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Assessment of Disease Burden and Immunization Rates for Vaccine-Preventable Diseases in People Living with HIV: The Korea HIV/AIDS Cohort Study

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ABSTRACT

Background: Prophylactic immunization is important for human immunodeficiency virus (HIV)-infected patients; however, there are insufficient data on the burden of vaccine-preventable diseases (VPDs), vaccination rates, and factors influencing vaccination.

Materials and Methods: The incidence and prevalence of VPDs in HIV-infected patients between 2006 and 2017 were estimated using the Korean HIV/acquired immune deficiency syndrome (AIDS) cohort database. In addition, we evaluated the vaccination rates and influencing factors for vaccination in HIV-infected patients through multilevel analysis of clinico-epidemiological factors, immune status, and psychological status. A questionnaire survey was conducted among experts to determine whether they recommend vaccination for HIV-infected patients.

Results: The incidence rates of hepatitis B virus (HBV) infection, herpes zoster, and anogenital warts were 1.74, 7.38, and 10.85 per 1,000 person-years, respectively. The prevalence of HBV infection and anogenital warts at enrollment was 4.8% and 8.6%, respectively, which increased to 5.3% and 12.0%, respectively, by 2017. In HIV-infected patients, HBV (21.7% in 2008, 56.3% in 2013, and 75.4% in 2017) and pneumococcal vaccination rates (3.0% in 2015, 7.6% in 2016, and 9.6% in 2017) increased annually, whereas the influenza vaccination rate remained similar by season (32.7 - 35.6%). In the multilevel analysis, peak HIV viral load (≥50 copies/mL: odds ratio [OR] = 0.64, 95% confidence interval [CI]: 0.44 - 0.93; reference, <50 copies/mL) was an influencing factor for pneumococcal vaccination, while

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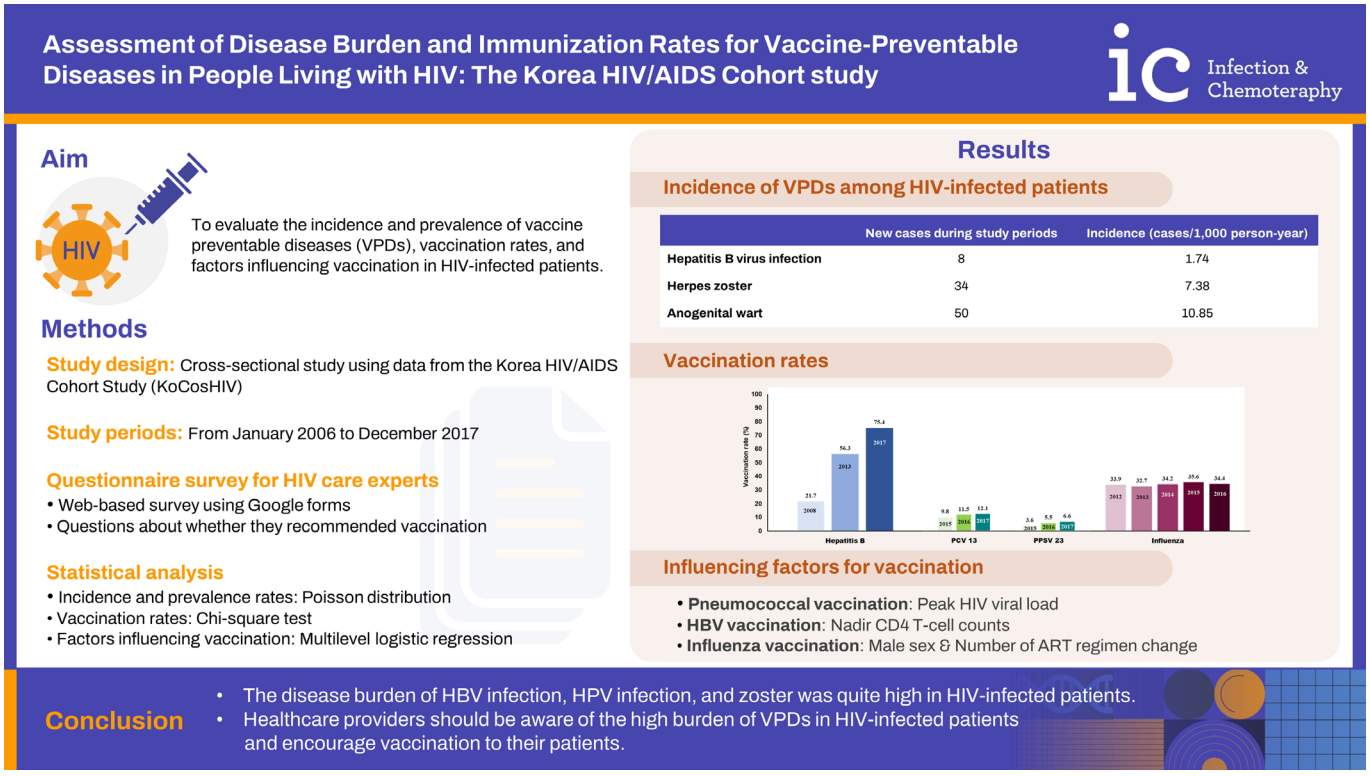
nadir CD4 T-cell counts (200 - 350 cells/mm^3: OR = 0.54, 95% CI: 0.38 - 0.76; <200 cells/mm^3: OR = 0.89, 95% CI: 0.62 - 1.28; reference, ≥350 cells/mm^3) was an influencing factor for HBV vaccination. Influenza vaccination was associated with male sex (OR = 1.94) and the number of antiretroviral therapy (ART) regimen change (OR = 1.16), but was not significantly associated with HIV viral load or CD4 T-cell counts. Most experts responded that they administer hepatitis A virus, HBV, pneumococcal, and influenza vaccines routinely, but not human papillomavirus (12.9%) or herpes zoster vaccines (27.1%).

Conclusion: The burden of vaccine-preventable diseases was quite high in HIV-infected patients. Nadir CD4 T-cell counts, peak HIV viral loads, and the number of ART regimen change are significant factors related to vaccination. Considering the low vaccination rates for VPDs, there was a discordance between experts' opinions and real clinical practice in the medical field.

Keywords: HIV; Disease burden; Vaccination; Risk factor; Vaccine-preventable diseases

GRAPHICAL ABSTRACT



INTRODUCTION

Prophylactic immunization is crucial to prevent vaccine-preventable diseases (VPDs) in human immunodeficiency virus (HIV)-infected patients. VPDs are not only more prevalent among HIV-infected patients, but also lead to poorer clinical outcomes than in healthy individuals [1]. Vaccination against influenza, pneumococcus, hepatitis A virus (HAV), hepatitis B virus (HBV), and human papilloma virus (HPV) is recommended for individuals living with HIV [2]. Several studies have highlighted the importance of prophylactic immunization in HIV-infected patients [3-6]. However, despite the importance of immunization, there are no available data on vaccination rates and the factors influencing vaccine acceptance in Korea.

Various factors, such as inadequate awareness about the importance of immunization among patients and healthcare providers and the immune status of HIV-infected patients, may hinder vaccine acceptance [7]. Therefore, it is necessary to understand the disease burden of VPDs, vaccination rates, and factors influencing

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vaccination in HIV-infected patients to improve their health outcomes.

This study aimed to evaluate the incidence and prevalence of VPDs, vaccination rates, and factors influencing vaccination in HIV-infected patients.

MATERIALS AND METHODS

1. Study design and data collection

This cross-sectional study used data from the Korea HIV/acquired immune deficiency syndrome (AIDS) Cohort Study (KoCosHIV), which includes 16 mid and large-scale general hospitals across six cities [8]. The incidence and prevalence of VPDs (HAV, HBV, pneumococcus, influenza, HPV, and herpes zoster) were estimated in HIV-infected patients registered in the KoCosHIV database between 2006 and 2017. The incidence rate was calculated as the number of new cases of VPDs per 1,000 person-years. Hepatitis vaccination rates and seroprevalence were estimated as the positive serological test results for IgG anti-HAV and anti-HBs antibodies at baseline and follow-up visits.

The demographic and clinical data of the patients were collected at baseline and every 6 months thereafter. Laboratory results, including CD4 T-cell counts, HIV viral loads, and serological tests for VPDs, were also collected simultaneously. In addition, information on vaccination status and reasons for non-vaccination were obtained through patient interviews.

2. Ethics statement

The KoCosHIV study was approved by the institutional review board of each participating center and was conducted in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent before enrollment in the study. This study was approved by the Institutional Review Board (IRB) of Korea University Guro Hospital (IRB approval no.: 2006GR0065), and written informed consent was obtained from all participants.

3. Evaluation of vaccination rates and influencing factors

The vaccination rates of the major vaccines recommended for HIV-infected patients, including HAV, HBV, pneumococcal, and influenza vaccines, were evaluated. For HBV, pneumococcal, and influenza vaccines, we analyzed the factors influencing vaccination in HIV-infected patients through a multilevel analysis of clinico-epidemiological factors, immune status, and psychological status.

4. Questionnaire survey for HIV care experts

From September 2020 to October 2020, a web-based survey using Google Forms was conducted among infectious disease (ID) specialists in HIV care to assess their opinions on vaccination of HIV-infected patients. A list of 267 ID specialists and their email addresses was obtained from the Korean Society of Infectious Diseases, and the survey forms were emailed to them, of which 70 (26.2%) participated in the survey. The survey included questions about whether they recommended vaccinations for HAV, HBV, pneumococcus, influenza, HPV, and herpes zoster.

5. Statistical analysis

Incidence and prevalence rates were calculated using a Poisson distribution. The vaccination rates were compared between different years using the Chi-square test. Seroconversion and seroreversion rates were compared between different groups using the chi-square test or Fisher's exact test. Multilevel logistic regression analysis was conducted to evaluate the factors influencing vaccination. Statistical significance was set at P <0.05. All statistical analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA).

Incidence and prevalence rates were identified by follow-ups since enrollment of the cohort study. The descriptive statistics and chi-square test compared the vaccination rates and all-related factors between years performed. Multiple multilevel logistic regression was performed to simultaneously consider individual-level factors (gender, age, etc.) with different response values across individuals and institution-level factors (number of beds) with different response values across survey sites (hospitals). The model fit was calculated using the Intra-class Correlation Coefficient (ICC), and the formula is shown below (τ: variance, π: 3.14).

$$\mathrm{ICC} = \tau/(\tau + \tau^2/3)$$

The ICC has a value between 0 and 1, with values closer to 1 indicating a strong influence on vaccination rates at the institutional level. Given that the ICCs are 33.0%, 26.0%, and 32.0% for the null model, which is the uncorrected model, respectively, this model confirms the appropriateness of conducting a multilevel analysis. The P value of the Between community variance (BCV) for ICC is less than 0.05, confirming that the differences in vaccination rates between institutions are significant.

Statistical significance was set at P <0.05. significant. All statistical analyses were performed using the SAS software (version 9.4; SAS Institute Inc., USA).

RESULTS

From 2006 to 2017, a comprehensive analysis was carried out on a cohort of 1,485 individuals who were enrolled in the KoCosHIV database. Among them, 1,388 individuals (93.5%) were male, while 97 individuals (6.5%) were female. The average age at enrollment was determined to be 41.3 years with a standard deviation of 12.6 years.

1. Disease burden of VPDs in HIV-infected patients

Tables 1 and **2** provide overviews of the burden of vaccine-preventable diseases, specifically HBV, herpes zoster, and anogenital warts. The incidence rates of HBV, herpes zoster, and anogenital warts were 1.74, 7.38, and 10.85 per 1,000 person-year, respectively. The prevalence of HBV at cohort entry was 4.8% and the cumulative prevalence in 2017 was 5.3%. The prevalence of anogenital warts at cohort entry was 8.6% and the cumulative prevalence in 2017 was 12.0%.

2. Vaccination rates and influencing factors to get vaccinated

Vaccination rates for VPDs in HIV-infected patients are presented in **Figure 1** and **Supplementary Tables 1-3**. Influenza vaccination rates remained consistent each year, ranging from 32.7% to 35.6%. In comparison, vaccination rates for HBV and pneumococcal vaccines showed a gradual increase over the study years: HBV vaccination rates (21.7% in 2008, 56.3% in 2013, and 75.4% in 2017) and pneumococcal vaccination rates (3.0% in 2015, 7.6% in 2016, and 9.6% in 2017).

3. Factors related to seroconversion and seroreversion

Supplementary Tables 4 and **5** present the year-specific seroprevalence and seroconversion/seroreversion rates of the anti-HB antibodies. In addition, we evaluated factors associated with seroconversion and seroreversion. Seroconversion from anti-HBs-negative to anti-HBs-positive was related to younger age (18 - 49 years), undetectable HIV viral load (<50 copies/mL), and low CD4 T-cell counts (<200 cells/mm^3) at enrollment. Conversely, seroreversion was associated with a detectable viral load (≥50 copies/mL) at enrollment, although this difference was not statistically significant.

Table 1. Incidence of hepatitis B virus infection, herpes zoster, and anogenital wart in HIV-infected patients

Diseases	New cases during study periods	Incidence (cases/1,000 person-year)
Hepatitis B virus infection	8	1.74
Herpes zoster	34	7.38
Anogenital wart	50	10.85

HIV, human immunodeficiency virus.

Table 2. Age-stratified prevalence of hepatitis B virus infection and anogenital wart in HIV-infected patients

Variables	Total	At enrolment		Cumulative until 2017	
		HBV	Anogenital wart	HBV	Anogenital wart
Total	1,485 (100.0)	71 (4.8)	128 (8.6)	79 (5.3)	178 (12.0)
Age at enrollment					
<30 y	297 (20.0)	7 (2.4)	40 (13.5)	7 (2.4)	62 (20.9)
30 - 39 y	401 (27.0)	15 (3.7)	39 (9.7)	16 (4.0)	49 (12.2)
40 - 49 y	399 (26.9)	24 (6.0)	35 (8.8)	29 (7.3)	48 (12.0)
≥50 y	388 (26.1)	25 (6.4)	14 (3.6)	27 (7.0)	19 (4.9)

Categorical variables were shown as numbers (percentage).
HIV, human immunodeficiency virus; HBV, hepatitis B virus.

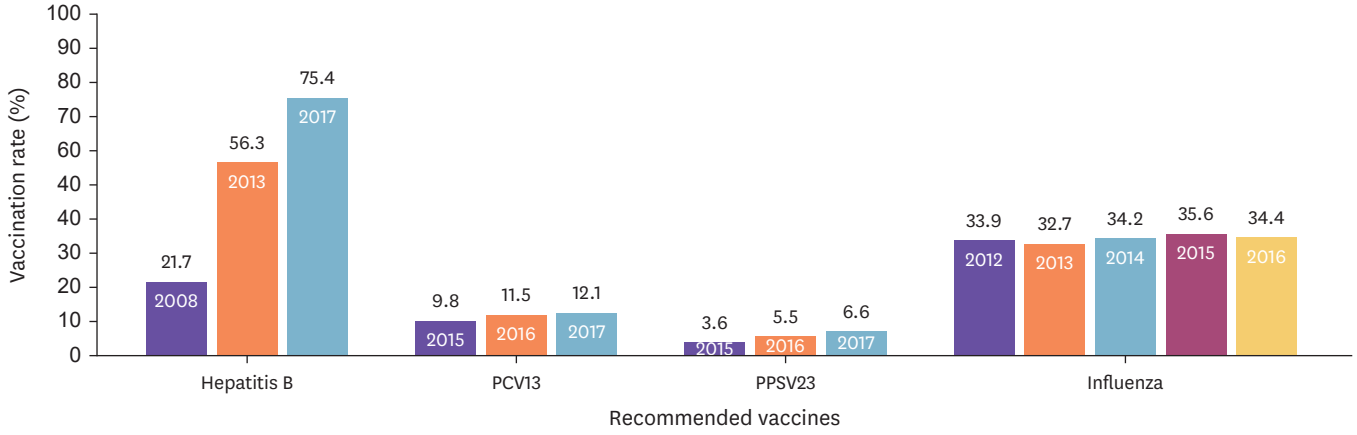

Figure 1. Vaccination rate of hepatitis B, PCV13, PPSV23, and Influenza by year.
PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.

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4. Influencing factors for vaccination

Tables 3 - 5 presented the results of the multilevel analyses conducted to identify the factors that influence vaccination against pneumococcus, HBV, and influenza. In the multilevel analysis, peak HIV viral load (≥50 copies/mL: odds ratio [OR] = 0.64, 95% confidence interval [CI]: 0.44 - 0.93; reference, <50 copies/mL) was an influencing factor for pneumococcal vaccination, while nadir CD4 T-cell counts (200 - 350 cells/mm^3: OR = 0.54, 95% CI: 0.38 - 0.76; <200 cells/mm^3: OR = 0.89, 95% CI: 0.62 - 1.28; reference, ≥350 cells/mm^3) was an influencing factor for HBV vaccination. In the multilevel analysis for influenza vaccination, higher vaccination rates were observed among men (OR = 1.94, 95% CI: 1.02 - 3.70) and individuals who had changed their antiretroviral regimen change one or more times (OR = 1.16, 95% CI: 1.08 - 1.24).

5. Survey for HIV care experts

The majority of experts believed that HIV-infected individuals should receive vaccinations for HAV, HBV, pneumococcus, and influenza routinely (**Supplementary Table 6**). However, few specialists have recommended vaccination for HPV and herpes zoster in HIV patients.

DISCUSSION

In this study, we evaluated the disease burden of VPDs and vaccination rates in patients with HIV infection. The burden of vaccine-preventable diseases was significantly higher in HIV-infected patients. CD4 T-cell counts, HIV viral loads, and the number of antiretroviral therapy regimen change are significant factors related to vaccination.

The incidence rate of herpes zoster in the general population has been reported to be lower (5.1 per 1,000 person-years) than that in HIV-infected individuals (7.38 per 1,000 person-years), indicating a higher incidence rate [9]. The prevalence rates of HBV infection and anogenital warts at enrollment were 4.8% and 8.6%, respectively, which were significantly higher than those in the general population (2.9% for HBV infection and 0.7% for anogenital warts) [10, 11]. Our finding of a high incidence and prevalence of VPDs in HIV-infected patients is consistent with those of previous studies that reported an increased risk of VPDs in this population [6, 12, 13]. Therefore, prophylactic immunization is crucial for HIV-infected patients to prevent morbidity and mortality due to VPDs.

In this study, the vaccination rates for HBV and pneumococcus increased annually, which is encouraging, whereas the influenza vaccination rate remained low despite the recommendations for high-priority annual immunization. A study conducted in the US showed that the influenza vaccination rate was almost 50.0% higher among people with HIV than among those without HIV, reflecting greater engagement with the healthcare system [14]. Therefore, integrated care may play a role in improving vaccination rates in this population.

We found that nadir CD4 T-cell count was significantly related to HBV vaccination. This may be because CD4 T-cell counts were used as a criterion for determining vaccination in HIV-infected patients [2]. We also found that the peak HIV viral load was negatively associated with pneumococcal vaccination. This may be due to the likelihood of pneumococcal vaccination being administered after the HIV viral load became undetectable. In addition, the positive association between the number of antiretroviral therapy regimen change and influenza vaccination may be attributable to increased contact with healthcare providers, resulting in more opportunities to receive influenza vaccination.

According to the survey results, most experts recommended routine vaccination for HBV, HAV, pneumococcus, and influenza but not for HPV and herpes zoster. This can be explained by the fact that only live-attenuated zoster vaccines were available during the study period, which could pose challenges for immunocompromised individuals with HIV, as the recombinant zoster vaccine received domestic approval in September 2021. The low rate of HPV vaccine recommendations might be related to lower awareness of the HPV disease burden and high vaccine cost. According to the Health Insurance Review and Assessment Service, the average price of HPV vaccine was 139,310 won (109.96 USD) per dose as of June 2023. HPV vaccination is covered only for females by the National Immunization Program (NIP), not including male patients who make up the majority of HIV patients. It would be reasonable to expand the NIP to include HPV vaccination for high-risk males to prevent HPV-related conditions such as penile cancer, anal cancer, genital warts, and oropharyngeal cancer.

Our study also revealed discordance between clinical practice and expert opinions regarding vaccination for HPV and herpes zoster. Systematic support and educational efforts are needed to improve vaccination awareness and practice in HIV care settings, particularly for HPV and herpes zoster vaccinations.

Table 3. Multilevel analysis of influencing factors for pneumococcal vaccination

Variables	Total (n = 1,158)	Pneumococcus vaccination		*P*-value	Odds ratio (95% confidential interval)			
		Yes (n = 248)	No (n = 910)		Null	Individual level	Hospital level	Multilevel
Individual level								
Age	41.3 ± 12.5	41.9 ± 11.5	41.1 ± 12.7	0.350		1.02 (1.00 - 1.04)		1.02 (1.00 - 1.04)
Sex (male)	1,076 (92.9)	229 (21.3)	847 (78.7)	0.688		0.83 (0.41 - 1.66)		0.83 (0.41 - 1.67)
Marital status				0.008				
Single	658 (56.8)	149 (22.6)	509 (77.4)			Ref		Ref
Married	283 (24.5)	65 (23.0)	218 (77.0)			0.71 (0.42 - 1.19)		0.71 (0.43 - 1.20)
Divorced/bereaved/separated	130 (11.2)	28 (21.5)	102 (78.5)			0.70 (0.37 - 1.30)		0.70 (0.37 - 1.31)
Others	87 (7.5)	6 (6.9)	81 (93.1)			0.33 (0.13 - 0.86)		0.33 (0.12 - 0.85)
Men who have sex with men	721 (62.3)	150 (20.8)	571 (79.2)	0.515		0.69 (0.47 - 1.01)		0.69 (0.47 - 1.00)
CD4 T-cell counts (nadir)				0.014				
<200 cells/mm^3	316 (27.3)	64 (20.2)	252 (79.8)			0.87 (0.56 - 1.36)		0.87 (0.56 - 1.35)
200 - 350 cells/mm^3	375 (32.4)	65 (17.3)	310 (82.7)			0.69 (0.45 - 1.04)		0.68 (0.45 - 1.04)
≥350 cells/mm^3	467 (40.3)	119 (25.5)	348 (74.5)			Ref		Ref
HIV viral load (peak)				<0.0001				
<50 copies/mL	430 (37.1)	120 (27.9)	310 (72.1)			Ref		Ref
≥50 copies/mL	728 (62.9)	128 (17.6)	600 (82.4)			0.64 (0.44 - 0.93)		0.64 (0.44 - 0.93)
HIV duration (years)	5.15 (4.08 - 7.90)	4.84 (4.03 - 7.18)	5.25 (4.08 - 8.07)	0.086		1.00 (0.95 - 1.05)		1.00 (0.95 - 1.05)
Number of ART regimen change	3.5 ± 2.4	3.58 ± 2.20	3.51 ± 2.43	0.683		1.03 (0.95 - 1.11)		1.03 (0.95 - 1.11)
Comorbidities								
Diabetes	114 (9.8)	19 (16.7)	95 (83.3)	0.193		-		-
Cardiovascular diseases	211 (18.2)	44 (20.8)	167 (79.2)	0.826		-		-
Lung diseases	53 (4.6)	8 (15.1)	45 (84.9)	0.251		-		-
Kidney diseases				0.913				
GFR <15 mL/min/1.73m^2	4 (0.4)	1 (25.0)	3 (75.0)			-		-
GFR 15 - 29 mL/min/1.73m^2	8 (0.7)	1 (12.5)	7 (87.5)			-		-
GFR 30 - 59 mL/min/1.73m^2	119 (10.3)	27 (22.7)	92 (77.3)			-		-
GFR ≥60 mL/min/1.73m^2	1,022 (88.6)	218 (21.3)	804 (78.7)			-		-
Malignancy				0.493				
None	1,121 (96.8)	239 (21.3)	882 (78.7)			-		-
AIDS defined	18 (1.6)	3 (16.7)	15 (83.3)			-		-
Non-AIDS related	19 (1.6)	6 (31.6)	13 (68.4)			-		-
Comorbidity, yes (%)	398 (34.4)	80 (20.1)	318 (79.9)	0.430		0.78 (0.53 - 1.15)		0.77 (0.52 - 1.14)
Hospital level				<0.0001				
No. of beds								
<1,000	290 (25.0)	43 (14.8)	247 (85.2)				Ref	Ref
<1,500	551 (47.6)	158 (28.7)	393 (71.3)				1.44 (0.31 - 6.61)	1.66 (0.36 - 7.63)
≥1,500	317 (27.4)	47 (14.8)	270 (85.2)				0.58 (0.09 - 3.59)	0.55 (0.08 - 3.63)
Between community variance					1.6222	1.6561	1.7377	1.7363
Percentage change in variance					-	2%	7%	7%
Between community variance (S.E.)					0.7044	0.7226	0.7913	0.8005
Between community variance (*P*-value)					<0.0001	0.003	<0.0001	0.006
Model fit-2 Res LL					5,792.84	5,916.30	5,806.79	5,931.22
Intra-class correlation					0.3305	0.3351	0.3459	0.3457

HIV, human immunodeficiency virus; ART, antiretroviral therapy; GFR, glomerular filtration rate; AIDS, acquired immune deficiency syndrome; S.E., standard error; LL, Log-Likelihood.

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Table 4. Multilevel analysis of influencing factors for Hepatitis B vaccination

Variables	Total (n = 962)	Hepatitis B vaccination		*P*-value	Odds ratio (95% confidential interval)			
		Yes (n = 405)	No (n = 557)		Null	Individual level	Hospital level	Multilevel
Individual level								
Age	41.1 ± 12.2	39.1 ± 11.7	42.6 ± 12.4	<0.0001		0.98 (0.96 - 0.99)		0.98 (0.96 - 0.99)
Sex (male)	895 (93.0)	381 (42.6)	514 (57.4)	0.281		0.85 (0.46 - 1.57)		0.84 (0.46 - 1.57)
Marital status				<0.0001				
Single	559 (58.1)	269 (48.1)	290 (51.9)			Ref		Ref
Married	242 (25.2)	82 (33.9)	160 (66.1)			0.78 (0.50 - 1.20)		0.77 (0.50 - 1.20)
Divorced/bereaved/separated	112 (11.6)	41 (36.6)	71 (63.4)			0.81 (0.48 - 1.36)		0.80 (0.48 - 1.35)
Others	49 (5.1)	13 (26.5)	36 (74.5)			0.80 (0.38 - 1.68)		0.81 (0.38 - 1.72)
Men who have sex with men	592 (61.5)	259 (43.7)	333 (56.3)	0.190		1.09 (0.79 - 1.49)		1.09 (0.80 - 1.50)
CD4 T-cell counts (nadir)				<0.0001				
<200 cells/mm^3	256 (26.6)	105 (41.0)	151 (59.0)			0.89 (0.62 - 1.28)		0.89 (0.62 - 1.28)
200 - 350 cells/mm^3	301 (31.3)	100 (33.2)	201 (66.8)			0.54 (0.38 - 0.76)		0.54 (0.38 - 0.76)
≥350 cells/mm^3	405 (42.1)	200 (49.4)	205 (50.6)			Ref		Ref
HIV viral load (peak)				0.041				
<50 copies/mL	370 (38.5)	171 (46.2)	199 (53.8)			Ref		Ref
≥50 copies/mL	592 (61.5)	234 (39.5)	358 (60.5)			0.87 (0.63 - 1.19)		0.87 (0.63 - 1.20)
HIV duration (years)	4.97 (4.01 - 7.84)	4.9 (3.90 - 7.54)	5.03 (4.08 - 7.88)	0.473		0.99 (0.95 - 1.03)		0.99 (0.95 - 1.03)
Number of ART regimen change	3.4 ± 2.2	3.1 ± 2.2	3.5 ± 2.2	0.005		0.96 (0.89 - 1.03)		0.96 (0.89 - 1.03)
Comorbidities								
Diabetes	96 (10.0)	35 (36.5)	61 (63.5)	0.238		-		-
Cardiovascular diseases	177 (18.4)	62 (35.0)	115 (65.0)	0.035		-		-
Lung diseases	41 (4.3)	13 (31.7)	28 (68.3)	0.168		-		-
Kidney diseases				0.744				
GFR <15 mL/min/1.73m^2	3 (0.3)	1 (33.3)	2 (66.7)			-		-
GFR 15 - 29 mL/min/1.73m^2	6 (0.6)	2 (33.3)	4 (66.7)			-		-
GFR 30 - 59 mL/min/1.73m^2	91 (9.5)	34 (37.4)	57 (62.6)			-		-
GFR ≥60 mL/min/1.73m^2	840 (89.6)	367 (42.7)	493 (57.3)			-		-
Malignancy				0.638				
None	932 (96.9)	391 (42.0)	541 (58.0)			-		-
AIDS define	13 (1.4)	5 (38.5)	8 (61.5)			-		-
Non-AIDS related	17 (1.8)	9 (52.9)	8 (47.1)			-		-
Comorbidity, yes (%)	322 (33.5)	127 (39.4)	195 (60.6)	0.236		1.39 (1.00 - 1.94)		1.40 (1.01 - 1.95)
Hospital level				0.169				
No. of beds								
<1,000	244 (25.3)	92 (37.7)	152 (62.3)				Ref	Ref
<1,500	448 (46.6)	189 (42.2)	259 (57.8)				0.59 (0.16 - 2.16)	0.51 (0.13 - 1.99)
≥1,500	270 (28.1)	124 (45.9)	146 (54.1)				1.25 (0.28 - 5.52)	1.31 (0.28 - 6.27)
Between community variance					1.1519	1.3203	1.3412	1.4945
Percentage change in variance					-	15%	16%	30%
Between community variance (S.E.)					0.5270	0.6035	0.6274	0.6964
Between community variance (*P*-value)					0.412	0.006	0.817	0.008
Model fit -2 Res LL					4,199.27	4,302.54	4,207.26	4,312.04
Intra-class correlation					0.2595	0.2866	0.2898	0.3126

HIV, human immunodeficiency virus; ART, antiretroviral therapy; GFR, glomerular filtration rate; AIDS, acquired immune deficiency syndrome; S.E., standard error; LL, Log-Likelihood.

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Table 5. Multilevel analysis of influencing factors for influenza vaccination

Variables	Total (n = 1,228)	Influenza vaccination		*P*-value	Odds ratio (95% confidential interval)			
		Yes (n = 301)	No (n = 927)		Null	Individual level	Hospital level	Multilevel
Individual level								
Age	41.3 ± 12.5	42.1 ± 12.5	41.0 ± 12.5	0.195		1.00 (0.99 - 1.02)		1.00 (0.99 - 1.02)
Sex (male)	1,143 (93.1)	286 (25.0)	857 (75.0)	0.127		1.95 (1.00 - 3.80)		1.94 (1.02 - 3.70)
Marital status				0.004				
Single	697 (56.8)	170 (24.4)	527 (75.6)			Ref		Ref
Married	298 (24.3)	82 (27.5)	216 (72.5)			1.23 (0.79 - 1.93)		1.24 (0.80 - 1.94)
Divorced/bereaved/separated	141 (11.5)	40 (28.4)	101 (71.6)			1.43 (0.85 - 2.40)		1.44 (0.86 - 2.41)
Others	92 (7.5)	9 (9.8)	83 (90.2)			0.40 (0.18 - 0.89)		0.41 (0.18 - 0.89)
Men who have sex with men	760 (61.9)	193 (25.4)	567 (74.6)	0.359		0.98 (0.71 - 1.35)		
CD4 T-cell counts (nadir)				0.971				
<200 cells/mm^3	326 (26.5)	81 (24.8)	245 (75.2)			0.89 (0.61 - 1.31)		0.88 (0.60 - 1.30)
200 - 350 cells/mm^3	393 (32.0)	97 (24.7)	296 (75.3)			0.95 (0.67 - 1.35)		0.94 (0.66 - 1.33)
≥350 cells/mm^3	509 (41.5)	123 (24.2)	386 (75.8)			Ref		Ref
HIV viral load (peak)				0.320				
<50 copies/mL	464 (37.8)	121 (26.1)	343 (73.9)			Ref		Ref
≥50 copies/mL	764 (62.2)	180 (23.6)	584 (76.4)			0.79 (0.57 - 1.10)		0.79 (0.57 - 1.10)
HIV duration (years)	5.13 (4.04 - 7.91)	4.97 (4.13 - 7.92)	5.18 (3.98 - 7.90)	0.260		1.01 (0.97 - 1.05)		
Number of ART regimen change	3.5 ± 2.4	4.1 ± 2.4	3.2 ± 2.3	<0.0001		1.16 (1.08 - 1.24)		1.16 (1.08 - 1.24)
Comorbidities								
Diabetes	117 (9.5)	37 (31.6)	80 (68.4)	0.060		-		-
Cardiovascular diseases	215 (17.5)	63 (29.3)	152 (70.7)	0.072		-		-
Lung diseases	53 (4.3)	14 (26.4)	39 (73.6)	0.742		-		-
Kidney diseases				0.864				
GFR <15 mL/min/1.73m^2	4 (0.3)	1 (25.0)	3 (75.0)			-		-
GFR 15 - 29 mL/min/1.73m^2	8 (0.7)	3 (37.5)	5 (62.5)			-		-
GFR 30 - 59 mL/min/1.73m^2	120 (9.8)	30 (25.0)	90 (75.0)			-		-
GFR ≥60 mL/min/1.73m^2	1,091 (89.2)	267 (24.5)	824 (75.5)			-		-
Malignancy				0.520				
None	1,191 (97.0)	289 (24.3)	902 (75.7)			-		-
AIDS define	18 (1.5)	6 (33.3)	12 (66.7)			-		-
Non-AIDS related	19 (1.5)	6 (31.6)	13 (68.4)			-		-
Comorbidity, yes (%)	407 (33.1)	114 (28.0)	293 (72.0)	0.045		1.01 (0.73 - 1.41)		1.01 (0.72 - 1.40)
Hospital level				<0.0001				
No. of beds								
<1,000	300 (24.4)	68 (22.7)	232 (77.3)				Ref	Ref
<1,500	583 (47.5)	185 (31.7)	398 (48.3)				0.71 (0.17 - 3.06)	0.81 (0.20 - 3.35)
≥1,500	345 (28.1)	48 (13.9)	297 (86.1)				0.19 (0.03 - 1.06)	0.19 (0.04 - 1.03)
Between community variance					1.5520	1.4563	1.6604	1.5530
Percentage change in variance					-	−6.17%	6.98%	0.06%
Between community variance (S.E.)					0.6992	0.6620	0.7909	0.7595
Between community variance (*P*-value)					<0.0001	<0.0001	0.001	<0.0001
Model fit-2 Res LL					5,821.98	5,908.39	5,852.95	5,938.02
Intra-class correlation					0.3208	0.3071	0.3356	0.3209

HIV, human immunodeficiency virus; ART, antiretroviral therapy; GFR, glomerular filtration rate; AIDS, acquired immune deficiency syndrome; S.E., standard error; LL, Log-Likelihood.

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This study had several limitations. First, the incidence and prevalence of VPDs may have been underestimated because some patients may have sought care outside the HIV/AIDS cohort system. Second, this study did not evaluate the effectiveness of vaccination in preventing VPDs or the impact of vaccination on clinical outcomes, such as hospitalization or mortality. Another limitation of this study is that we only evaluated a subset of VPDs. Finally, we did not assess factors such as the reasons for vaccine refusal or hesitancy, socioeconomic status, and education level, which could influence vaccination rates.

In conclusion, the disease burdens of HBV, HPV, and herpes zoster were quite high in HIV-infected patients than in the general population. Healthcare providers should be aware of the high burden of VPDs in HIV-infected patients and encourage vaccination to their patients.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Hepatitis vaccination rates by year

Click here to view

Supplementary Table 2
Pneumococcal vaccination rates by year

Click here to view

Supplementary Table 3
Influenza vaccination rates by year

Click here to view

Supplementary Table 4
Seroprevalence and seroconversion/seroreversion rates for anti-HBs antibody by year

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Supplementary Table 5
Factors associated with seroconversion/seroreversion for anti-HBs antibody

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Supplementary Table 6
Survey for experts on vaccination of people living with HIV

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Conflict of Interest
HJC, JYS, JYC are editorial board members of Infect Chemother; however, they did not involve in the peer reviewer selection, evaluation, and decision process of this article. Otherwise, no potential conflicts of interest relevant to this article was reported.

Author Contributions
Conceptualization: JYS, HS. Data curation: JYC, SWK, SIK, HJH, JGY, JYN. Formal analysis: YSC, KHA. Investigation: HS, JYS, YSC, KHA, JYC, SWK, SIK, BYC, BYP, HJH, JGY, JYN, HJC, WJK. Methodology: YSC, KHA, MKK, BYC, BYP. Project administration: JYS. Resources: YSC, BYC, BYP. Supervision: JYS. Validation: JYS, YSC, HS. Visualization: HS. Writing - original draft: HS. Writing - review & editing: JYS, YSC, KHA, JYC, SWK, SIK, BYC, BYP, HJH, JGY, JYN, HJC, WJK.

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