J Korean Med Sci. 2026 Apr 13;41(14):e115
https://doi.org/10.3346/jkms.2026.41.e115
eISSN 1598-6357·pISSN 1011-8934

JKMS

Original Article
Medicine General & Health Policy

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Clinical Characteristics and Risk Factors for Syphilis Among People Living With Human Immunodeficiency Virus: A Nationwide Population-Based Cohort Study in Korea

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Received: Jan 16, 2025
Accepted: Jul 17, 2025
Published online: Mar 12, 2026

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ABSTRACT

Background: The incidence of syphilis, a re-emerging infection linked to human immunodeficiency virus (HIV) through shared transmission routes, is increasing among people living with human immunodeficiency virus (PLH) in Korea. This study evaluate the prevalence, temporal trends, and risk factors for syphilis among PLH in the Republic of Korea.
Methods: Data from the National Health Insurance Service of Korea between 2002 and 2021 were analyzed to determine the incidence of syphilis in PLH. Syphilis was defined by the assigned Korean Standard Classification of Diseases code, with prescription codes for benzathine penicillin G, ceftriaxone, and doxycycline. Syphilis was classified as early or late based on the antibiotic dose. Multivariable logistic regression analysis was performed to assess risk factors for syphilis among PLH.
Results: The prevalence of syphilis in PLH was 25.53% (4,193/16,422 patients). Early syphilis accounted for 85.19% (3,572/4,193) of cases, and 34.80% of PLH with syphilis experienced multiple episodes. Additionally, 23.73% of PLH with syphilis received treatment for syphilis before HIV diagnosis. In the multivariable analysis, male sex (adjusted odds ratio [aOR], 10.78; 95% confidence interval [CI], 7.87–14.78), living in the Seoul metropolitan area (comprising Seoul, Incheon, and Gyeonggi-do) (aOR, 1.24; 95% CI, 1.15–1.34), the presence of acquired immunodeficiency syndrome-related cancer (aOR, 1.36; 95% CI, 1.24–1.48), longer duration of HIV diagnosis (pre-2009 vs. 2019–2021: aOR, 1.94; 95% CI, 1.71–2.20), and the lowest economic status (aOR, 1.35; 95% CI, 1.18–1.54) were associated with higher risks of syphilis. New PLH cases and early syphilis among PLH revealed correlated trends over the study period (Spearman's $\rho = 0.71$, $P < 0.01$).

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Funding

This work was supported by the research grant (#2022-E1901-02, #2022-ER1907-02) of the Korea Disease Control and Prevention Agency (KDCA) and the Soonchunhyang University Research Fund.

Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Kim S, Baek Y, Choi Y, Choi JY, Lee E. Data curation: Jeong O, Jung J, Kim TH. Formal analysis: Kim S, Baek Y, Lee E. Methodology: Kim S, Baek Y, Lee E. Visualization: Kim S, Baek Y, Lee E. Writing - original draft: Kim S, Baek Y, Lee E. Writing - review & editing: Kim S, Baek Y, Choi Y, Jeong O, Jung J, Choi JY, Lee E, Kim TH.

Conclusion: Syphilis is highly prevalent among PLH, particularly low-income males in the Seoul metropolitan area with longer HIV disease duration. Enhanced surveillance and targeted interventions are urgently needed to control syphilis transmission among high-risk PLH.

Keywords: Syphilis; HIV Infections; Coinfection; Risk Factors; Republic of Korea

INTRODUCTION

Syphilis is a preventable and curable sexually and vertically transmitted infection caused by *Treponema pallidum*. The World Health Organization (WHO) estimated that 8 million adults aged between 15 and 49 years would develop syphilis by 2022. High-income countries have experienced a resurgence of syphilis among men who have sex with men (MSM), which is associated with human immunodeficiency virus (HIV) infection and high-risk sexual behaviors.[1] An epidemiological association between syphilis and HIV infection has been observed owing to their shared transmission routes.[2] They interact synergistically, thereby increasing the risk of acquisition and transmission, as well as accelerating disease progression. Individuals infected with syphilis are more susceptible to HIV infection, partly because the genital sores and inflammation caused by syphilis can serve as a portal for HIV infection. Moreover, HIV-infected individuals are more susceptible to contracting syphilis and other sexually transmitted infections (STIs) owing to their compromised immune systems.[3]

Both types of infections have long been a public health concern owing to their high infectiousness and chronic manifestations. Although the number of HIV cases began to decrease globally during the 2000s, the number of syphilis cases began to increase in high-income countries, including European countries and the United States.[4,5] The WHO Global Health Sector Strategy aims to reduce the global incidence of syphilis by 90% between 2018 and 2030.[6] Syphilis among people living with HIV (PLH) is particularly critical, as coinfection can synergistically impact health outcomes.[7] Atypical features of syphilis have been reported in HIV-infected individuals, and HIV infection accelerates the course of neurosyphilis.[8]

An increasing trend of syphilis has been observed in HIV-infected individuals in the Republic of Korea.[9] However, limited research has been conducted regarding the epidemiology and risk factors of syphilis among PLH. Therefore, this study aimed to evaluate the prevalence, temporal trends, and risk factors of syphilis among PLH in Korea.

METHODS

Data source and operational definitions

In Korea, the National Health Insurance mandates the enrollment of all healthcare providers and citizens. By the end of 2020, health insurance benefits had been extended to 52,870,000 individuals in Korea. The National Health Insurance Service (NHIS) covers 51,340,000 of these individuals, representing 97.1% coverage, while the remaining 1,530,000 are beneficiaries of medical aid.[10] The NHIS dataset includes demographic information, eligibility information, health check-up data, hospital utilization history, treatment materials, outpatient care history, and prescriptions. Diagnoses are coded according to the Korean Standard Classification of Diseases (KCD, which is based on the International Classification of Diseases).[11] In this study, we used NHIS claims data from January 1, 2002, to December 31, 2021.

https://doi.org/10.3346/jkms.2026.41.e115

The operational definition of PLH, based on diagnosis codes, describes individuals who received the "V103" diagnosis code two or more times. The V code is a special diagnostic code unique to Korea, used to reduce the medical expense burden of patients with rare and intractable diseases. The V103 code refers to patients with HIV and indicates patients with conditions classified under the billing codes B20–B24. In this study, 20,423 patients received V103 diagnostic codes at least once. According to the operational definition, 2,350 patients who did not receive V103 claims two or more times were excluded. The initial diagnosis date for HIV infection was determined by selecting the earlier date between V103 and B20–B24. During the washout period from 2002 to 2003, patients diagnosed with HIV (n = 1,073), those whose first HIV diagnosis occurred below the age of 15 years (n = 34), and those who did not meet the definition of syphilis (n = 544) were excluded from the study cohort. Therefore, the study population included 16,422 PLH (**Fig. 1**).

The criteria for syphilis in this study were established based on individuals diagnosed with syphilis using diagnosis codes (A50–A53) and had received treatment for the disease. They were categorized into early and late syphilis according to the main and sub-diagnosis in the diagnosis claim. Early syphilis was defined as treatment with either a single intramuscular injection of benzathine penicillin G, a 14-day prescription of doxycycline, or daily injections of ceftriaxone 1g for 10- to 14-days. Late syphilis was defined as cases in which individuals received either two or more doses of benzathine penicillin G or a 28-day prescription of doxycycline following diagnosis. Multiple episodes of syphilis were defined as cases in which a new course of syphilis treatment was initiated at least one year after completion of the previous treatment.

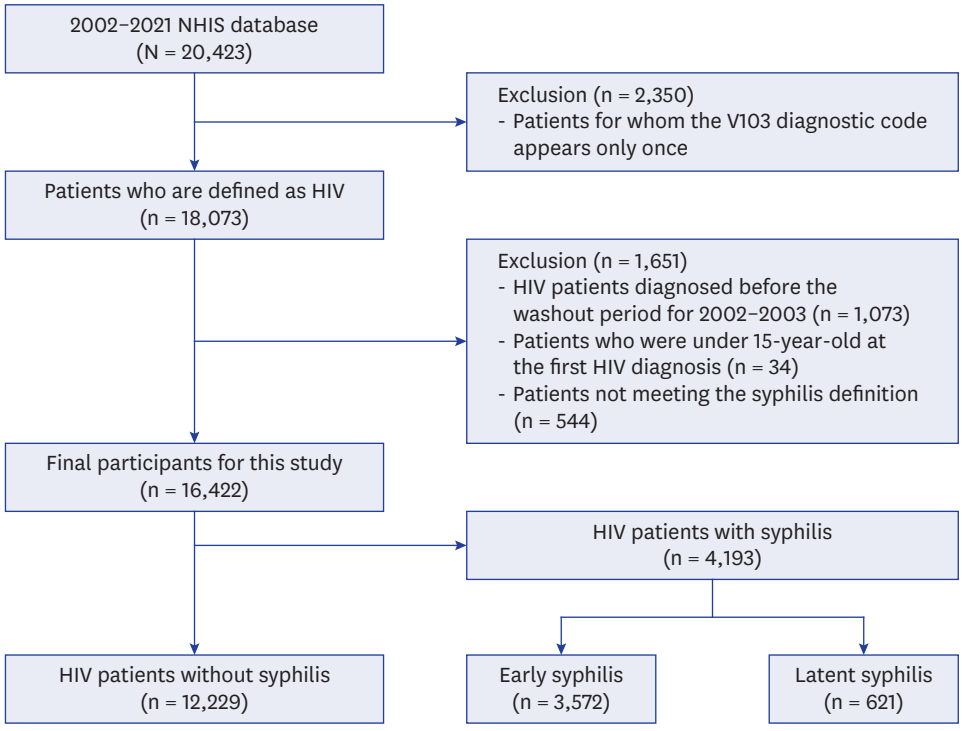

Fig. 1. Flowchart of the study cohort.
NHIS = National Health Insurance Service, HIV = human immunodeficiency virus.

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Variables

The dependent variable in this study was the incidence of syphilis in HIV-infected individuals. Syphilis was defined as PLH with a diagnosis code for syphilis, and who had received treatment (benzathine penicillin G, ceftriaxone, or doxycycline). The PLH cohort defined in this study was dichotomized dichotomized into those who were and were never diagnosed with syphilis. For explanatory variables, we included factors such as sex, economic status, duration of HIV infection, age at first HIV diagnosis, residential area, presence of opportunistic infections or acquired immunodeficiency syndrome (AIDS)-related cancer, and adherence to antiretroviral therapy (ART). These variables were selected based on prior knowledge and availability in the NHIS database. Age at first HIV diagnosis was categorized into 10-year intervals (< 30, 30–39, 40–49, 50–59, and ≥ 60 years). Sex was categorized as male and female, and income level was classified into five groups: medical aid, and quartiles (Q1, Q2, Q3, and Q4). Residential areas were coded as living in the Seoul metropolitan area (comprising Seoul, Incheon, and Gyeonggi-do) or non-Seoul metropolitan areas. Opportunistic infections and AIDS-related cancers were categorized using KCD codes. Opportunistic infections included invasive candidiasis, cryptococcosis, cytomegalovirus disease, progressive multifocal leukoencephalopathy, *Mycobacterium tuberculosis*, Pneumocystis pneumonia, and brain toxoplasmosis. AIDS-related cancers included Kaposi's sarcoma, Burkitt's lymphoma, other lymphomas, and cervical cancer. The disease codes for opportunistic infections and AIDS-related cancers are listed in **Supplementary Table 1**. The presence of opportunistic infections and AIDS-related cancers was determined if the relevant diagnosis codes were recorded at any time during the entire study period (2004–2021), regardless of their temporal relationship with HIV diagnosis. This approach was chosen to comprehensively evaluate the association between these conditions and HIV. ART was assessed using the pharmacy refill rate and was calculated as the number of days the ART prescription was filled divided by the total follow-up period until the earliest of December 31, 2021, or death. Adherence was classified into optimal (≥ 90%) and suboptimal (< 90%) adherence.

Statistical analysis

We conducted a frequency analysis to evaluate the population characteristics and compared the differences in categorical variables using the χ^2 test. Two-sided statistical significance was set at $P < 0.05$. Spearman's correlation analysis was used to assess the linear relationship between the number of new patients with HIV and the number of new syphilis patients. The method for calculating incidence rates differed by disease: for syphilis, person-years were used as the denominator based on each individual's observation period, whereas for HIV incidence rate, the number of cases per 100,000 population was calculated using the mid-year resident population from national registry data for each year. Univariate analysis was conducted to assess the association between syphilis in patients with HIV and explanatory variables, and a multivariable logistic regression model was used to identify the risk factors. All statistical analyses were performed using SAS statistical software (version 9.4; SAS Institute, Cary, NC, USA), and all figures were generated using RStudio (version 4.3.0; R Studio, PBC, Boston, MA, USA).

Ethics statement

This study was approved by the Institutional Review Board of the Severance Hospital of the Yonsei University Health System (Approval No. 4-2022-0676). The requirement for patient consent was waived because public data provided by the NHIS was used in the study.

https://doi.org/10.3346/jkms.2026.41.e115

RESULTS

The study population comprised 16,422 individuals, of whom 4,193 (25.53%) received treatment for either early syphilis or late latent syphilis during the study period. Among them, 3,572 (85.19%) and 621 (14.81%) were diagnosed with early and late syphilis, respectively (**Fig. 1**). In terms of antimicrobial type, benzathine penicillin G were administered to 4,028 patients (96.06%), eight patients (0.19%) received ceftriaxone, and the remaining 157 patients (3.74%) were treated with doxycycline, regardless of syphilis stage. Specifically, among patients with early syphilis, 3,471 received benzathine penicillin G, eight received ceftriaxone for 10–14 days, and 93 patients were treated with doxycycline for 14 days. Among patients with late syphilis, 557 individuals were treated with benzathine penicillin G in more than two doses, while 64 received doxycycline for 28 days (**Supplementary Table 2**). Additionally, among all patients with syphilis, 2,734 (65.20%) had a single episode, whereas 1,459 (34.80%) experienced multiple episodes.

Table 1 presents the demographic and clinical characteristics of the participants. Among those with HIV who had syphilis, most were male (98.93%), and the household income levels of individuals were predominantly in the medical aid and Q1 group (34.25%). The highest proportion of first HIV diagnoses among all study participants occurred between 2014 and 2018, accounting for 34.01%. Regarding residence, 2,861 individuals (68.23%) resided in the Seoul metropolitan area (Seoul, Incheon, and Gyeonggi-do). Age at HIV diagnosis was highest in the order of < 30, 30–39, 40–49, 50–59, and ≥ 60 years. *M. tuberculosis* was the most prevalent, accounting for 53.06% (572 cases) of opportunistic infections, followed by Pneumocystis pneumonia (28.11%, 303 cases). AIDS-related cancers included immunoblastic lymphoma (n = 24; 2.23%), Kaposi's sarcoma (n = 22; 2.04%), and primary central nervous system lymphoma (n = 19; 1.76%). Among the PLH with syphilis, 793 (19.20%) displayed suboptimal ART adherence. Male sex, lower income level, longer duration since HIV diagnosis, younger age at HIV diagnosis, and residence in the Seoul metropolitan area were significantly associated with syphilis among PLH compared to those without syphilis. Although not statistically significant, tuberculosis was more frequent among PLH without syphilis, whereas Pneumocystis pneumonia was more common among those with syphilis.

Table 1. Demographic and clinical characteristics of PLH stratified by syphilis status

Variables	PLH without syphilis		PLH with syphilis		*P* value
	Cases	%	Cases	%	
Sex					< 0.001
Male	10,825	88.52	4,148	98.93	
Female	1,404	11.48	45	1.07	
Income level[a]					< 0.001
Medical aid	1,414	11.72	588	14.19	
Q1	2,378	19.71	831	20.06	
Q2	2,989	24.78	1,062	25.63	
Q3	2,718	22.53	853	20.59	
Q4	2,565	21.26	809	19.53	
Year of HIV diagnosis					< 0.001
2004–2008	2,385	19.5	1,026	24.47	
2009–2013	3,252	26.59	1,156	27.57	
2014–2018	4,231	34.6	1,426	34.01	
2019–2021	2,361	19.31	585	13.95	
Patient residence					< 0.001
Seoul metropolitan area[b]	7,549	61.73	2,861	68.23	
Others	4,680	38.27	1,332	31.77	

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https://doi.org/10.3346/jkms.2026.41.e115

Table 1. (Continued) Demographic and clinical characteristics of PLH stratified by syphilis status

Variables	PLH without syphilis		PLH with syphilis		*P* value
	Cases	%	Cases	%	
Age group at first HIV diagnosis, yr					< 0.001
15–29	3,481	28.48	1,432	34.15	
30–39	3,154	25.81	1,169	27.88	
40–49	2,068	21.34	836	19.94	
50–59	1,820	14.89	514	12.26	
60+	1,158	9.48	242	5.77	
Opportunistic infections					
Invasive candidiasis					0.993
No	3,665	99.54	1,073	99.54	
Yes	17	0.46	5	0.46	
Cryptococcosis					0.765
No	3,661	99.43	1,071	99.35	
Yes	21	0.57	7	0.65	
Cytomegalovirus disease					0.303
No	3,403	92.42	986	91.47	
Yes	279	7.58	92	8.53	
PML					0.915
No	3,575	97.09	1,046	97.03	
Yes	107	2.91	32	2.97	
Mycobacterium tuberculosis					0.060
No	1,848	50.19	506	46.94	
Yes	1834	49.81	572	53.06	
Pneumocystis pneumonia					0.050
No	2,532	68.77	775	71.89	
Yes	1150	31.23	303	28.11	
Toxoplasmosis of the brain					< 0.001
No	3,653	99.21	1,078	100.00	
Yes	29	0.79	0	0	
Yes	0.95–1.61	0.113	1.17	0.277	
AIDS-related cancers					
Kaposi's sarcoma					0.163
No	3,629	98.56	1,056	97.96	
Yes	53	1.44	22	2.04	
Burkitt's lymphoma					0.576
No	3,648	99.08	1,070	99.26	
Yes	34	0.92	8	0.74	
Immunoblastic lymphoma					0.426
No	3,584	97.34	1,054	97.77	
Yes	98	2.66	24	2.23	
Primary CNS lymphoma					0.445
No	3,629	98.56	1,059	98.24	
Yes	53	1.44	19	1.76	
Cervical cancer					< 0.007
No	3,657	99.32	1,078	100.00	
Yes	25	0.68	0	0	
Adherence to ART[c]					0.398
High (> 90%)	9,329	81.4	3,337	80.80	
Low (< 90%)	2,132	18.6	793	19.20	

HIV = human immunodeficiency virus, PLH = people living with human immunodeficiency virus, PML = progressive multifocal leukoencephalopathy, AIDS = acquired immunodeficiency syndrome, CNS = central nervous system, ART = antiretroviral therapy.
[a]Income level: data were divided into quartiles based on income level.
[b]Seoul metropolitan area: Seoul, Incheon, and Gyeonggi-do.
[c]Adherence to ART was assessed by the pharmacy refill rate (0–100%).

Cerebral toxoplasmosis was significantly more prevalent in PLH without syphilis compared to those with syphilis.

https://doi.org/10.3346/jkms.2026.41.e115

The number of new HIV infections consistently increased from 2004 to 2014, with occasional fluctuations. This upward trend continued until just before the onset of the coronavirus disease 2019 (COVID-19) pandemic in 2020. However, following the emergence of COVID-19, a significant decrease (22.9%) was observed in 2020 compared with the previous year.
The number of new early syphilis cases remained relatively stable until 2012, began to rise in 2013, and peaked in 2016, followed by a subsequent decline. Among PLHIV, the number of new HIV cases and early syphilis cases exhibited similar temporal trends (Spearman's ρ = 0.71, P = 0.001) (**Fig. 2A**). The incidence rate of early syphilis consistently increased after 2010, peaking at 2,390.75 per 100,000 person-years in 2016. Although a subsequent decline was observed, the trend reversed again around 2020 (**Fig. 2B**).

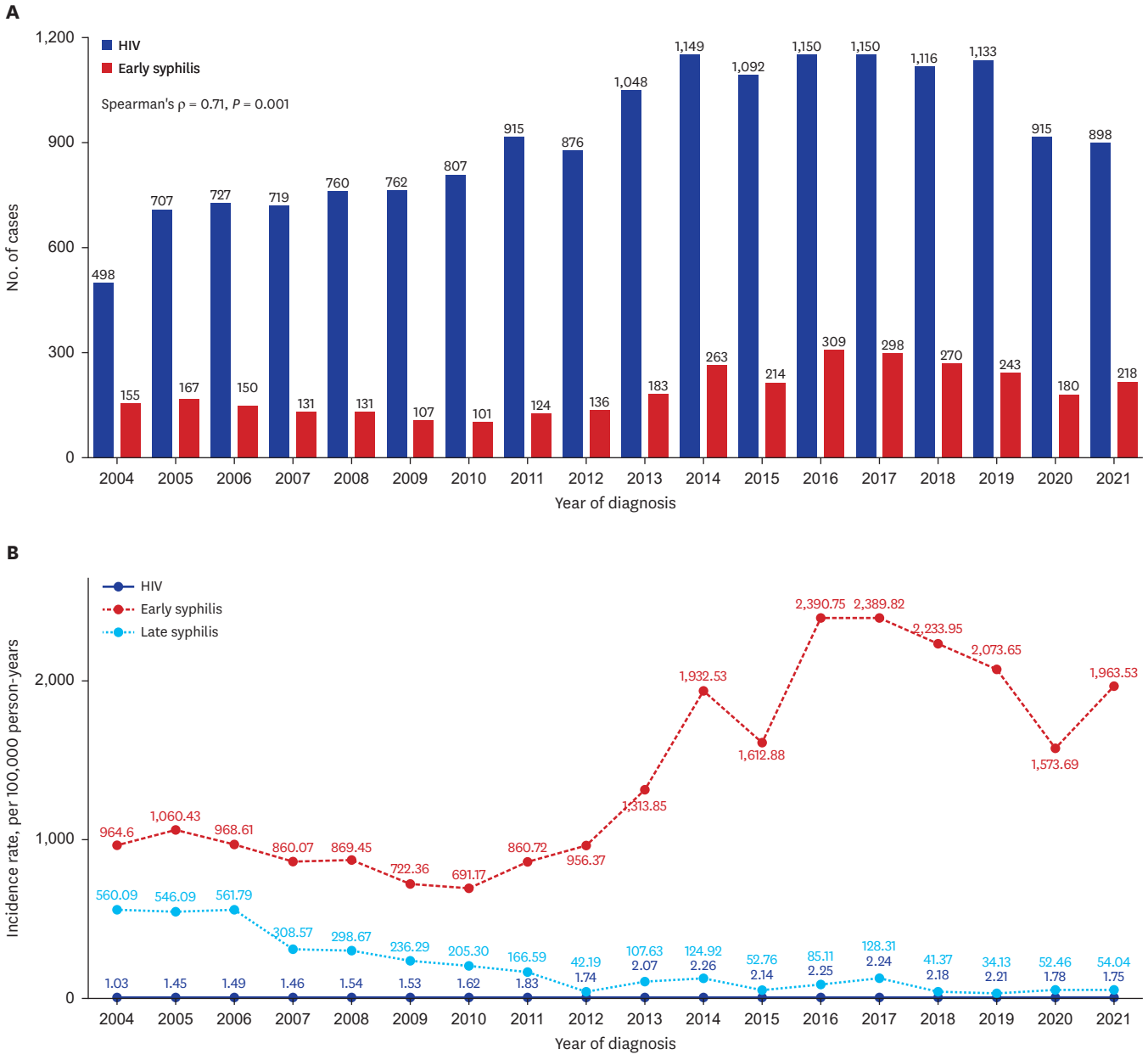

Fig. 2. Temporal trends of new HIV infections and syphilis incidence among PLH (**A**). Number of new HIV infections and early syphilis cases among PLH, showing similar increasing trends before the coronavirus disease 2019 era (Spearman's ρ = 0.71, P = 0.001). (**B**) Incidence rates of HIV and syphilis for HIV and syphilis.
HIV = human immunodeficiency virus, PLH = people living with human immunodeficiency virus.

https://doi.org/10.3346/jkms.2026.41.e115

Examination of the timing of HIV diagnosis and initial syphilis diagnosis revealed that 76.27% of syphilis cases were diagnosed after HIV diagnosis. Notably, cases diagnosed within 1 year after the date of HIV diagnosis constituted the highest proportion, including 1,145 cases (27.31%). Among individuals with early syphilis, 2,873 cases (80.43% of 3,572) were diagnosed with syphilis after the diagnosis of HIV. In contrast, among those with late syphilis, the timing of diagnosis was more evenly distributed, with 52.33% diagnosed after HIV diagnosis (**Fig. 3**).

The age distribution for initial syphilis diagnoses showed that before 2010, the highest incidence proportions were primarily observed among individuals aged 30–39 or 40–49 years. However, from 2010 onwards, there was an evident increase in the number of initial syphilis cases occurring among younger demographics, particularly those aged 15–29 years (**Supplementary Fig. 1**).

Table 2 summarizes the results of bivariate and multivariable logistic regression analyses for factors associated with syphilis among PLH. In the multivariable analysis, statistically significant factors associated with increased odds of syphilis were male sex (adjusted odds ratio [aOR], 10.78; 95% confidence interval [CI], 7.87–14.78), the lowest economic status (aOR, 1.35; 95% CI, 1.18–1.54), longer duration since HIV diagnosis (pre-2009 vs. 2019–2021: aOR, 1.94; 95% CI, 1.71–2.20), residence in the Seoul metropolitan area (aOR, 1.24; 95% CI, 1.15–1.34), younger age at HIV diagnosis (aged 15–29: aOR, 1.37; 95% CI, 1.16–1.61; aged 30–39: aOR, 1.27; 95% CI, 1.08–1.50), and history of AIDS-related cancer (aOR, 1.36; 95% CI, 1.24–1.48). Conversely, history of opportunistic infections (P = 0.277) and suboptimal ART adherence (P = 0.922) were not significantly associated with syphilis incidence. Notably, the effect of the residence reversed direction after adjusting for confounders, highlighting the influence of correlated variables such as age and economic status on the unadjusted estimates.

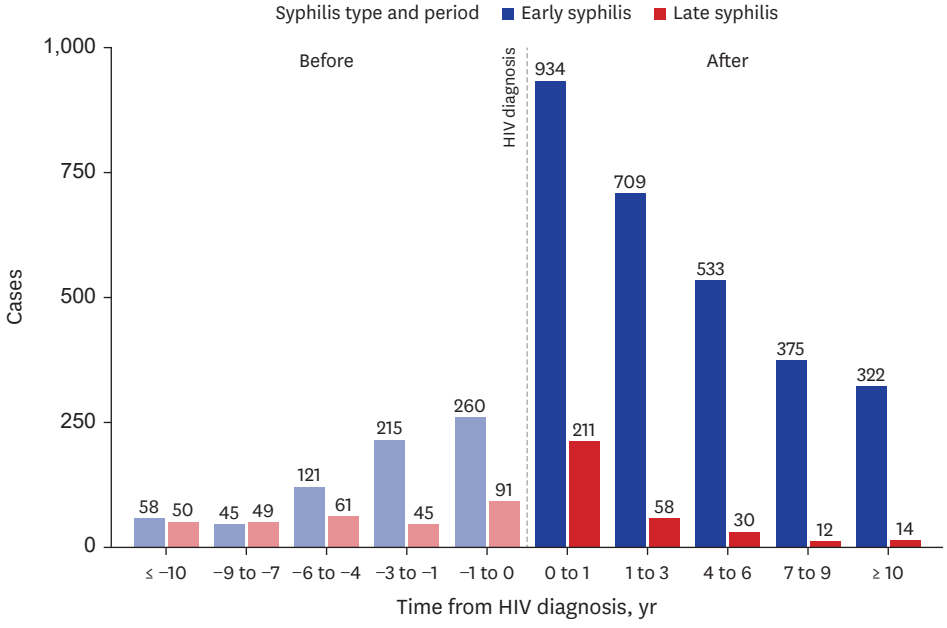

Fig. 3. Distribution of syphilis diagnosis timing relative to HIV diagnosis. Cases diagnosed within 1 year following initial HIV diagnosis include instances where syphilis and HIV diagnosis dates coincided.
HIV = human immunodeficiency virus.

https://doi.org/10.3346/jkms.2026.41.e115

Table 2. Unadjusted and aORs for syphilis in people living with HIV

Variables	cOR	95% CI	*P* value	aOR	95% CI	*P* value
Gender						
Male	11.96	8.87–16.12	< 0.001	10.78	7.87–14.78	< 0.001
Female (ref)						
Income level						
Medical aid	1.32	1.16–1.49	< 0.001	1.35	1.18–1.54	< 0.001
Poor Q1	1.11	0.99–1.24	0.914	1.13	1.00–1.27	0.630
Moderate Q2	1.13	1.01–1.25	0.537	1.10	0.98–1.23	0.825
Rich Q3	1.00	0.89–1.11	0.004	1.00	0.89–1.12	0.005
Richest Q4 (ref)	1.00			1.00		
Year of HIV diagnosis						
< 2009	1.74	1.55–1.95	< 0.001	1.94	1.71–2.20	< 0.001
2009–2013	1.43	1.28–1.61	0.069	1.57	1.40–1.77	0.004
2014–2018	1.36	1.22–1.52	0.930	1.39	1.24–1.55	0.258
2019–2021 (ref)	1.00			1.00		
Region						
Seoul metropolitan area	0.75	0.70–0.81	< 0.001	1.24	1.15–1.34	< 0.001
Non-Seoul metropolitan area (ref)	1.00			1.00		
Age group at first HIV diagnosis, yr						
15–29	1.97	1.69–2.29	< 0.001	1.37	1.16–1.61	< 0.001
30–39	1.77	1.52–2.07	< 0.001	1.27	1.08–1.50	0.007
40–49	1.53	1.31–1.80	0.393	1.08	0.91–1.28	0.114
50–59	1.35	1.14–1.60	0.032	1.08	0.90–1.30	0.171
60+ (ref)	1.00			1.00		
Opportunistic infection						
None (ref)	1.00			1.00		
Yes	1.24	0.95–1.61	0.113	1.17	0.88–1.54	0.277
AIDS-related cancer						
None (ref)	1.00			1.00		
Yes	1.23	1.14–1.34	< 0.001	1.36	1.24–1.48	< 0.001
ART adherence						
High (ref)	1.00			1.00		
Low	1.04	0.95–1.14	0.395	1.01	0.91–1.10	0.922

aOR = adjusted odds ratio, HIV = human immunodeficiency virus, cOR = crude odds ratio, CI = confidence interval, AIDS = acquired immunodeficiency syndrome, ART = antiretroviral therapy.

DISCUSSION

In this study, the prevalence of syphilis in PLH was 25.53%. The prevalence varies across different regions and countries. The estimated prevalence of syphilis among PLHIV was 19.9% (95% CI, 15.4–24.8%) in China,[12] 20.5% in Brazil,[13] 8% in Turkey,[14] and 3.1% in Africa.[15] Compared with these countries, our study showed a higher prevalence; however, marginalized participants belonging to the Black sexual and gender minorities in Georgia showed a high lifetime prevalence of syphilis (55.7%).[16] Therefore, the prevalence could vary according to regional and population-specific characteristics. As syphilis is the most common STI among PLH in many countries,[17] substantial efforts are needed to control HIV-syphilis coinfection.

Among PLH with syphilis, 23.73% had been diagnosed with syphilis before HIV diagnosis. This finding aligns with evidence that syphilis shares common risk factors with HIV and facilitates both HIV acquisition and sexual transmission.[18] Given the frequent co-occurrence of syphilis and HIV, individuals diagnosed with syphilis should undergo HIV testing. A new syphilis diagnosis warrants both initial and repeat HIV testing. If the results are negative, patients should be counseled regarding pre-exposure prophylaxis (PrEP) to prevent HIV infection,[19,20] thereby contributing to the reduction of HIV transmission.

https://doi.org/10.3346/jkms.2026.41.e115

Within 1 year after HIV diagnosis, 27.30% of PLH (1,145 cases) were diagnosed with syphilis. Among these, 934 individuals (81.57%) had early syphilis, while 211 individuals (18.43%) had late syphilis. These findings underscore the importance of retention in HIV care, including initial syphilis screening and ongoing routine STI monitoring, for early diagnosis and treatment of syphilis and other STIs.

Among PLH with syphilis, 34.80% experienced multiple episodes. In another study performed in the USA, 34% of PLH had a repeat syphilis diagnosis within 3 years, and males living with HIV had a higher risk of multiple episodes.[21] A study of PLHIV in Italy reported a high rate of subsequent syphilis episodes and a slow serological response after treatment.[22] Because HIV and syphilis coinfection impair immune recovery and antiretroviral effects,[23] periodic screening with the correct interpretation of test results and appropriate treatment are required.

In this analysis, male sex, low economic status, residence in the Seoul metropolitan area (Seoul, Incheon, and Gyeonggi-do), and younger age at HIV diagnosis were identified as risk factors for syphilis among PLH. A longer duration since HIV diagnosis and the presence of AIDS-related cancer were also associated with syphilis. However, the association with longer HIV duration since HIV diagnosis should be interpreted with caution, as age was not adjusted for in the multivariable analysis. Since older MSM and PLH had higher syphilis seropositivity,[24,25] longer HIV duration since HIV diagnosis may reflect a longer period of exposure to syphilis rather than a causal relationship. Another study in Korea suggested that a younger age at enrollment, treponemal test positivity at baseline, MSM, and a history of incarceration were risk factors for syphilis.[26] Considering these factors, enhanced syphilis surveillance and targeted interventions are needed to limit its transmission among PLH.

The temporal trend of early syphilis among PLH and new HIV cases were correlated in this analysis (Spearman's $\rho = 0.71$, $P = 0.001$). This suggests that both STIs exhibit similar epidemiological dynamics due to their shared transmission routes and risk factors. Notably, the number of early syphilis cases decreased between 2016 and 2020. Since 2016, efforts to enhance HIV detection through voluntary counseling and testing (VCT) and to initiate rapid HIV treatment have been ongoing. These initiatives may have contributed to better control of syphilis among PLH.

This study has several limitations inherent to claims data analysis. First, we could not identify neurosyphilis cases as the recommended treatment—aqueous penicillin G—is not covered by insurance. Second, syphilis codes used in this study did not distinguish between subtypes of syphilis. However, to improve classification accuracy, patients with a syphilis diagnosis code but without corresponding treatment prescriptions were not considered as syphilis cases. Additionally, defining syphilis based on both diagnostic codes and treatment prescriptions minimized potential overestimation due to the use of antibiotics like ceftriaxone or doxycycline, which are also prescribed for other STIs (e.g., gonorrhea, chlamydia). Future studies should incorporate cross-sectional analyses of coinfections with other STIs using billing codes, as well as a more detailed evaluation of prescription patterns by treatment type. Third, PLH who were uninsured or received care outside the national health insurance system were excluded. Although HIV and syphilis are highly stigmatized, resulting in delayed treatment, 97% of Koreans are covered by the National Health Insurance system, and the relatively simple syphilis treatment regimen mitigates this limitation to some extent. Finally, this study, designed as a cross-sectional analysis, precluded assessment of temporal causal

https://doi.org/10.3346/jkms.2026.41.e115

relationships between HIV and syphilis infections. This limitation is inherent to claims data and observational study designs that focus on associations rather than causality; further longitudinal research is warranted. Additionally, our nationwide population-based approach minimizes selection bias and enhances the generalizability of findings to the entire Korean HIV population.

In conclusion, syphilis is highly prevalent among PLHIV, particularly low-income males in the Seoul metropolitan area with longer HIV disease duration. Enhanced syphilis surveillance and targeted interventions are therefore needed to prevent transmission among high-risk PLHIV.

ACKNOWLEDGMENTS

We express our sincere gratitude to Professor Boyoung Park of Hanyang University for her exceptional guidance and oversight throughout this project. We also thank the Korea HIV/AIDS Cohort Study team for their valuable feedback and contributions to the research topic and study design.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
AIDS-defining illness

Supplementary Table 2
Antimicrobial types used for syphilis treatment

Supplementary Fig. 1
Age distribution at the first syphilis diagnosis.

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