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Human Immunodeficiency Virus (HIV) and Hepatitis Virus Coinfection among HIV-Infected Korean Patients: The Korea HIV/AIDS Cohort Study

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Background: Despite declines in mortality and morbidity rates of patients with human immunodeficiency virus (HIV) infection as the result of highly active antiretroviral therapy, liver diseases due to chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are a leading cause of death among HIV-infected patients. However, HIV and HBV or HCV coinfection is still poorly documented, and more information is needed to better understand the characteristics of HIV-infected patients in Korea.

Materials and Methods: A cross-sectional study was performed to investigate clinical characteristics and prevalence of HBV and HCV infection in HIV patients enrolled in the Korea HIV/acquired immune deficiency syndrome (AIDS) cohort study from 17 institutions between December 2006 and July 2013.

Results: Among the 1,218 HIV-infected participants, 541 were included in this study. The prevalence of HBV-HIV and HCV-HIV coinfection was 5.0% (27/541) and 1.7% (9/541), respectively. There was no patient who was positive for both HBs antigen and HCV antibody. In multivariate logistic regression analysis, HBV unvaccinated status was a significant risk factor for HBV-HIV coinfection (odds ratio = 4.95, 95% confidence interval = 1.43–17.13).

Conclusion: HBV and HCV infection was more common in HIV-infected persons enrolled in the Korean HIV/AIDS cohort, than in the general population in Korea.

Key Words: HIV infection; Hepatitis B virus; Hepatitis C virus; Coinfection

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Introduction

Therapy for human immunodeficiency virus (HIV)-infected patients has progressed remarkably since the introduction of antiretroviral therapy (ART). Furthermore, since the early start of effective ART, the incidence of opportunistic infections as well as the mortality rate in patients with HIV has decreased [1-3]. Liver disease is currently the major concern in HIV-infected patients coinfected with hepatitis B virus (HBV) or hepatitis C virus (HCV) [4, 5]. HBV-HIV or HCV-HIV patients have more rapid progression of liver disease than those with HBV or HCV mono-infection. End-stage liver disease, such as liver cirrhosis or hepatocellular carcinoma, is commonly observed in patients with HBV-HIV or HCV-HIV coinfection [6-9]. Furthermore, HBV or HCV coinfection may increase the risk of ART-related hepatotoxicity or influence the selection of ART regimen [10].

HIV and HBV or HCV coinfection is still poorly documented in Korea. Although some studies have evaluated viral hepatitis coinfection in HIV-infected patients, these were retrospective single-center studies and reported little data about HBV-HIV coinfection [11, 12]. Thus, more information is needed to better understand the characteristics of HIV-infected patients in Korea.

We therefore conducted a prospective multicenter study to investigate the prevalence and epidemiological features of both HBV and HCV coinfections among HIV-infected Korean patients.

Materials and Methods

1. Study design and population

The Korea HIV/acquired immune deficiency syndrome (AIDS) cohort study is a prospective multicenter study with ongoing enrollment of HIV-infected adult patients older than 18 years from 17 hospitals in South Korea (Gachon University Gil Hospital, Seoul St. Mary's Hospital, Hallym University Kangdong Sacred Heart Hospital, Kyungpook National University Hospital, Korea University Guro Hospital, Korea University Ansan Hospital, Seoul Asan Hospital, Soon Chun Hyang University Hospital Seoul, Ajou University Hospital, Severance Hospital, Wonju Severance Christian Hospital, Ewha Womans University Mokdong Hospital, Inha University Hospital, Chungbuk National University Hospital, Hallym University Anyang Sacred Heart Hospital, Hallym University Kangnam Sacred Heart Hospital, and Yeungnam University Hospital). To evaluate the prevalence and epidemiological features of HBV or HCV coinfection among HIV-infected persons, we investigated the presence of HBV surface antigen (HBs Ag) and anti-HCV antibody (Ab). Patients who tested negative for HBs Ag and anti-HCV Ab were defined as HIV mono-infection patients. Among patients with HIV infection, HBV coinfection was defined based on positive test results for HBs Ag and HCV coinfection was defined based on positive test results for anti-HCV Ab. Trained researchers from all centers prospectively collected information every 6 months using a standardized protocol. Information included medical history, socioeconomic status, physical findings, laboratory findings including immunological and virological status, and opportunistic diseases. All participants provided written informed consent and ethics approval was obtained from the Institutional Review Board of each participating institute. This study analyzed data for 1,218 HIV-infected persons enrolled between December 2006 and July 2013.

2. Laboratory tests and data collection

HIV infection was screened for using enzyme immunoassays (EIA) and confirmed using western blotting. HBV infection was defined based on HBs Ag positivity without protective antibodies. HCV infection was detected via EIA for anti-HCV Ab presence, and reactive samples were confirmed using recombinant immunoblot assay. To evaluate the prevalence and epidemiological features of HBV or HCV coinfections, we used baseline data at the time of registration in the Korea HIV/AIDS cohort study. These data included age, sex, body mass index, race, socioeconomic status, sexual habit, first year of HIV diagnosis, history of smoking and alcohol use, route of transmission, CD4/CD8 count, HIV viral load, ART history, HBV vaccination status, history of liver disease, and serum chemistry at study enrollment.

3. Statistical analysis

Continuous variables are presented as medians with interquartile ranges (IQR) and categorical variables are expressed as numbers with percentages. To compare variables between two groups, an independent sample *t*-test or the Mann-Whitney *U* test was used for continuous variables, and a Brown-Mood median two-sample test or Fisher's exact test was used for categorical variables. Factors associated with HBV or HCV coinfection were analyzed by univariate and multivariate logistic regression models. Variables with a *P* value less than 0.25 in baseline characteristic analyses were included in univariate analyses, and multivariate analyses included variables with a

P value less than 0.16 in univariate analyses. The relationships between clinical factors and HBV or HCV coinfection were summarized by odds ratios (ORs) and 95 % confidence intervals (CIs). Statistical analyses were performed using the SPSS, version 16.0 (SPSS Inc., Chicago, IL, USA). A *P* value less than 0.05 was considered statistically significant.

Results

1. Baseline characteristics of patients

Among 1,218 participants, 677 were excluded because of missing data. 541 participants were included for analysis. The prevalence of HBV and HCV coinfection was 5.0% (27/541) and 1.7% (9/541), respectively (Fig. 1). The baseline characteristics of the 541 HIV-infected patients are shown in Table 1. Most patients were men (92.8%) and of Korean ethnicity (98.7%). The median age was 42 years (IQR, 33–51 years). According to a self-reported questionnaire, HIV was transmitted mainly by sexual contact (97.6%), and the proportion of homosexual patients (33.1%) was similar to that of heterosexual patients (36.4%). The median CD4 cell count was 356 cells/mm^3 (IQR, 206–512 cells/mm^3) and the median HIV viral load was 157 copies/mL (IQR, 20–19,645 copies/mL). 375 patients (69.3%) were treatment naïve.

Among the 541 HIV patients who had results of HBs Ag and anti-HCV Ab testing, 36 patients (6.7%) had HBV or HCV coinfection. There were significant differences in age, sex, transmission route of HIV, history of liver cirrhosis, and HBV vaccination status between HIV mono-infection patients and HBV

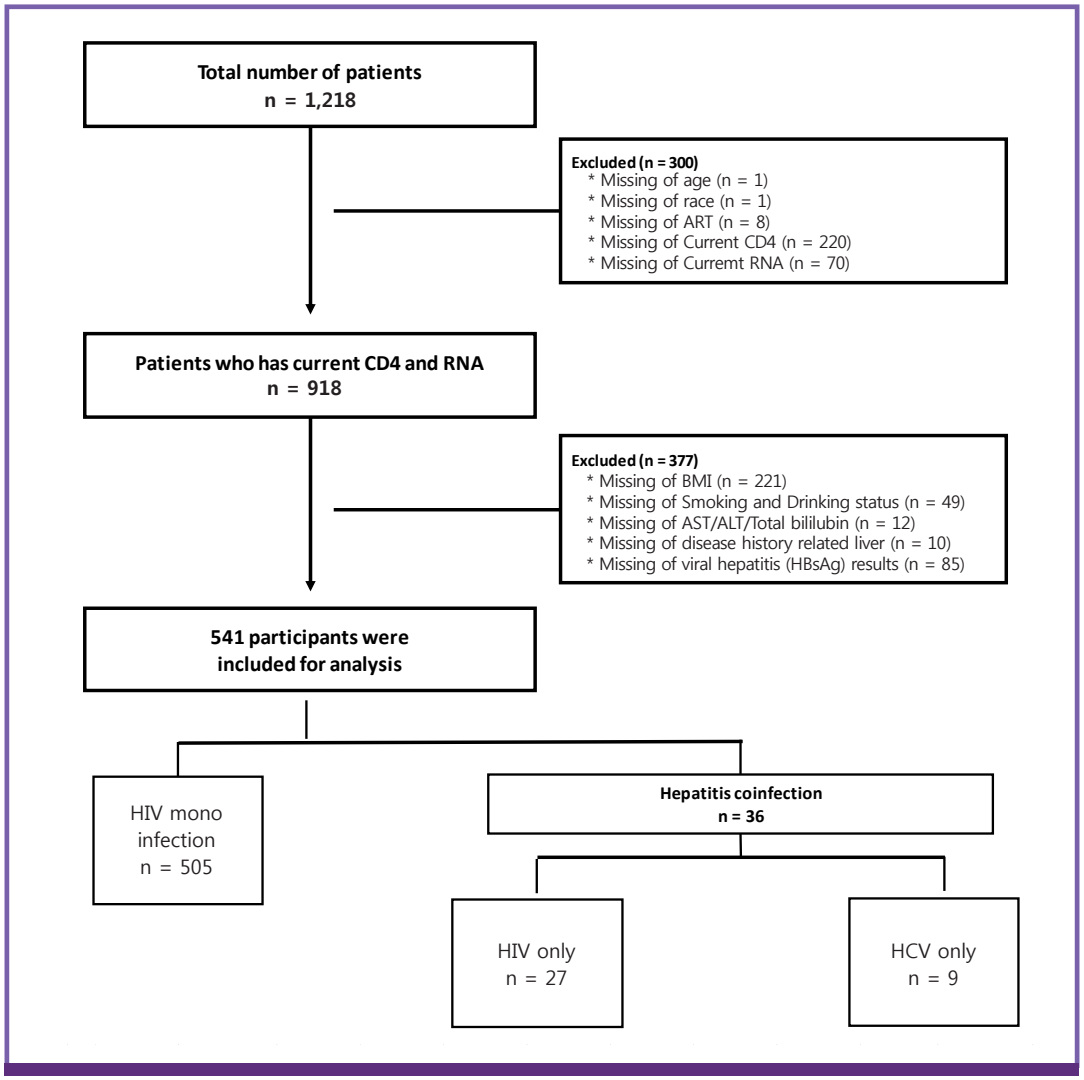

Figure 1. Profile of enrolled patients.
ART, antiretroviral therapy; RNA, ribonucleic acid; BMI, body mass index; AST, aspartate transaminase; ALT, alanine transaminase; HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus.

Table 1. Patients' baseline characteristics

Variables	n (%)			*P*-value
	Total	HIV mono infection	Hepatitis coinfection	
n	541 (100.0)	505 (93.4)	36 (6.7)	<0.0001
Age (yrs)[a]	42 (33–51)	41 (33–50)	45 (37–51.5)	0.039[b]
<30	91 (16.8)	86 (17.0)	5 (13.9)	0.077
<40	151 (27.9)	145 (28.7)	6 (16.7)	
<60	252 (46.6)	228 (45.2)	24 (66.7)	
≥60	47 (8.7)	46 (9.1)	1 (2.8)	
Sex				
Male	502 (92.8)	472 (93.5)	30 (83.3)	0.037[c]
Female	39 (7.2)	33 (6.5)	6 (16.7)	
Race				
Korean	534 (98.7)	500 (99.0)	34 (94.4)	0.073[c]
Foreigner	7 (1.3)	5 (1.00)	2 (5.7)	
Transmission route of HIV				
Reception of blood/product	1 (0.2)	0 (0.0)	1 (0.2)	0.042[c]
Others (include unknowing)[d]	12 (2.2)	11 (2.2)	1 (2.8)	
Sexual contact	528 (97.6)	494 (97.8)	34 (94.4)	
Homosexual	179 (33.1)	173 (33.7)	6 (22.2)	0.179
Heterosexual	197 (36.4)	182 (35.4)	15 (55.6)	
Bisexual	152 (28.1)	146 (28.4)	6 (22.2)	
Baseline CD4 cell count (cells/mm^3)[a]	356 (206–512)	360 (208–512)	310 (175–501.5)	0.306[b]
Baseline HIV RNA (copies/mL)[a]	157 (20–19,645)	196 (20–17,415)	74.5 (20–26,574)	0.307[b]
Treatment naïve	375 (69.3)	348 (68.9)	27 (75.0)	0.444
Body mass index (BMI, kg/m^2)				
Mean ± SD	22.2 ± 2.91	22.2 ± 2.91	21.9 ± 2.94	0.305[b]
Median (IQR)	21.8 (20.31–23.88)	21.85 (20.32–23.88)	21.56 (19.72–23.94)	
Smoking history				
Current	267 (49.4)	251 (49.7)	16 (44.4)	0.086
Previous	99 (18.3)	96 (19.0)	3 (8.3)	
Non smoker	175 (32.4)	158 (31.3)	17 (47.2)	
Alcohol history				
Current	285 (52.7)	270 (53.5)	15 (41.7)	0.380
Previous	91 (16.8)	84 (16.6)	7 (19.4)	
Non drinker	165 (30.5)	151 (29.9)	14 (38.9)	
Laboratory results[a]				
AST (IU/L)	22 (18–30)	22 (18–30)	23 (20–28.5)	0.660[b]
ALT (IU/L)	21 (15–32)	21 (15–33)	20.5 (15.6–26.0)	0.403[b]
Total bilirubin (mg/dL)	0.60 (0.43–0.90)	0.60 (0.43–0.90)	0.57 (0.455–0.805)	0.122[b]
Liver disease				
Fatty liver	6 (1.1)	5 (1.0)	1 (2.8)	0.267[c]
Liver cirrhosis	4 (0.7)	1 (0.2)	3 (8.3)	0.001[c]

Values are presented as medians (interquartile ranges (IQR)) or numbers (percentages).
HIV, human immunodeficiency virus; RNA, ribonucleic acid; SD, standard deviation; IQR, interquartile range; AST, aspartate transaminase; ALT, alanine transaminase.
[a]Median (Interquartile range, IQR).
[b]Brown-Mood's median two-sample test.
[c]Fisher's exact test.
[d]Others include vertical transmission and unknowing.

Table 2. Factors associated with hepatitis B virus coinfection

Variables	HBV coinfection (n = 104)			
	Univariate OR (95 % CI)	*P*-value	Multivariate OR (95% CI)	*P*-value
Age (years) (*vs.* <42[a])				
≥42	2.06 (0.91–4.68)	0.083	1.52 (0.63–3.65)	0.353
Male sex (vs. female sex)	0.42 (0.114–1.28)	0.128	0.59 (0.17–2.05)	0.405
Race (*vs.* foreigner)				
Korean	0.31 (0.04–2.65)	0.283		
Sexuality (*vs.* homosexual)				
Heterosexual	2.38 (0.90–6.27)	0.587		
Bisexual	1.19 (0.37–3.75)	0.05		
Smoking history (*vs.* nonsmoker)				
Current	0.76 (0.33–1.74)	0.799		
Previous	0.47 (0.13–1.71)	0.313		
Liver disease (*vs.* no)				
Liver cirrhosis	64.10 (6.43–639.12)	0.0004		
HBV vaccination (*vs.* yes)				
No	6.28 (1.85–21.32)	0.0005	4.95 (1.43–17.13)	0.001
Unknown	1.09 (0.18–6.63)	0.286	0.69 (0.10–4.79)	0.17

Values are presented as medians (interquartile ranges) or numbers (percentages).
HBV, hepatitis B virus; OR, odds ratio; CI, confidence interval.
[a]Median criteria.

or HCV coinfection patients. Patients with HBV or HCV coinfection were older than HIV mono-infection patients (median, 45 years; IQR, 37–51 years vs. median, 41 years; IQR, 33–50 years, P <0.039). Patients with liver cirrhosis were more common in the HBV or HCV coinfection group than the HIV mono-infection group (8.3% *vs.* 0.2%, P = 0.001). In contrast, male sex was more common in the HIV mono-infection patients than the HBV or HCV coinfection patients (93.5% *vs.* 83.3%, P = 0.037), and the rate of HBV vaccination was significantly different between the HIV mono-infection group and HBV or HCV coinfection group (P = 0.0002).

2. Factors associated with HBV and HCV coinfection

Univariate logistic regression analysis showed that age, sex, sexual contact, history of liver cirrhosis, and HBV vaccination status were associated with HBV coinfection in HIV patients (Table 2). Sexuality and history of liver cirrhosis were not included in multivariate analysis because of unmatched number of participants. In multivariate analysis, HBV unvaccinated status was an independent risk factor for HBV coinfection (OR = 4.95, 95% CI = 1.43–17.13). Factors associated with HCV coinfection were not analyzed because of small number of HCV coinfection patients.

Discussion

In this study, we investigated the prevalence and epidemiological features of HBV and HCV coinfection in HIV-infected Korean patients. The rate of HBV or HCV coinfection in HIV patients was 6.7%. The prevalence of HBV-HIV coinfection and HCV-HIV coinfection was 5.0% and 1.7%, respectively. Multivariate logistic regression analysis showed that the risk of HBV coinfection was associated with HBV unvaccinated status. Factors associated with HCV infection were not identified in this study because of small number of HCV coinfection patients.

Previous studies have reported hepatitis virus coinfection among HIV-infected Korean patients [11, 12]. However, they did not report the demographic characteristics of patients with HBV-HIV coinfection. To the best of our knowledge, our study is the first to evaluate the prevalence and demographic characteristics of both HBV-HIV and HCV-HIV coinfections in HIV-infected Korean patients.

HBV or HCV infection in HIV patients is more common than in the general population [13]. This may be caused by similarities in routes of transmission and risk factors between HBV or HCV and HIV, for example, injection drug use, sexual contact, and reception of blood products [14-16]. Our study also showed

a higher prevalence of HBV or HCV infection in HIV patients than in the general population. According to the Korea National Health and Nutrition Examination Survey, the HBV infection rate in the general population is 2.9% [17]. Kim et al. reported that the nationwide prevalence of HCV in Korea was 0.78% [18].

The rates of HBV or HCV coinfection among HIV patients have been studied in several countries [19-23]. The prevalence of HBV-HIV coinfection reported in our study is similar to that of other countries [19]. However, we found a lower prevalence of HCV-HIV coinfection than that reported in previous studies [24, 25]. A possible cause is that the regions from which patients were drawn for this study did not include regions with a high prevalence of anti-HCV. A Korean study, implemented in a region with a high prevalence of anti-HCV, reported an HCV-HIV coinfection prevalence of 5.2% [12].

Our study had several limitations. First, we did not show the factors associated with HCV-HIV coinfection because of small number of patients with HCV-HIV coinfection. Second, our HCV-HIV coinfection data is insufficient to represent the characteristics of HCV-HIV coinfection throughout Korea because we did not include the institutions in regions with a high prevalence of HCV-HIV coinfection. Third, a large number of participants were excluded due to missing data. Therefore, there is a possibility of selection bias. Also, there is the potential for recall bias because the history of HBV vaccination was confirmed by questionnaire to the participants. Further studies are required to be conducted with nationwide and accurate data for HBV and HCV coinfection.

In conclusion, this study showed that the prevalence of HBV and HCV infection in HIV patients was higher than that in the Korean general population. The prevalence of HBV-HIV coinfection was higher than that of HCV-HIV coinfection. HBV unvaccinated status was an independent risk factor for HBV-HIV coinfection. A nationwide study is needed to analyze the prevalence and epidemiological features of HCV-HIV coinfection in the Korean population as a whole.

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Conflicts of Interest

No conflicts of interest.

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Supplementary material

Supplementary data including one table can be found with this article online http://www.icjournal.org/src/sm/ic-49-268-s001.pdf.

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