23.4)	
40-49	2,001 (23.5)	1,386 (23.2)	197 (24.7)	149 (22.8)	269 (25.2)	
≥50	1,938 (22.8)	1,325 (22.2)	162 (20.3)	129 (19.7)	322 (30.1)	
AIDS defining illness	1,655 (19.5)	1,114 (18.6)	168 (21.1)	125 (19.1)	248 (23.2)	0.001
Requiring prophylactic antibiotics	3,213 (37.8)	2,029 (33.9)	332 (41.6)	286 (43.7)	566 (53.0)	<.0001
Comorbidity						
Diabetes	1,861 (21.9)	1,356 (22.7)	153 (19.2)	120 (18.3)	232 (21.7)	0.07
Hypertension	1,274 (15.0)	891 (14.9)	101 (12.7)	87 (13.3)	195 (18.3)	0.07
Malignancy	849 (10.0)	554 (9.3)	74 (9.3)	65 (9.9)	159 (14.9)	<.0001
Psychiatric disorder	3,341 (40.4)	2,498 (41.8)	302 (37.8)	242 (37.0)	389 (36.4)	<.0001
Viral hepatitis	2,196 (25.8)	1,608 (26.9)	201 (25.2)	165 (25.2)	222 (20.8)	<.0001
Financial status						
NHI	7,878 (92.7)	5,648 (94.4)	737 (92.4)	582 (89.0)	911 (85.3)	<.0001
National Medical Aid	623 (7.3)	333 (5.6)	61 (7.6)	72 (11.0)	157 (14.7)	
Hospital type						
Designated tertiary hospital	5,722 (67.3)	4,044 (67.6)	540 (67.7)	449 (68.7)	689 (64.5)	0.1

Others[b]	2,779 (32.7)	1,937 (32.4)	258 (32.3)	205 (31.3)	689 (64.5)	
Hospital region						
Metropolitan cities	6,442 (75.8)	4,516 (75.5)	613 (76.8)	515 (78.7)	798 (74.7)	0.8
Rural	2,059 (24.2)	1,465 (24.5)	185 (23.2)	139 (21.3)	270 (25.3)	
Diagnosed year						
2009	781 (9.2)	412 (6.9)	122 (15.3)	91 (13.9)	156 (14.6)	<.0001
2010	866 (10.2)	483 (8.1)	120 (15.0)	102 (15.6)	161 (15.1)	
2011	965 (11.4)	568 (9.5)	136 (17.0)	98 (15.0)	163 (15.3)	
2012	981 (11.5)	620 (10.4)	122 (15.3)	91 (13.9)	148 (13.9)	
2013	1,098 (12.9)	777 (13.0)	96 (12.0)	88 (13.5)	137 (12.8)	
2014	1,251 (14.7)	936 (15.6)	99 (12.4)	79 (12.1)	137 (12.8)	
2015	1,237 (14.6)	1,018 (17.0)	63 (7.9)	56 (8.6)	100 (9.4)	
2016	1,322 (15.6)	1,167 (19.5)	40 (5.0)	49 (7.5)	66 (6.2)	
Long term follow-up loss[c]	477 (5.6)	16 (0.3)	30 (3.8)	208 (31.8)	223 (20.9)	<.0001

Abbreviation: AIDS, acquired immune deficiency syndrome; NHI, National Health Insurance

a= Mantel-Haenszel Chi-Square test to assess trends in the four MPR groups, b= Others of hospital type include public health centres, primary medical clinics, general hospitals, c= Individuals who had no clinic visit for antiretroviral treatment for same or more than a year.

The value denotes the subject number (%)

Hospital visit characteristics

In the high adherence group, average numbers of clinic visit for follow-up tests (HIV RNA quantification test, T cell subset analysis, HIV drug resistance mutation sequencing) or ART prescription were larger, and ART prescription days per visit was longer (p <.0001) (Table 3-2). The number of concomitant medication except ART was not different among the four groups. Although the proportion of individuals who visited emergency department at least once for any reason was not significantly different among the MPR groups, the number of hospital admission did show a significant difference, with higher frequency in lower adherence group (p <.0001).

Table 3-2. Characteristics of hospital visits of HIV patients by medication possession ratio

	≥ 95% (n=5,981)	80-95% (n=798)	50-80% (n=654)	<50% (n=1,068)	*p* value
Clinic visit for follow-up test[a]	13±8.3	16±8.1	15±8.5	6±5.3	<.0001
Clinic visit for ART	19±13.2	25±13.4	22±12.9	8±8.3	<.0001
ART prescription days per visit	67±23.0	63±19.7	53±20.7	32±20.2	<.0001
Co-medication number[b]	1.2±2.4	1.1±2.6	1.3±2.6	1.3±3.4	0.4
Emergency visit	3,265 (54.6)	447 (56.0)	408 (62.4)	513 (48.0)	0.06
Hospital admission	4,409 (73.7)	629 (78.8)	528 (80.7)	930 (87.1)	<.0001

Abbreviation: ART, antiretroviral therapy; HIV, human immunodeficiency virus

a= HIV RNA quantification test, T cell subset analysis, HIV drug resistance mutation sequencing, b= The maximum number of co-medication except ART divided by the number of observed months. Mean±standard deviation in case of clinic visit, ART prescription days, and co-medication number. Number of patients (% in each group) in case of emergency visit

and hospital admission.

Risk factors for suboptimal ART adherence

Risk factors for suboptimal ART adherence were analysed by comparing the ≥95% MPR group to the remaining three groups using a multivariable logistic regression model (Table 3-3). Patients who required prophylactic antibiotics were more likely to exhibit inadequate adherence (OR 1.7, 95% CI 1.5–2.0), while AIDS defining illness did not show statistical significance after adjustment. When comparing age groups, 20-29 and same or over 50 showed a significant association with suboptimal adherence than 30-39 group (OR 1.6, 95% CI 1.1–2.4, and OR 1.4, 95% CI 1.2-1.7, respectively). Being supported by the NMA, a proxy for lower financial status, was also significantly associated with suboptimal adherence when compared to being supported by the NHI (OR 2.1, 95% CI 1.7–2.6). In contrast, patients with psychiatric disorders had a lower likelihood of suboptimal adherence(OR 0.6, 95% CI 0.4–0.9); the directionality of this association remained when behavioural disorders related to only depression or alcohol use were separately included in the model.

Table 3-3. Risk factors for suboptimal adherence (medication possession ratio <95%) among newly diagnosed human immunodeficiency virus-infected individuals

	cOR	95% CI	aOR[a]	95% CI
Women	1.8	1.5-2.2	1.6	1.3-2.0
AIDS-defining illness	1.3	1.1-1.5		
Requiring prophylactic antibiotics	2.0	1.8-2.3		
Age				
0-19	1.2	0.8-1.8	1.6	1.1-2.4
20-29	0.8	0.7-1.0	1.0	0.8-1.3
30-39	1(ref)		1(ref)	
40-49	1.2	1.0-1.5	1.1	0.9-1.3
≥50	1.6	1.3-1.9	1.4	1.2-1.7
Comorbidity				
Diabetes	1.0	0.8-1.2		
Hypertension	1.3	1.1-1.6		
Malignancy	1.7	1.4-2.0	1.6	1.3-1.9
Psychiatric disorder	0.8	0.7-0.9	0.8	0.7-0.9
Viral hepatitis	0.7	0.6-0.8	0.8	0.6-0.9
Financial status				
NHI	1(ref)		1(ref)	
National Medical aid	1.2	1.0-1.3	1.2	1.1-1.4
Hospital type				
Designated tertiary hospital	1(ref)		1(ref)	
Others[b]	1.2	1.0-1.3	1.2	1.1-1.4
Diagnosed year				
2009	4.8	3.5-6.4	3.7	2.7-5.0

2010	4.3	3.2-5.9	3.8	2.8-5.1
2011	3.9	2.9-5.2	3.4	2.5-4.6
2012	3.4	2.5-4.6	3.2	2.3-4.3
2013	2.7	1.7-3.2	2.5	1.8-3.4
2014	2.3	1.7-3.2	2.3	1.7-3.1
2015	1.7	1.2-2.3	1.6	1.2-2.3
2016	1(ref)		1(ref)	

Abbreviation: AIDS, acquired immune deficiency syndrome; aOR, adjusted odds ratio; CI, confidence interval; cOR, crude odds ratio; NHI, National Health Insurance; ref, reference

a = Adjusted for all the variables in the table in addition to hospital region and the maximum number of all co-medication except ART divided by the number of observed months, b= Others of hospital type include public health centres, primary medical clinics, general hospitals

Stratification analysis for risk factors for suboptimal ART adherence

Stratified analysis was conducted for the women. There was a higher odds ratio of suboptimal adherence among age groups in their teens and 20s, and a lower odds ratio in their 40s and over 50s (Table 3-4). In particular, risk for teenage women was as high as 14.9 (95% CI 4.9-44.8). In stratified analysis of National Medical Aid group considering as lower socioeconomic level, other variables lost statistical significance after analysis and only psychiatric history was associated with significantly higher medication adherence (OR 0.6, 95% CI. 0.4-0.8). AIDS patients did not show any difference from unstratified results (Table 3-5). Patients who visited hospitals other than tertiary hospitals had higher odds ratio of low medication adherence when visiting hospitals at metropolitan cities or rural area. (Table 3-6).

Table 3-4. Risk factors for suboptimal adherence (medication possession ratio <95%) among newly diagnosed human immunodeficiency virus-infected individuals who are women

	OR[a]	95% CI	*P*
Age			
0-19	14.9	4.9-44.8	<.0001
20-29	2.8	1.8-4.4	<.0001
30-39	2.2	1.5-3.4	0.0001
40-49	0.8	0.5-1.4	0.53
≥50	1(ref)	0.3-0.8	
AIDS	1.7	1.2-2.3	0.003
National Medical Aid	3.0	2.0-4.6	<.0001
Diagnosed year			
2009	2.7	1.4-5.2	0.003
2010	3.4	1.8-6.6	<.001
2011	2.2	1.1-4.3	0.02
2012	2.6	1.4-4.8	0.003
2013	1.5	0.8-2.8	0.26
2014	2.0	1.0-3.7	0.04
2015	1.0	0.5-2.0	0.97
2016	1(ref)		

Abbreviation: AIDS, acquired immune deficiency syndrome; OR, odds ratio; CI, confidence interval; NHI, National Health Insurance; ref, reference

a = Adjusted for all the variables in the table in addition to AIDS, diabetes, hypertension, viral hepatitis, psychiatric disorder, hospital region, diagnosed year, hospital type and the maximum number of all co-medication except ART divided by the number of observed months. Hospital type indicates tertiary hospital vs. others. Other hospitals include public health centres, primary medical clinics, and general hospitals

Table 3-5. Risk factors for suboptimal adherence (medication possession ratio <95%) among newly diagnosed AIDS patients

	aOR[a]	95% CI
Women	1.3	1.0-1.7
Comorbidity		
Diabetes	0.8	0.7-0.9
Malignancy	1.4	1.1-1.6
Psychiatric disorder	0.8	0.7-0.9
Financial status		
NHI	1(ref)	
National Medical aid	2.2	1.8-2.8
Hospital type		
Designated tertiary hospital	1(ref)	
Others[b]	1.2	1.1-1.4

Abbreviation: AIDS, acquired immune deficiency syndrome; OR, odds ratio; CI, confidence interval; NHI, National Health Insurance; ref, reference

a = Adjusted for all the variables in the table in addition to age, hypertension, viral hepatitis, hospital region, diagnosed year and the maximum number of all co-medication except ART divided by the number of observed months, b= Others of hospital type include public health centres, primary medical clinics, general hospitals

Table 3-6. Risk factors for suboptimal adherence (medication possession ratio <95%) among newly diagnosed human immunodeficiency virus-infected individuals with other hospital visit[a]

	OR[b]	95% CI
Women	1.7	1.3-2.2
Comorbidity		
Malignancy	1.4	1.1-1.9
Psychiatric disorder	0.7	0.6-0.8
Financial status		
NHI	1(ref)	
National Medical aid	2.1	1.6-2.8
Hospital region		
Seoul	1(ref)	
Metropolitan cities	1.2	1.1-1.4
Rural	1.6	1.2-2.3

Abbreviation: AIDS, acquired immune deficiency syndrome; OR, odds ratio; CI, confidence interval; NHI, National Health Insurance; ref, reference

a = Others of hospital type include public health centres, primary medical clinics, general hospitals. b = Adjusted for all the variables in the table in addition to age, AIDS, diabetedi, hypertension, viral hepatitis, diagnosed year and the maximum number of all co-medication except ART divided by the number of observed months

3-4. Discussion

This study demonstrates the levels of adherence to ART in HIV-infected individuals in Korea. When the study population was stratified into four groups according to the MPR, 70.4% showed an adherence of ≥95%. Although this does not meet the UNAIDS target of 90%, it seems acceptable when compared to previous studies in other developed and developing countries. (35, 47-51) In a study conducted in Malawi, 70% of patients had a MPR >90%, and a study conducted in another sub-Saharan African country reported that 52% of patients showed an adherence of >80% based on a pharmacy dispense records. (35, 47) A meta-analysis of 27 studies from 12 sub-Saharan African countries and 31 North American studies revealed that 77% of HIV-infected individuals achieved adequate adherence based on the criteria used in the respective studies; in contrast, only 55% of HIV-infected individuals did in North American studies. (48) A study in France reported that 65.2% of HIV patients showed an MPR of >80%. (49) Last, a study conducted in the United States revealed an adherence of >90% in only 38% of the study participants. (50)

In this study, we show that patients requiring prophylactic antibiotics, age of 20-29 or ≥50 compared to 30-39, those who werewomen, age under 20 and same or over 50 compared to 30–39, and having a history of malignancy, lower socioeconomic status, not visiting a tertiary-level hospital, and being diagnosed in the earlier years were at a higher risk for becoming less adherent. All costs for HIV treatment, including ART and outpatient or inpatient clinic care, are completely covered by the government in Korea. The proportion of patients supported by the NMA among the entire HIV population was higher (7%) than that among the national population (3%), showing that HIV-infected individuals tend to have a lower socioeconomic status in general. Based on the stratified results, the lower

socioeconomic stats might be confounding. Data on whether socioeconomic status is important for adequate ART adherence have been inconsistent. (52, 53) In addition to the cost of medical treatment, labour loss time and transportation problems are barriers to adequate adherence. (53, 54) As a lower socioeconomic status is frequently accompanied by a lower educational level, an incomplete understanding of treatment importance or simply forgetting taking medication is another barrier to adequate adherence. (54, 55) However, a recent survey among men who have sex with men in Korea revealed that education or financial status was not a barrier for the intention to take HIV screening test. (56) In addition, patients who visit hospitals either than government designated tertiary teaching hospitals were at higher risk of suboptimal adherence compared to those who visit designated ones. Since there is no difference in financial barrier among medical institutions for ART, patients with high motivation of treatment tend to visit government designated tertiary teaching hospitals. This implies more interest in the care of HIV-infected individuals outside the range of tertiary hospitals, both the attention of the clinicians and policy makers regarding lower level of medical institutions.

In terms of comorbid conditions, having a psychiatric disorder and viral hepatitis were both negatively associated with suboptimal adherence. When we analysed the diagnoses within psychiatric disorder by subcategories, the majority of diagnoses (45%; data now shown) were depressive illnesses. The direction of the association did not change when only depression (instead of psychiatric disorders as a whole) was included in the model. This result is not in agreement with previous studies, which reported depression itself as a risk factor for lower adherence. (37, 57, 58) However, compared to the prevalence of depression of 22–32% among HIV-infected individuals in a previous report, (59) the prevalence in the

current data set is similar. Considering the social stigma associated with depression, (60) it is possible that HIV patients who had a better relationship with their physician were more likely to report their depressive symptoms than those with a poorer relationship. In addition, ART adherence study of HIV and viral hepatitis C (HCV) co-infected individuals also revealed that proportion of days covered >95% group had higher proportion of HCV treatment using the 2005-2007 Medicaid claims data. (61) Overall, improved patient-clinician relationships could enhance ART adherence. (62) Counselling and more in-depth communications between patients and clinicians can facilitate the detection of comorbidities such as depression, improve ART adherence and the treatment outcome of comorbid conditions.

While HIV-infected individuals in Korea are mostly men, women was a risk factor for suboptimal adherence. In particular, teenage women among PLHIV showed a high risk for suboptimal adherence (OR 14.9, 95% CI 4.9-44.8). This is in line with other studies where in one study, women had 1.5 times greater incidence of non-adherence initiating ART in a 2001-2002 cohort in Brazil, (63) and in another study, women had a lower likelihood (OR 0.7) of being 95% adherent in Canada. (64) Also in Korea where HIV is commonly known to transmit through sexual contact, women tend to be reluctant to expose themselves. As confirmed by stratification analysis, stigma is expected to be an important factor in young women in their teens. Teenage women comprise approximately 2% of Korean PLHIV. This is an important epidemiological issue because younger patients take antiretroviral agents for longer periods during their lives, and there is a higher risk of transmission in sexually active populations. Issues such as pregnancy, childbirth, and vertical transmission of HIV must also be in considered for teenage women populations.

Higher proportion of women also explains the higher risk of low adherence among

those with malignancy history since 49% of whose with malignancy were women. Among 8,501 total study population, 59 had a primary diagnosis of malignancy when initial ART treatment was prescribed, and the type and frequency were the following: stomach: 1, colon: 1, anus: 1, liver: 7, biliary tract: 1, pancreas: 1, lung: 1, Kaposi sarcoma: 2, soft tissue: 1, breast: 1, kidney: 1, bladder: 1, brain: 2, Hodgkin lymphoma: 1, all other types of lymphoma: 30, leukaemia: 2. Even though there are identified challenges for cancer patients to initiate ART such as drug-drug interactions, overlapping toxic effects, or immunodeficiency associated with malignancy, most ART regimen can be implemented. Therefore, cancer history should not be a barrier for ART treatment and the cooperation of both specialists of cancer and infectious disease should be encouraged while most of the HIV-infected individuals in Korea visit highly specialized tertiary hospitals.

The main limitations of this study comes from the reimbursement-based claims databases which generally contain only the information provided by health services and lack some demographic data such as education or clinical manifestations such as viral load or CD4+ T cell values. In Korea, however, all HIV-related medical care is reimbursed; thus, we assume that all services that HIV patients received were fully recorded in the database. Even though the values of the follow-up tests were not available, we analysed the frequency of relevant tests and used the prescription history of prophylactic antibiotics as a proxy for CD4+ T cell counts <200 cells/mm3 as prophylactic antibiotics are prescribed in those patients with advanced HIV infection. In addition, there is a limitation that claims data analysis could not distinguish taking medication from prescription. However, none of the study population changed the hospital during the study period. In actual clinic, the CD4 + T cell count and the interval of the patient's visit would be checked to evaluate the treatment

and the patient would get feedback. Therefore, the possibility is low that a patient get prescription without taking the medication for a long time. Another limitation is the potentially inaccurate recruitment of HIV-infected individuals. Since we selected HIV-infected individuals starting from ART receivers, those who were diagnosed with HIV infection but never visited healthcare could have been excluded while those who received ART for other purpose could have been falsely included.

However, when the number of incident HIV patients from this database was compared to the actual national report, the number was slightly higher in this database. More importantly, we excluded those who seemed to have received ART for PEP, PrEP, or other reasons using various ways. Last, we may not have detected all cases of deaths by using the ICD-10 codes, and this could have resulted in a lower adherence than real since the time after one is deceased was counted as long term follow-up loss. However, this was the only information available, and among a population of 20-49 consisting of 75%, this was relatively a minor issue.

In previous studies, adherence to ART was assessed in retrospective or prospective cohorts, which demands a huge financial burden and effort. The database of KCDC is the number of reported cases and these individuals are not periodically monitored by the KCDC, but by individual clinics when those individuals seek healthcare facilities. This study used claims data to analyse the nationwide adherence to ART with minimum effort and revealed comparable findings to previous studies, indicating a potential use of NHI database in ART adherence monitoring in a national level.

In conclusion, the current policy for HIV control focuses more on improving the continuum of HIV care from diagnosis to viral suppression. In particular, high medication

adherence is an essential factor for achieving optimal HIV care. Our results showed that approximately 70.4% of PLHIV in Korea had adequate adherence to ART and there were modifiable risk factors affecting suboptimal adherence. Based on our results, health authority should take into consideration of how to establish sustainable monitoring system at national level using the NHI system for HIV care and how to increase the medication adherence for population with risk factors.

CHAPTER 4.

Association of HIV-syphilis coinfection with optimal antiretrovial adherence: A nation-wide claims study

4-1. Introduction

The Undetectable = Untransmittable (U = U) initiative led to a medical-scientific basis that influenced behavioral and social science to remove the fear or guilt from HIV infection. (6) In a study of serodiscordant couples, HIV infection did not occur when the virus was undetectable (65) and based on this, it was claimed that if the HIV viral load was undetectable, it was untransmittable. Moreover, the possibility of condomless sex was suggested, with the condition that there were no other STDs. (66)

However, the percentage of concomitant STD infection in people living with HIV varies. A systematic review reported that the median seroprevalence of HIV-syphilis coinfection was 15.7%, but among men in the US who have sex with men, it was 64.3–90.0%. (7) A retrospective study reported that the HIV-positive rate in syphilis patients in the UK was 6–47%. (67) Certain STDs are likely to be transmitted during asymptomatic infections and are thus transmitted without awareness. (68) Confirmation of the STD coinfection rate in people with an undetectable HIV viral load can be obtained from optimal medication adherence data. Before suggesting condomless sexual relationships among people living with controlled HIV, it is reasonable to identify the current status of unsafe sex and then develop a policy.

Korea has adopted a single national health insurance plan since 1963, so it is possible to analyze nationwide data by using claim data for people living with HIV. This study estimated the status of unsafe sex in people living with HIV based on their treatment history of syphilis and identified the characteristics of the high-risk group for unsafe sex, presenting with HIV-syphilis coinfection. In particular, we compared the percentage of syphilis coinfection between optimal and suboptimal adherence groups based on ART adherence using MPR.

4-2. Materials and methods

Study design

This was a retrospective study using the claims database, from which data were collected between 2007 and 2016. During the study period, people living with HIV were identified who had a combined ART prescription and follow-up tests (Fig. 4-1). We defined an incident HIV infection after a period of no visits for ART for at least one year, and excluded subjects with ART prescriptions for 2007. Therefore, the study period was 2008–2016. Next, we identified syphilis coinfection among people living with HIV. We compared the characteristics including sex, age, percentage of AIDS, comorbidities, ART adherence and hospital region of people living with HIV with or without syphilis coinfection. The percentageof HIV-syphilis coinfection was compared in two groups with regard to ART-adherence based on antiretroviral agent prescriptions. The institutional review board of the Seoul National University Boramae Medical Center approved the study protocol and waived the need for informed consent due to its retrospective nature and the use of an existing secondary database (IRB No. 07-2017-8/052).

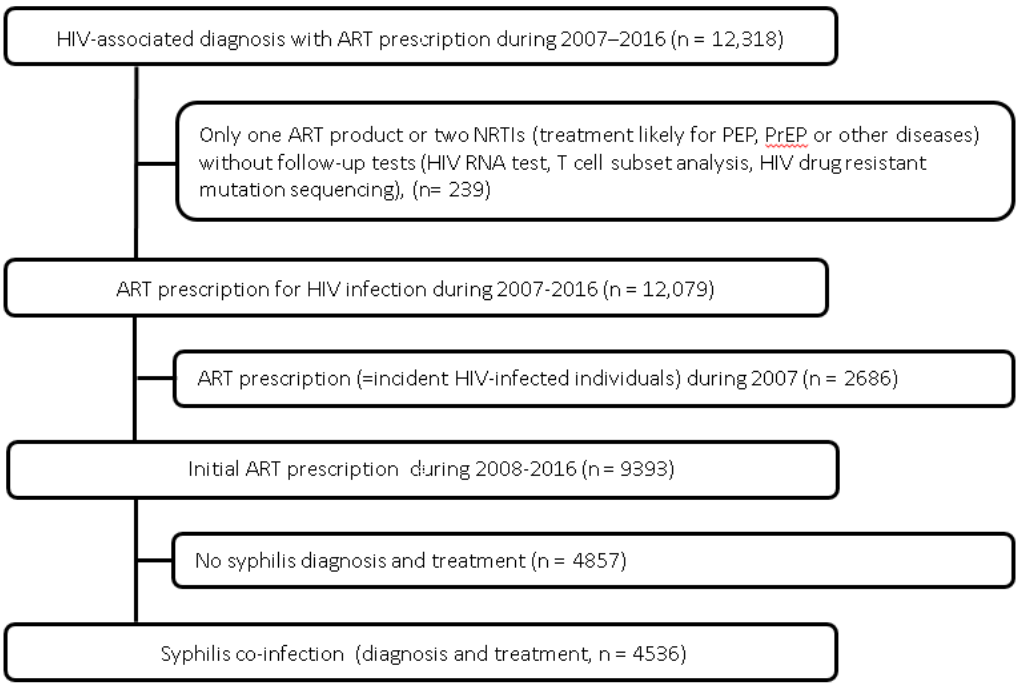


Figure 4-1. Study design to investigate HIV-syphilis coinfection in people living with incident HIV.

Database

This study was conducted using claims data from the Korean NHI database. Korea adopted a single NHI system in 1963: all medical institutions in Korea charge claims to the NHI after patient visits and the NHI reviews the claims before reimbursing them. All diagnoses, prescriptions, and laboratory or imaging tests are recorded in the claims data.

For people living with HIV, the NHI covers 90% of all HIV-related treatment costs. The Korean government supports the remaining 10% of the total cost not covered by the NHI to encourage people to seek treatment and prevent the transmission of HIV. Almost all hospital visits for people living with HIV, including ART prescription, follow-up blood tests, and any related STD treatments are covered by insurance, removing the financial burden from the patient. The entire medical history of people living with HIV is available through analysis of the claims data.

Definitions

HIV infection was defined as the presence of combined ART prescriptions with HIV-associated diagnosis and three tests that are required for people living with HIV (69): the HIV antigen/antibody, HIV RNA quantification, and HIV drug-resistant mutation tests. Syphilis infection was defined if benzathine penicillin G was prescribed on the same day as a syphilis-related diagnosis. No *in vitro* resistance has developed to penicillin for the treatment of *Treponema pallidum* infections, which is in contrast to most other bacteria (e.g., *Neisseria gonorrhoeae, Streptococcus pneumoniae, Staphylococcus aureus*), (70) and the prescription of this antibiotic agent for syphilis is considered appropriate.

ART adherence was calculated as per our previous study using the MPR. (16) The MPR was calculated as the sum of the number of days of treatment supplied by all ART prescriptions filled, from the first round of ART until the last day of 2016, divided by the number of days during that same time period.

AIDS was defined as one or more of the following: (1) diagnosis of AIDS-defining illnesses or (2) prescription of prophylactic antibiotic agents for pneumocystis pneumonia, suggesting a CD4+ T cell count less than 200/mm^3. (13) Co-morbidities identified by means of diagnostic codes before the onset of ART were investigated to prevent post-treatment co-morbidities leading to reverse causation.

Statistical analysis

The epidemiologic characteristics of the HIV with syphilis coinfection group and the HIV without syphilis group were compared using the chi-squared method. To assess the risk factors for HIV-syphilis coinfection, characteristics that differed significantly between the two groups (HIV with and without syphilis) were included in the multiple logistic regression model. The follow-up duration in years was included in the multiple model to adjust for bias due to the observation period, because the management of HIV, including ART recommendations, changed from 2008–2016. Patients infected with syphilis after the diagnosis of HIV infection were further analyzed to determine the time-relevant relationship between syphilis infection experience and ART adherence. *P* values <0.05 were considered significant in all analyses. All statistical analyses were conducted using SAS Enterprise Guide, Version 6.1 (SAS Institute., Inc., Cary, NC, USA).

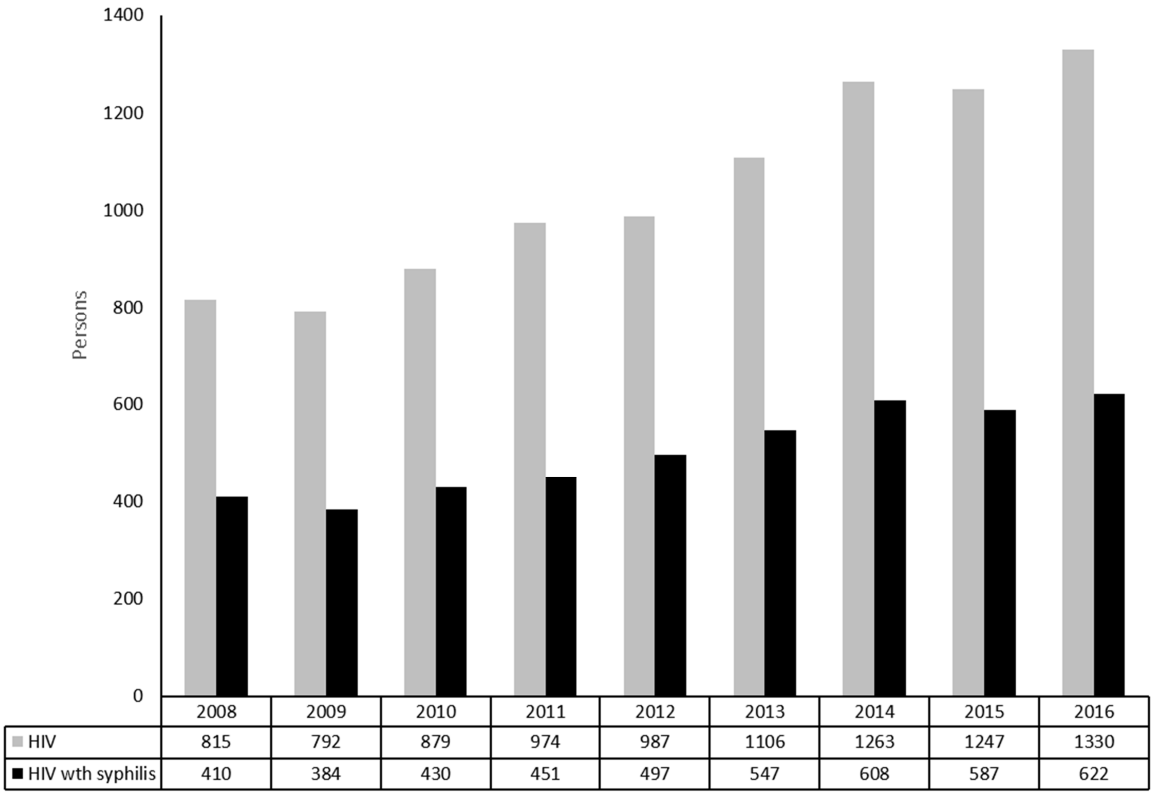
4-3. Results

Baseline characteristics of people living with HIV-syphilis coinfection

In total, 12,318 people visited medical facilities for any ART prescription between 2007 and 2016 (Fig. 4-1). Of these, we excluded any patients without any specific follow-up tests, as well as patients who were prescribed only one ART product or two nucleoside reverse transcriptase inhibitors, which were considered to be prescribed for post-exposure prophylaxis, pre-exposure prophylaxis, or other diseases. The database included 12,079 people living with HIV who were receiving ART. We excluded 2686 people living with HIV who had visited a hospital during 2007 and finally identified 9393 people with HIV infection who had started ART since the beginning of 2008. Of these, 4536 (48.3%) had HIV-syphilis coinfection. The number of HIV-syphilis coinfection did not differ annually from 2008−2016 (Fig. 4-2). The number of syphilis treatments ranged from 1−125 in the group with HIV-syphilis coinfection: of these, 90% had fewer than 8 syphilis treatments. The mean number of syphilis treatments was 4.2 and the standard deviation was 5.0.

In the HIV with syphilis group, 94.3% were men, a significantly higher percentage than in the HIV without syphilis group (88.8%, P< .0001) (Table 4-1). People living with HIV who were younger than 20 years of age had significantly fewer HIV-syphilis coinfections than the older age groups, but no particular age group exhibited any noticeable differences. There was no significant difference in the number of people with HIV-syphilis coinfection in terms of the presence or absence of AIDS. With regard to ART adherence, the optimal adherence with a 95% or more medication possession ratio was significantly higher at 70.3% in the HIV with syphilis group than in the HIV without syphilis group (66.2%, P< .0001). There was also more concomitant of psychiatric disorders, bacterial/protozoa

STDs, genital herpes simplex virus (HSV), and human papillomavirus (HPV) infection/anal neoplasm, presenting at the hospital in Seoul (the capital of Korea) in the HIV-syphilis coinfection group (41.3% *vs.* 36.3%; *P*< .0001, 11.0% *vs.* 2.1%; *P*< .0001, 5.8% *vs.* 2.5%; *P*< .0001, 11.7% *vs.* 8.4%; *P*< .0001, 51.2% *vs.* 47.8%; *P*= .001, respectively).



	2008	2009	2010	2011	2012	2013	2014	2015	2016
HIV	815	792	879	974	987	1106	1263	1247	1330
HIV wth syphilis	410	384	430	451	497	547	608	587	622

Figure 4-2. Trends for the number of people living with HIV and syphilis treatment in the Republic of Korea. Cases of incident HIV infection have increased annually from 2008 to 2016 and among these, syphilis coinfection was 46.3–50.4%, or 48.3% overall. There was no significant change in the syphilis coinfection rate by year.

Table 4-1. Characteristics of people living with HIV-syphilis coinfection among incidental HIV population during 2008-2016

	Total (n=9,393)	HIV with syphilis (n=4,536)	HIV without syphilis (n=4,857)	p value[a]
Gender				
Men	8592(91.5)	4278(94.3)	4314 (88.8)	<.0001
Women	801(8.5)	258(5.7)	543(11.2)	
Age (in years)				
Under 20	234(2.5)	84(1.9)	150 (3.1)	<.0001
20-29	2325(24.8)	1150(25.4)	1175(24.2)	
30-39	2476(26.4)	1269(28.0)	1207(24.9)	
40-49	2238(23.8)	1068(23.5)	1170(24.1)	
50 and over	2120(22.6)	965(21.3)	1155(23.8)	
AIDS[b]	2150(47.4)	4405(46.9)	2255(46.4)	0.346
ART Adherence				
Optimal[c]	6404(68.2)	3189(70.3)	3215(66.2)	<.0001
Suboptimal	2989(31.8)	1347(29.7)	1642(33.8)	
Comorbidity				
HBV coinfection	612(6.5)	316(7.0)	296(6.1)	0.087
HCV coinfection	825(8.8)	406(9.0)	419(8.6)	0.579
Psychiatric disorder	3638(38.7)	1875(41.3)	1763(36.3)	<.0001
Bacterial/protozoa STD	598(6.4)	497(11.0)	101(2.1)	<.0001
Genital HSV	386(4.1)	263(5.8)	123(2.5)	<.0001
HPV/anal neoplasm	938(10.0)	531(11.7)	407(8.4)	<.0001
Hospital region				
Seoul (capital city)	4648(49.5)	2324(51.2)	2324(47.8)	0.001
Metropolitan cities	2486(26.5)	1199(26.4)	1290(26.6)	
Rural	2256(24.0)	1013(22.3)	1243(25.6)	

HIV; human immunodeficiency virus, AIDS; acquired immunodeficiency syndrome, ART; antiretroviral therapy, HBV; hepatitis B virus, HCV; hepatitis C virus, STD; sexually transmitted diseases, HSV; herpes simplex virus, HPV; human papilloma virus, NHI; national health insurance

a: P value for chi-square test, b: AIDS defining diagnosis or prophylactic antibiotic agent prescription for pneumocystis pneumonia, c: Optimal adherence means MPR ≥95%, suboptimal adherence means MPR < 95%

Values represents numbers and (%).

Risk factors for HIV-syphilis coinfection

A multiple regression model was constructed for the variables that differed significantly between two groups. The variables included age, gender, ART adherence, the presence of a psychiatric disorder, bacterial/protozoa STD, genital HSV infection, HPV infection/anal neoplasm, hospital region, and follow-up duration (calculated by subtracting the diagnostic year from 2016). Optimal ART adherence was associated with HIV-syphilis coinfection after adjusting other relevant variables (OR 1.18; 95% CI 1.08-1.30; *P*= .001) (Table 4-2). Male sex was also associated with HIV-syphilis coinfection (OR 2.48; 95% CI 2.10-2.93; *P*< .0001). In terms of age, all adult ages from 20 years and older were associated with syphilis coinfection with an increased OR of 1.36, compared to 1.63 for the <20 years age group. The presence of other STDs such as bacterial/protozoa STD, genital HSV infection, and HPV infection/anal neoplasm was also associated with HIV-syphilis coinfection (OR 6.14, OR 2.25, and OR 1.24, respectively), and all three values were statistically significant. Having a psychiatric disorder was also associated with HIV-syphilis coinfection, with an OR of 1.27. The association of HIV-syphilis coinfection in terms of follow-up duration tended to increase gradually from an OR of 1.02 to 1.53 if the follow-up duration was < 1 year.

Table 4-2. Risk factors for HIV-syphilis coinfection in incidental people living with HIV in 2008-2016

	OR	95% CI	*P* value[a]
Men	2.48	2.10-2.93	<.0001
Age			
Under 20	1(ref)		
20-29	1.62	1.22-2.16	0.001
30-39	1.63	1.23-2.16	0.001
40-49	1.45	1.09-1.93	0.011
50 and over	1.36	1.02-1.81	0.036
Optimal ART adherence[b]	1.18	1.08-1.30	0.001
Comorbidity			
Psychiatric disorder	1.27	1.16-1.38	<.0001
Bacterial/protozoa STD	6.14	4.91-7.67	<.0001
Genital HSV	2.25	1.79-2.82	<.0001
HPV/anal neoplasm	1.24	1.08-1.43	<.0001
Hospital region			
Seoul (capital city)	1(ref)		
Metropolitan cities	0.97	0.88-1.07	0.537
Rural	0.86	0.77-0.95	0.004
Follow up duration			
<1year	1(ref)		
1-2 year	1.02	0.87-1.20	0.771
2-3 year	1.15	0.98-1.35	0.090
3-4 year	1.25	1.06-1.47	0.010
4-5 year	1.34	1.13-1.59	0.001
5-6 year	1.17	0.98-1.39	0.080
6-7 year	1.34	1.12-1.61	0.001
7-8 year	1.39	1.15-1.68	0.001
8-9 year	1.53	1.27-1.84	<.0001

HIV; human immunodeficiency virus, OR; odds ratio, CI; confidence interval, ART; antiretroviral therapy, STD; sexually transmitted disease, HSV; herpes simplex virus, HPV; human papilloma virus

a: P value for linear logistic regression analysis

b: Optimal adherence means MPR ≥95%, suboptimal adherence means MPR < 95%

HIV-syphilis coinfection in terms of medication adherence

A subgroup analysis was performed by dividing the HIV with syphilis group into an optimal adherence group and a suboptimal adherence group. The optimal adherence with a >95% medication possession ratio in the HIV with syphilis group was 3189 (68.2%). The mean numbers of syphilis treatments in the optimal adherence group and the suboptimal adherence group were 4.31 (± 5.50) and 3.79 (± 3.59), respectively (P< .0001).

HIV-syphilis coinfection with syphilis infection after diagnosis of HIV infection

During the study period, 2428 experienced syphilis infections after HIV infection diagnosis. There was no significant difference in gender and age and the number of AIDS between the total syphilis-HIV coinfection at anytime group and syphilis infection after HIV infection diagnosis group (Table 4-3). There was no significant difference in ART adherence. Rather, the syphilis infection after HIV infection diagnosis group had slightly lower proportion of optimal adherence. When multiple regression models were applied based on the syphilis infection after HIV infection diagnosis, optimal adherence was still identified as a risk factor (OR 1.25; 95CI 1.12-1.39; P <.0001, Table 4-4).

Table 4-3. Characteristics of people living with HIV-syphilis coinfection in terms of HIV infection diagnosis during 2008-2016

	Syphilis with HIV at anytime (n=4,536)	Syphilis before HIV (n=2,108)	Syphilis after HIV (n=2,428)	p value[a]
Gender				
Men	4278(94.3)	1964(93.2)	2314(95.3)	<.0001
Women	258(5.7)	144 (6.8)	114(4.7)	
Age				
1<20	84(1.9)	37(1.8)	47(1.9)	0.01
20-29	1150(25.4)	514(24.4)	636(26.2)	
30-39	1269(28.0)	576(27.3)	693(28.5)	
40-49	1068(23.5)	483(22.9)	585(24.1)	
Over 50	965(21.3)	498(23.6)	467(19.2)	
AIDS	2150(47.4)	982(46.6)	1168(48.1)	0.31
ART Adherence				
Optimal[b]	3189(70.3)	1531(72.6)	1658(68.3)	<.0001
Suboptimal	1347(29.7)	577(27.4)	770(31.7)	

HIV; human immunodeficiency virus, AIDS; acquired immunodeficiency syndrome, ART; antiretroviral therapy, HBV; hepatitis B virus, HCV; hepatitis C virus, STD; sexually transmitted diseases, HSV; herpes simplex virus, HPV; human papilloma virus, NHI; national health insurance

a: P value for chi-square test of Syphilis before HIV and after HIV infection diagnosis

b: Optimal adherence means MPR ≥95%, suboptimal adherence means MPR < 95%

Values represents numbers and (%).

Table 4-4. Risk factors for syphilis infection after HIV infection diagnosis in incidental people living with HIV in 2008-2016

	OR	95% CI	P value[a]
Men	2.42	1.960-2.989	<.0001
Age			
<20	1(ref)		
20-29	1.45	1.028-2.032	0.034
30-39	1.30	0.923-1.822	0.135
40-49	1.22	0.867-1.721	0.252
Over 50	1.11	0.783-1.576	0.555
Optimal ART adherence[b]	1.25	1.12-1.39	<.0001
Comorbidity			
Bacterial/protozoa STD	1.83	1.517-2.202	<.0001
Genital HSV	1.62	1.292-2.040	<.0001
HPV/anal neoplasm	1.35	1.155-1.571	0.0001
Hospital region			
Seoul (capital city)	1(ref)		
Metropolitan cities	0.96	0.851-1.079	0.486
Rural	0.72	0.632-0.809	<.0001
Follow up duration			
<1year	1(ref)		
1-2 year	1.81	1.455-2.255	<.0001
2-3 year	2.18	1.755-2.704	<.0001
3-4 year	3.04	2.445-3.768	<.0001
4-5 year	3.65	2.929-4.547	<.0001
5-6 year	3.49	2.790-4.357	<.0001
6-7 year	4.36	3.482-5.460	<.0001
7-8 year	5.04	4.003-6.333	<.0001
8-9 year	5.71	4.541-7.167	<.0001

HIV; human immunodeficiency virus, OR; odds ratio, CI; confidence interval, ART; antiretroviral therapy, STD; sexually transmitted disease, HSV; herpes simplex virus, HPV; human papilloma virus

a: P value for linear logistic regression analysis

b: Optimal adherence means MPR ≥95%, suboptimal adherence means MPR < 95%

4-4. Discussion

This study investigated the epidemiology of HIV-syphilis coinfection at a national level using the universal NHI system in Korea. It was interesting to note that optimal ART adherence was associated with HIV-syphilis coinfection. Male sex and having a previous history of other STDs were also associated with syphilis coinfection in newly diagnosed people living with HIV since 2008.

The percentage of syphilis was in decline but has increased since 2000, especially among men who have sex with other men and people with multiple sexual partners. (71) This epidemiological trend has also been observed in Korea, (72) and major transmission mode of HIV infections in Korea are related to homosexual or bisexual relationship. (73) A previous study based at a tertiary hospital reported that HIV-syphilis coinfection among people living with HIV increased from 5.5 per 100 person-years in 1999 to 18.8 per 100 person-years in 2003. (74) Our study revealed that nearly half of people living with HIV had syphilis coinfection and that the optimal adherence group, in which people were expected to achieve HIV viral suppression, had more cases of syphilis infection. The higher proportion of men and the higher percentage of other STDs in the syphilis coinfection group confirmed the results of previous epidemiological studies. (75) We conducted an additional analysis with the patients who acquired syphilis after being diagnosed with HIV infection, in order to determine if having a syphilis infection prior to an HIV infection affects ART adherence. The sample size of the HIV-syphilis coinfection group decreased from 4,536 to 2,468. The multiple logistic regression analysis revealed that optimal ART adherence remained a significant risk factor (OR 1.25, 95% CI 1.12-1.39) for acquiring a HIV-syphilis coinfection. Other than optimal ART adherence, follow–up duration showed a higher odds ratio in this

analysis (OR for 1–2years 1.81, OR for 5–6years 3.49, OR for 8–9 years 5.71).

Continued condom use is known to be difficult. A previous study found that only 15% of HIV-positive men who have sex with men used condoms consistently and only 18% of HIV-positive men used condoms 100% of the time after 12 months. (76) Another qualitative study reported that difficulty in maintaining consistent condom use was the reason underlying applications made by discordant couples to join a pre-exposure prophylaxis clinical trial. (77) The difficulty of consistent condom use appears to apply to people living with controlled HIV in this study. The guidelines recommend the use of condoms regardless of viral status, but consistent use of condoms is limited and the promotion of condom use is not perfect. (78) If there is no risk of HIV transmission, it might be easier to choose condomless sex. In a report on pre-exposure prophylaxis for HIV, Kojima et al. reported that the risk of contracting other STDs such as syphilis was increased 44.6-fold in men who have sex with other men with pre-exposure prophylaxis. (79)

The optimal adherence group had a higher percentage of HIV-syphilis coinfection, and syphilis treatment frequency was significantly higher. Longer HIV follow-up duration is known to be linked to increased syphilis diagnoses. (80) We included the follow-up duration in years in our multivariate analysis model, and the association of the optimal adherence group with HIV-syphilis coinfection was maintained after adjusting for the follow-up duration. It is possible that the optimal adherence group is more likely to be exposed to condomless sex based on their history of more frequent treatments for syphilis as well as the higher syphilis coinfection proportion in this group.

This study is meaningful in that it presents nationwide data that were analyzed using the claims data of the NHI. Almost half of the people living with HIV had HIV-syphilis

coinfection, despite recommendations for correct and consistent condom use. (81) These epidemiological data can be used to develop preventive measures for STDs in people living with HIV, such as raising awareness of coinfection, encouraging the use of condoms, and seeking STD testing.

This study had some limitations. First, only benzathine penicillin G treatment was accepted as a valid syphilis treatment. Alternative regimens such as doxycycline or ceftriaxone were not included because those antibiotics have numerous indications, and the reasons underlying their prescription could not be identified in this study. However, the number of cases identified with doxycycline use with a diagnosis of syphilis was found to be not significant in an additional screening. Second, it is possible that people living with HIV in the higher ART adherence group visited the hospital more frequently and received more regular screening for STDs, which may lead to a biased result. However, patients with optimal ART adherence might have an extended interval between visits. Even when interpreted as a minimum value, syphilis coinfection is not negligible in people with optimal ART adherence.

In conclusion, HIV-syphilis coinfection was confirmed in 48.3% of Korean people living with HIV. The risk of HIV-syphilis coinfection was higher in the optimal adherence group, suggesting that those in the optimal adherence group are exposed to STDs such as syphilis via unprotected sex and that consistent condom use is required, even when their HIV RNA is undetectable.

CHAPTER 5.

Discussion and Conclusion

5-1. Usefulness of the Korean National Health Insurance database in establishing surveillance systems of treatment cascade for HIV infection

This study compares the two databases, NHI and KCDC, using the nationwide claims database. It showed that most of the PLHIV visited hospitals and elucidated their epidemiological characteristics including age and sex distribution. Moreover, important epidemiological characteristics such as CD4-positive T-cell counts, which were not appropriately identified in the KCDC reports, were revealed in the claims data.

In Korea, 97% of the total population is registered in the obligatory NHI database, and the remaining 3% (those with the lowest socioeconomic status) are supported by the NMA. All medical utilization within the NHI is monitored for reimbursement, and any use of healthcare resources for the purpose of treating a medical condition is reimbursed in various proportions. The NHI claims database contains retrospective cohort data including basic information on the patients' sociodemographic characteristics and visits to medical institutions as well as precise information on their diagnoses, prescriptions or diagnostic procedures and the characteristics of the medical clinics they visited. All HIV-related medical fees, not only for ART but also for comorbidities relevant to HIV infection, are supported by the NHI in Korea. Therefore, information on medical clinic visits, including data on prescriptions and diagnostic procedures can be obtained for both outpatient clinics and hospital admissions for all HIV-infected individuals.

Compared with the claims data and the KCDC annual report since 2010, the number of PLHIV who visited hospitals gradually increased from 84.8% in 2010 to 90.9% in 2015. Regarding incident PLHIV, almost all of those diagnosed between 2009 and 2014 visited the

hospital. These results indicate that the proportion of PLHIV receiving ART after their HIV diagnosis has increased, close to the goal of the 90-90-90 target.

We defined AIDS patients among PLHIV using prophylactic antibiotic prescriptions and diagnosis of AIDS-defining diseases. The proportion of AIDS patients among PLHIV was 35.2% (1,185/3,367) in 2007, which gradually decreased to 4.8% (459/9,544) in 2015. We estimate that the generalization of early treatment contributed to a reduction in the proportion of AIDS patients. The number of AIDS patients was not identified by the KCDC report.

5-2. Adherence to antiretroviral therapy and factors affecting low medication adherence among incident HIV-infected individuals during 2009–2016: A nationwide study

The second study demonstrates the levels of adherence to ART in HIV-infected individuals in Korea. According to the MPR, 70.4% of PLHIV showed an adherence of ≥95%. Although this does not meet the UNAIDS target of 90%, it seems acceptable when compared to previous studies in other developed and developing countries. The results showed that women, age under 20 and same or over 50 compared to 30–39, and having a history of malignancy, lower socioeconomic status, not visiting a tertiary-level hospital, and being diagnosed in the earlier years were risk factorsfor becoming less adherent.

It is necessary to encourage ART adherence for PLHIV, but it is more necessary to identify these individuals and link them to care in order to manage the increase in the number of new PLHIV in Korea. We also showed that there were modifiable risk factors affecting

suboptimal adherence. Based on our results, health authorities should take into consideration how to establish a sustainable monitoring system at the national level using the NHI system for HIV care, and how to increase medication adherence for key populations affected by these risk factors.

Our findings suggest that the reason for the increase in the number of new PLHIV increases in Korea might be something other than the issue of medication adherence. One suggestion is that a major cause for this increase is late linkage to care. This is indicated in the increase in late diagnoses based on the CD4-positive T cell count at the time of diagnosis. (82) A lower CD4-positive T cell count represents a significant period after HIV infection and is suggestive of HIV transmission occurring during that period. By applying the extended back-calculation model to the number of new PLHIV and AIDS patients diagnosed each year in the claims data, we estimated that the time lag from HIV infection to diagnosis was 6.9 years on average in Korea. The extended back-calculation takes advantage of the fact that the CD4-positive T cell count decreases over time after HIV infection, so that the number of undiagnosed patients and the time to diagnosis can be estimated when the number of new PLHIV and the CD4-positive T cell count at the time of diagnosis are identified. This time lag is longer than what is observed in developed countries such as the Netherlands (2.6 years), France (37–53 months), and the United States (5.6 years). (83-85)

5-3. Association of HIV-syphilis coinfection with optimal antiretroviral adherence: A nation-wide claims study

The third study investigated the epidemiology of HIV-syphilis coinfection at a national level using the NHI system in Korea. This study revealed that nearly half of PLHIV had a syphilis coinfection; individuals in the optimal adherence group, who were expected to have achieved HIV viral suppression, reported more cases of syphilis infection. Men and having a history of other STDs were also found to be associated with an HIV-syphilis coinfection.

The guidelines recommend the use of condoms regardless of viral status, but consistent use of condoms is known to be difficult. If there is no risk of HIV transmission, it might be easier to choose condomless sex. The optimal adherence group had a higher percentage of HIV-syphilis coinfection, and syphilis treatment frequency was significantly higher. It is possible that the optimal adherence group is more likely to be exposed to condomless sex based on their history of more frequent treatments for syphilis as well as the higher syphilis coinfection proportion in this group.

These epidemiological data can be used to develop preventive measures for STDs in people living with HIV, such as raising awareness of coinfection, encouraging the use of condoms, and seeking STD testing.

5-4. Implication for HIV infection control policy and future research

The number of newly diagnosed PLHIV has declined globally since 1997, according to UNAIDS. (8) However, this number has been increasing steadily in the Republic of Korea. (9) In this study, we showed that about 70% of PLHIV who visited hospitals had high medication adherence, with an MPR of more than 95%. Nevertheless, the continual increase in the number of new PLHIV in Korea suggests that there are a large number who are

infected but not diagnosed, or who do not visit hospitals. In particular, PL HIV who are not diagnosed or who do not visit the hospital have a high titer of HIV, so it is likely that they can transmit the infection. Therefore, finding these patients and linking them to care is an important issue in Korea. The claims database could be an important source for the investigation of HIV epidemiology. National–level claims data could be used to monitor hospital visits and patient retention among PLHIV. Furthermore, it is possible to identify PLHIV who do not visit hospitals on a regular basis, using the claims data. With this information, the government can plan a program to manage and track PLHIV who are lost to follow–up. This algorithm can be achieved when the NHIS and the KCDC establish a linked system to share roles and functions (Fig. 2–4). It is very important to identify medical adherence to ART for HIV infection management. The claims data have the advantage of being able to provide information on the same. Therefore, if PLHIV are properly linked using the algorithm, patients who did not visit the hospital after registry enrollment can still expect to receive appropriate treatment.

A surveillance system using claims data is advantageous in that valuable epidemiological information can be obtained using existing data with little to no additional manpower and cost. This epidemiological information includes changes in the region of the hospitals used by patients over time, treatment adherence to prescribed drugs, economic status using a type of health insurance, and cost of treatment. These data are possibly more accurate than those obtained from individual surveys.

Another way to assess medication adherence from claims data is to take advantage of the fact that patients with suboptimal medication adherence in the clinic are prescribed more drug resistance mutation tests. If this method reflects the results of our medication adherence study, it would provide a more convenient indicator than direct medication adherence.

Future research should be focused on the identification of the total HIV infection burden in Korea, including undiagnosed PLHIV, to clarify the HIV treatment cascade. It is suspected that undiagnosed PLHIV play an important role in HIV transmission — conducting investigations in this population would be meaningful for HIV infection control efforts.

Further research into non–AIDS–defining illnesses is also necessary. As the life expectancy of PLHIV has increased, chronic diseases such as cardiovascular disease or age-related diseases are emerging problems in PLHIV. The epidemiology of non–AIDS–defining illnesses could provide physicians with information on how to address long–term care in PLHIV.

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국문초록

연구의 배경과 목적

인간면역결핍바이러스 (Human Immunodeficiency virus, HIV) 감염은 성매개감염의 일종이고 만성 감염이다. 1985년 첫 환자가 보고된 이후 한국에서 HIV 감염인 수는 지속적으로 증가하고 있다. HIV 감염 관리를 위해서는 진단과 치료, 유지의 각각의 단계가 원활하게 이루어지는 것이 필요하며, UNAIDS (The Joint United Nations Programme on HIV/AIDS) 에서는 90-90-90 target을 목표로 하여 감염자의 90%를 진단하고, 그 중 90%를 치료하며, 90%를 바이러스가 억제된 상태로 유지하자는 계획을 세웠다. 이후 여러 나라에서 목표를 성취했다는 보고가 발표되었지만 한국에서는 아직 HIV 감염에 대한 정확한 역학 통계가 알려져 있지 않다. 한국에서 HIV 감염은 질병관리본부에서 전수 조사를 하고 있지만, 감염 사실만을 조사하고 있어 이후의 약제 복용이나 순응도에 대한 분석을 할 수 없다. 한편 한국은 국가단일 건강보험 체계를 가지고 있고, HIV 치료는 건강 보험으로 대부분 급여 진료가 행해지므로 HIV 감염인의 병원 내원과 약제 처방을 국가 전수조사 할 수 있다. 이 연구는 건강보험 청구자료를 이용하여 HIV 감염인의 국내 역학을 파악하는 것을 목적으로 한다. 세부적으로는,

(1) 건강보험 청구자료를 분석하여 국내 HIV 감염인의 숫자와 역학적 특성을 기술한다.

(2) 약물 소지 비율 (medication possession ratio)을 이용하여 국내 HIV 감염인의 항레트로바이러스 약물 순응도를 평가하고, 낮은 약물 순응도와 관련이 있는 인자를 알아본다.

(3) 국내 HIV-매독 중복감염 현황을 건강 보험 청구자료를 분석하여 알아보고, 약물 순응도가 HIV-매독 중복감염에 미치는 영향을 평가한다.

연구 방법

(1) 건강보험 청구자료에서 수집된 2007년부터 2015년까지 HIV 진단을 받고 HIV 치료를 위해 반드시 필요한 검사를 한 사람을 연구 대상으로 정의하였다. 후천성면역결핍증후군 (Acquired Immune Deficiency Syndrome; AIDS)는 AIDS 관련 진단이 있거나 예방적 화학요법을 받는 경우로 정의하였다. 확인된 HIV 감염인의 수를 질병관리본부의 보고서와 비교하였다.

(2) 건강보험 청구자료에서 확인된 2007년부터 2016년까지 HIV 진단을 받고 항레트로바이러스 복합 처방이 있는 HIV 감염인을 확인하고, 2009년부터 2016년까지 신규 감염인을 연구 대상으로 하였다. 약물 소지비율을 평가하여 95%이상 높은 약물 순응도를 보이는 대상자의 분율을 확인하고, 낮은 약물 순응도와 연관되는 인자를 확인하였다.

(3) 건강보험 청구자료에서 확인된 2008년부터 2016년까지의 신규 감염인을 연구 대상으로 하였다. HIV 감염인 중 매독 진단과 치료 약제 처방이 있는 매독 중복감염 환자를 확인하였다. 대상자의 인구학적 특성과 95% 이상의 높은 약물 순응도를 보이는 환자의 비율을 중복 감염 여부를 기준으로 비교하였다.

결과

(1) 건강보험 청구자료와 질병관리본부 보고서는 HIV 감염인 수에서 10% 정도의 차이를 보였다. 그러나 나이와 성별 추이는 연간 누적 환자와 신규 환자에서 모두 비슷한 양상을 보였다. 특히 질병관리본부 보고서에서는 상당 수의 환자에서 CD4 세포 수를 확인할 수 없었던 반면에 건강보험 청구자료에서는 예방적 화학요법 처방을 이용하여 CD4 세포수가 200/mm^3 미만인 환자의 수를 확인하였다.

(2) 8,501 명의 신규 HIV 감염인 중에서 70.4%의 환자가 약물소지비율 95% 이상의 높은 약물 순응도를 보였다. 예방적 화학요법, 여성, 20-29세 또는 50세 이상의 나이, 악성 종양의 과거력, 낮은 사회경제적 상황, 3차 병원 이외의 종류의 병원 진료, 그리고 상대적으로 과거에 진단되는 경우가 낮은 약물 순응도와 관련이 있었다 (각각 Odds ratio 1.7, 1.6, 1.6, 1.4, 1.6, 2.1, 1.2, 1.6 to 3.8).

(3) 9,393 명의 신규 HIV 감염인 중 4,536 (48.3%)가 매독 중복감염으로 치료받았다. 높은 약물 순응도는 HIV-매독 중복감염과 통계적인 연관이 있었다 (odds ratio 1.18; 95% confidence interval 1.08-1.30; P=0.001). 이외에 남성, 세균/원충 성매개감염, 그리고 생식기 단순포진바이러스 감염 또한 HIV-매독 중복감염과 연관이 있었다.

결론

(1) 첫 번째 연구는 건강보험 청구자료를 HIV 감염인의 역학연구에 활용할 수 있다는 것을 기술하고 있다. 질병관리본부 보고서는 전체 국내 HIV 감염인의 수에 대한 통계를 제공하며, 건강보험 청구자료는 이들의 병원 진료 현황을 보여준다. 특히 본 연구를 통해 AIDS 환자에 대한 추가적인 정보를 알 수 있다. 건강보험 청구자료와 질병관리본부 보고서의 두 가지 자료를 종합하여 이용하면 진단

된 HIV 감염인을 치료로 연계하는 것에 도움을 받을 수 있다. 두 가지 자료를 종합하여 HIV 감염인 관리 체계를 구축할 수 있을 것이다.

(2) 두 번째 연구는 건강보험 청구자료를 분석하여 이상적인 약물 순응도를 보이는 국내 HIV 감염인의 분율을 기술하고 있다. 연구 결과에 따르면 우리나라에서 항레트로바이러스 약물을 복용하는 환자들의 높은 약물 순응도를 보이는 비율은 다른 선진국과 비교했을 때에 양호하다. 낮은 약물 순응도와 관련이 있는 여성과 10대 그룹에는 약물 순응도를 높이기 위한 관심이 필요하다.

(3) 세 번째 연구는 국내 HIV-매독 중복감염의 현황을 기술하고 있다. 높은 약물 순응도는 오히려 매독 중복감염과 관련이 있어 HIV 바이러스 억제가 되는 상태에서도 콘돔을 사용한 안전한 성관계에 대한 강조가 여전히 필요하다.