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Original Article

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Characterization of Incident Hepatitis C Virus Infection among People Living with HIV in a HIV Clinic in Korea

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ABSTRACT

Background: Coinfection with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) can cause more rapid progression to cirrhosis than HCV-monoinfection. In this study, incident HCV case (IHCV)s were investigated in a HIV clinic in Korea.

Materials and Methods: A retrospective HIV cohort was constructed who visited National Medical Center in Korea from 2013 to 2022 and performed ≥1 anti-HCV antibody tests (anti-HCV) during the study period. IHCV was defined as newly confirmed HCV infection by PCR with a prior negative anti-HCV and factors associated with IHCV were investigated among alanine aminotransferase (ALT) >150 IU/mL sub-cohort without plausible reasons for ALT elevation.

Results: Overall, 2,567 HIV clinic visitors were recruited during the study period and 42 (1.63%) were confirmed as HIV/HCV co-infection. Fifteen IHCVs were identified during the study period. While no IHCV was observed in 2013–2015, incidence of 2016–2019 and 2020–2022 were 0.84 and 1.48 per 1000 person-year, respectively. Subtype 1a were more common among IHCVs in 2020–2022 (8/9) while subtype 2 dominated in 2016–2019 (5/6, P=0.003). Most IHCVs were identified during the evaluation of de novo liver enzyme elevation which was identified through the regularly performed blood tests (86.7%, 13/15). Comparing twelve IHCVs with ALT>150 IU/mL with 58 HIV mono-infection comparators whose peak ALT exceeded 150 IU/mL during the study period, age, sex, HIV/HCV infection risk factor, CD4 cell count, and HIV-RNA viral load were not different between two groups. However, mean peak ALT of IHCVs was higher than comparators (776 *vs.* 237, P<0.001) and syphilis treatment within prior 24 months of ALT elevation was more common in IHCV group (41.7% *vs.* 12.7%, P=0.026).

Conclusion: Incidence rate of HCV among PLH revealed increasing trend between 2013 and 2022 among visitors at a HIV clinic in Korea. Subtype 1a dominated among IHCVs after 2020 and recent syphilis treatment was associated with IHCVs.

Keywords: HIV infections; Hepatitis C; Epidemiolog

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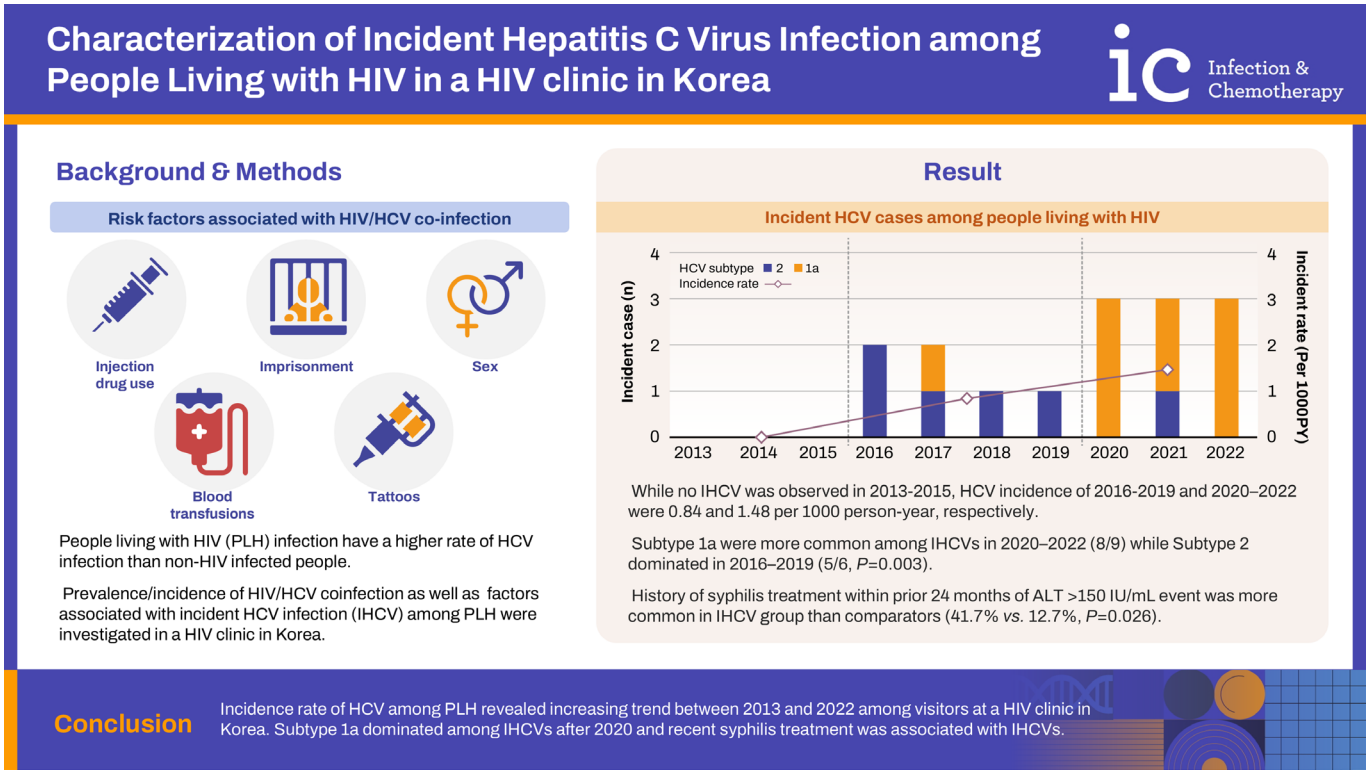
GRAPHICAL ABSTRACT



INTRODUCTION

The global prevalence of viraemic hepatitis C virus (HCV) infection is estimated as 0.7% [1]. About 70% to 85% of patients with HCV infection develop chronic hepatitis, and 30% of these patients progress to end-stage liver disease such as liver cirrhosis or hepatocellular carcinoma [2]. Because effective HCV vaccination is not yet available, prevention of transmission and appropriate treatment are the best way to reduce the burden of HCV-related liver diseases. Fortunately, highly efficacious direct antiviral agents (DAA) against HCV are available. Therefore, early detection and treatment of patients with HCV infection are recommended to prevent advanced liver diseases and new HCV infection [3, 4]. And the World Health Organization promote this strategy for the elimination of HCV infection by 2030 [5].

People with human immunodeficiency virus (HIV) infection have a higher rate of HCV infection than non-HIV infected people [6]. HIV and HCV are transmitted by similar routes, and although intravenous drug injection is the main route, HCV transmission among men who have sex with men (MSM) has been observed. Among MSM, the transmission of HCV is largely sexual, and risk factors include having multiple partners, traumatic sexual practices, and chemsex [7]. HIV-positive MSM have been reported to have about four times higher HCV infection rates than non-HIV-infected MSM [8].

In Korea, HCV prevalence of people living with HIV (PLH) has been known as 1.7% in nationwide study [9] what is higher that general population of 0.63% in 2015 [10]. A study from single center reported higher HCV prevalence of 5.2% among 966 PLH in 2015 and experience of injecting drug use (IDU) was related with HCV coinfection [11]. In this study, we investigated recent trend of HIV/HCV coinfection in a large HIV clinic focusing incident HCV infection cases (IHCV) among PLH.

MATERIALS AND METHODS

1. Study population

A retrospective cohort study was conducted targeting PLHs who visited National Medical Center, a 500 bed hospital in Seoul, Korea, from January 2013 to December 2022 for HIV care. To investigate the incidence and

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prevalence of HCV infection, annual PLH cohort visiting for HIV care was constructed with whom got HIV-RNA quantification tests more than two time in each year. Thereafter, every annual cohort was integrated and person based total cohort was generated throughout the study period.

In our clinic, anti-HCV antibody test (anti-HCV) is routinely performed on the initial visit for HIV care. Participants were excluded from the total cohort if whose anti-HCV result was not available throughout the study period. Confirmation of HCV infection was done by the presence of HCV RNA. Demographics and clinical data were collected from a retrospective review of medical records.

2. Ethics statement

The Institutional Review Board of National Medical Center approved the study protocol (MC-2022-08-091) and informed consent was waived.

3. Definitions

1) Prevalence and incidence of HCV coinfection

Annual prevalence of HCV was based on the number of individuals who were confirmed as HCV infection at each cohort year or before among the participants of year cohort. IHCV was defined as confirmation of HCV infection during the study period in the presence of prior negative anti-HCV result. HCV incidence was estimated as the number of IHCV cases among the person-year of target cohort period. Inclusion of a participant in each year cohort was considered as one person-year.

2) Clinical features related with incident HCV among ALT elevation events

To evaluate the clinical features associated with IHCV among ALT elevation events, cohort of ALT elevation of >150 IU/mL event (ALT>150) was constructed. Initially, peak ALT was investigated among total cohort and cut off for ALT elevation was set as 80, 100, 150, 200, and 300. The number of participants whose ALT with over each ALT cut off were 701, 501, 253, 160, and 77, respectively and ALT>150 IU/mL was arbitrarily selected considering the efficiency of analysis. Cases were excluded if anti-HCV was not available after ALT>150. Additionally, cases with plausible reasons of ALT elevation were excluded from ALT>150 cohort such as accompanying acute morbidity, toxic hepatitis, and alcohol dependency. Age, sex, HIV/HCV infection risk factors, CD4 cell count/HIV-RNA viral load of nearest time point from ALT>150, and treatment against incident syphilis within prior 24 months were investigated. Incident syphilis was defined as primary, secondary, and early latent syphilis.

4. Statistical analysis

SPSS (version 18.0, SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Pearson chi-square test was used for categorical variables, and the Student *t*-test for continuous variables. Tests of significance were 2-tailed and $P<0.05$ was considered significant.

RESULTS

1. Prevalence and incidence of HCV coinfection

During the study period, 2,567 PLHs were recruited. Year cohort participants increased from 1,019 in 2013 to 2,065 in 2022 (**Fig. 1A**). During the study period, 42 confirmed HIV/HCV co-infection were identified and overall HCV prevalence was 1.63%. The prevalence of HIV/HCV co-infection of 2013 was 1.47% and it was 1.79% in 2022. Subtype 2 was most common (n=20, 48.7%) followed by 1a (29.3%) and 1b (12.2%) among 41 participants with available subtype information (**Fig. 1B**).

Fifteen IHCVs were identified during the study period (**Table 1**). While no IHCV was observed in 2013–2015, incidence rate of 2016–2019 and 2020–2022 period were 0.84 and 1.48 per 1,000 person-year, respectively (**Fig. 1C**). Among the IHCVs since 2016, subtype 2 was more common in 2016–2019 (5/6) while most were subtype 1a in 2020–2022 (8/9) with significant difference ($P=0.003$). Most IHCVs were identified during the evaluation of de novo liver enzyme elevation which was identified through the regularly performed blood tests for HIV care (86.7%, 13/15). The other two IHCVs were asymptomatic and they were identified during pre-operation evaluation and private health screening, respectively. Among the fifteen IHCVs, DAA was prescribed to fourteen participants except one who refused the treatment due to the expense of DAA. Besides one participant whose post-DAA HCV viral test result unavailable, all thirteen participants were in the status of sustained viral response for at least 48 weeks.

2. Clinical features related with incident HCV among ALT elevation events

Among 2,567 PLH, 214 revealed history of the ALT>150. Among them, 24 were HCV/HIV coinfection including 15 IHCVs. 75 were excluded because HCV Ab was not performed after the ALT>150. In 36 cases, comorbidity was considered as a reason of ALT>150 such as pneumocystis

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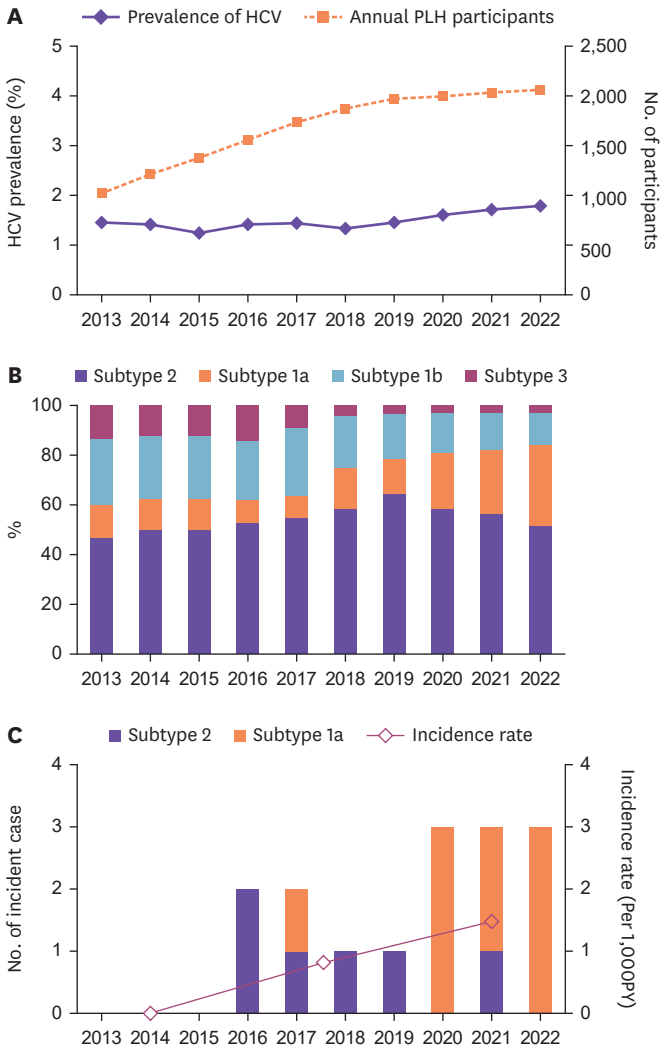

Figure 1. Prevalence and incidence of HCV coinfection. People living with HIV participants number and HCV prevalence of each year cohort (A). HCV subtype proportion of each year cohort (B). Number and subtype of incident HCV cases and incidence rate of HCV during the study period (C).
HCV, hepatitis C virus; HIV, human immunodeficiency virus.

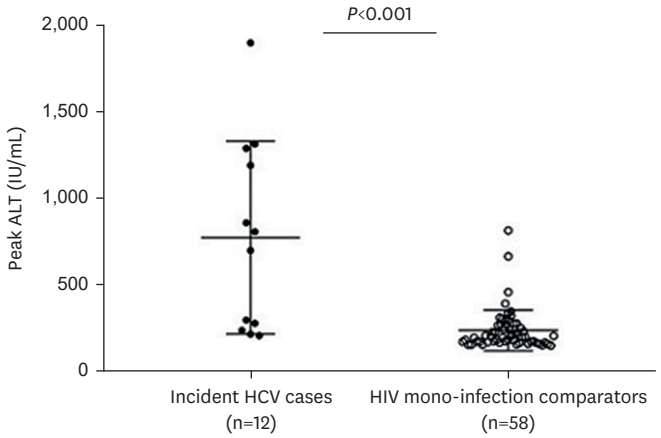

Figure 2. Peak ALT comparison between incident HCV cases and HIV mono-infection comparators among ALT>150 cohort.
ALT, alanine aminotransferase ; HCV, hepatitis C virus ; HIV, human immunodeficiency virus.

pneumonia, tuberculosis, acute HIV syndrome and acute hepatitis A infection. 11 were considered as toxic hepatitis and the other cases were related with alcohol dependency and chronic hepatitis B infection. Eventually, cohort of 58 HIV mono-infection with ALT>150 were constructed without plausible reason for ALT elevation and available negative Anti-HCV result after ALT>150 elevation events.

Twelve IHCVs cohort with ALT>150 was also constructed. Actually all 15 IHCV cases revealed ALT>150 at least once during the study period. However, three of them were excluded because ALT>150 occurred after HCV infection confirmation irrespective of IHCV event.

Comparing between twelve ALT>150 IHCVs with 58 HIV mono-infection ALT>150 comparators, mean peak ALT of IHCVs was higher than comparators (776 *vs.* 237, *P*=0.006, **Fig. 2**). While age, sex, HIV/HCV infection risk factor, and CD4/HIV-RNA viral load about the ALT>150 were not different between two groups, syphilis treatment within prior 24 months of ALT>150 was more frequent in IHCV group (41.7% *vs.* 12.7%, *P*=0.026).

DISCUSSION

In this study, prevalence of HCV among PLH was 1.63% and it is higher than general population of 0.6% in Korea [10]. Additionally, the prevalence/incidence rate of HCV among our study population revealed increasing trend of 1.43%/0.84 per 1000 person-year in 2016–2019 period and 1.79%/1.48 in 2020–2022, what was not observed in other studies targeting general population [12] and PLH cohort [11]. Korea Disease Control and prevention Agency (KDCA) report is revealing decreasing trend in nationwide HCV incidence, as 20.87 per 100,000PY in 2018, 18.92 (2019), 22.86 (2020), 19.55 (2021), 16.12 (2022), and 14.02 (2023) [13].

Regarding the genotype, subtype 2 was most common (48.7%) in our study followed by 1a (29.3%) and 1b (12.2%). According to the KDCA report, the prevalent genotypes in Korea are 2 (50%) and 1b (26.2%) in 2022 and these two types have constituted 80–90% of all cases irrespective of study period [12, 14]. Among HIV/HCV coinfection cohorts in Korea, the genotype distribution was also consistent with general population

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Table 1. Characterization of incident HCV infection cases

Conversion	Age	Sex	HCV infection risk factor[a]	Reason of HCV test	Peak ALT at seroconversion	Subtype	Antiviral treatment	Treatment outcome
2016	48	M	No record	Private medical check up	47	2	PEG-INF+RBV, 2017[b] SOF+RBV, 2019 SOF/VEL/VOX, 2023	Treatment failure Recur in 2023 SVR 48 wks
2016	34	M	None	LFT elevation	131	2	GLE/PIB, 2020	SVR 3 yrs
2017	38	M	No record	Pre-operation work up	209[c]	2a	SOF+RBV, 2018	Not available
2017	30	M	None[d]	LFT elevation	280	1a	GZR/EBR, 2017	SVR 7 yrs
2018	23	M	None	LFT elevation	1,901	2a	GLE/PIB, 2019	SVR 4 yrs
2019	66	M	None	LFT elevation	1,192	2a	GLE/PIB, 2021	SVR 2 yrs
2020	36	M	None	LFT elevation	1291	1a	LDV/SOF, 2021	SVR 2 yrs
2020	43	M	None	LFT elevation	217	1a	GLE/PIB, 2020	SVR 4 yrs
2020	36	M	None	LFT elevation	861	1a	GLE/PIB, 2020	SVR 3 yrs
2021	31	M	None[d]	LFT elevation	700	1a	Refuse to treat	Viremia state
2021	49	M	None	LFT elevation	809	1a	LDV/SOF, 2022[e] GLE/PIB, 2023	Recur in 40 wks SVR 48 wks
2021	51	M	None	LFT elevation	299	2	GLE/PIB, 2023	SVR 48 wks
2022	31	M	Tatoo	LFT elevation	144	1a	LDV/SOF, 2022	SVR 2 yrs
2022	42	M	No record	LFT elevation	1,316	1a	GLE/PIB, 2022	SVR 2 yrs
2022	42	M	None	LFT elevation	239	1a	GLE/PIB, 2022	SVR 2 yrs

[a]Injecting drug use, tatoo, transfusion, and acupuncture were considered as HCV infection risk factor.
[b]PEG-INF+RBV failed to obtain SVR. While SOF+RBV obtained SVR, HCV subtype 2 replication recurred in 2023 and SOF/VEL/VOX was administered.
[c]LFT elevation was considered as toxic hepatitis before the pre operation work up.
[d]Partner was HCV positive.
[e]HCV subtype 1a replication recurred 40 weeks after LDV/SOF treatment and GLE/PIB was administered.
HCV, hepatitis C virus; ALT, alanine aminotransferase; PEG-INF, pegylated interferon; RBV, ribavirin; SOF, sofosbuvir, VEL, velpatasvir; VOX, voxilaprevir; SVR, sustained viral response; LFT, lever function test; GLE, glecaprevir; PIB, pibrentasvir; GZR, grazoprevir; EBR, elbasvir; LDV, ledipasvir.

[11, 15]. In a recent study targeting 9,747 RNA confirmed HCV infection cases in Korean general population, the proportion of 1a was 2.2% [12], and 29.3% of our study is very uniquely high. The proportion of 1a among our clinic visitors was usually less than 10% until 2019. However, incidence rate of HCV revealed increasing trend from 0.84 per 1,000 person-year in 2016–2019 period to 1.48 in 2020–2022, and 88.9% (8/9) of IHCVs were 1a in 2020–2022 period. Notably, there has been healthcare associated genotype 1a outbreak in Korea reaching 41 cases in 2015 [16]. Patients were known to have received injections at a clinic between 2008 through 2015, where the infection control for injection practice had been breached. However, the injection practice in the clinic were for routine medical treatments such as intravenous fluid administration and there is no plausible relationship with genotype 1a IHCV cases of our clinic. HCV genotype proportion is variable according to geographic area and 1a is a prevalent one in North America, parts of South America, the United Kingdom, Scandinavia, and Australia [17]. Actually, global tracing of subtype 1a is of importance given that subtype 1a is associated with lower response rates for DAA treatment compared with other common genotypes [18].

Regarding the factors associated with IHCV among PLH or MSM, high risk sexual behavior, sexually transmitted infection, and IDU have been suggested [19-21]. One prior study about HIV/HCV coinfection in Korea, HCV was 16.2 times more prevalent among the IDU group and incidences of HCV of IDU and non-IDU group were 164.89 per 1,000PY and 1.40, respectively [11]. However, IDU was not documented as HCV risk factor among 12 IHCVs whose HCV risk factor information was available in our study. One case was with history of tattoo and two reported that their partners were contracted with HCV infection. While information regarding high risk sexual behavior such as condomless receptive anal sex was not available in our retrospective medical record review study, recent treatment history against incident syphilis within prior 24 months was more frequent in IHCVs among ALT>150 cohort in our study and this is in line with prior study [21].

Our study has several limitations. First, this study was a retrospective observational study and risk factors for HCV infection was available in limited cases. Second, our study was conducted at a single center and our findings may not be generalized.

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In conclusion, incidence of HCV among PLH revealed increasing trend and genotype 1a were more common among IHCVs after 2020. Among ALT>150 cohort, peak ALT of IHCVs was higher than comparators and syphilis treatment within prior 24 months of ALT elevation was more common in IHCV group.

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Conflict of Interest
No conflict of interest.

Author Contributions
Conceptualization: BSC, JYJ. Data curation: BSC. Formal analysis: BSC, YJK, JJH, MKK, HCK, SWN. Methodology: BSC, YJK, JJH, MKK, HCK, SWN. Project administration: BSC. Supervision: BSC, JYJ. Writing - original draft: BSC. Writing - review & editing: BSC, YJK, JJH, MKK, HCK, SWN.

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