Hepatitis C Virus Coinfection in People With Human Immunodeficiency Virus in Iran: A Systematic Review and Meta-Analysis

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Background. Hepatitis C virus (HCV) coinfection is associated with higher mortality and morbidity in people with human immunodeficiency virus (PWH).

Methods. We aimed to characterize the epidemiology and factors associated with HCV coinfection among PWH in Iran. In this systematic review, we searched 3 English databases (MEDLINE, SCOPUS, Embase) and 2 Farsi databases (Scientific Information Database and Magiran) for studies that measured the prevalence of HCV coinfection among PWH, published between 2000 and January 1, 2021. We included studies with a minimum sample size of 5 PWH. Reviews, editorials, conference abstracts, theses, studies with no relevant data, and unclear serological assays were excluded.

Results. We summarized the HCV coinfection prevalence by random-effect meta-analysis and assessed the sources of heterogeneity by a meta-regression model. Of the 858 records identified, 69 eligible studies with 12 996 PWH were included. Overall, HCV coinfection prevalence was 64% (95% confidence interval [CI], 58–69). The prevalence was higher among older (mean age ≥35 years) PWH (69%; 95% CI, 64–74) and PWH who inject drugs (77%; 95% CI, 71–82). Furthermore, we found that coinfection was higher among studies conducted between 2000 and 2014 (67%; 95% CI, 59–75) versus 2015–2020 (57%; 95% CI, 50–64).

Conclusions. The prevalence of HCV coinfection is high in Iranian PWH, with significant geographical variations. Hepatitis C virus screening and treatment among PWH are warranted to avoid the future burden of HCV-related liver damage, cancer, and mortality.

Keywords. coinfection; hepatitis C; human immunodeficiency virus; Iran; people with HIV.
2.8% of injection drug users are diagnosed with HIV [16]. Specific harm reduction standards were applied in Iran from 2002 until now. These programs included education, opioid substitution treatment by methadone and buprenorphine, and providing access to sterile syringes, needles, and condoms [14]. High-risk participants with confirmed HIV infection were referred to a voluntary counseling and testing center that developed an opportunity to undergo HCV antibody (Ab) testing and care [17].

Human immunodeficiency virus-HCV coinfection is associated with a markedly high risk of developing cirrhosis, hepatoma, and liver fibrosis progression [18, 19]. In the natural history of chronic HCV, viral and host factors play a considerable role in the course of HCV. In the setting of HIV-HCV coinfection, disrupted immune reaction and low CD4+ T-lymphocyte counts have consistently been shown to accelerate liver fibrosis progression [19, 20]. In addition, chronic HCV infection results in increased T-lymphocyte activation, thereby leading to increasing the possibility of sustained HIV infection. A multicenter, randomized clinical trial of 97 HIV-1 patients showed that HIV-HCV-coinfected patients seem to show a greater HIV-1 reservoir size compared to HIV monoinfected patients [21].

Although several national studies have estimated the prevalence of HIV-HCV coinfection, the exact size of coinfection is poorly evaluated. In Iran, several studies reported the prevalence of HIV-HCV coinfection with a wide range of 1.16% to 98% [11, 22–30]. Factors associated with such wide heterogeneity have not been studied. In previous studies, the impact of important factors including IDU, sex, age, and time of study on estimating the coinfection has been neglected [29, 30]. In this comprehensive systematic review and meta-analysis, we sought to estimate the prevalence of HIV-HCV coinfection in PWH in Iran and assessed the demographic and behavioral factors (IDU) associated with a heterogeneity of results.

METHODS

Search Strategy and Study Selection

This systematic review and meta-analysis were performed according to the Meta-analysis of Observational Studies in Epidemiology checklist [31] and PRISMA (preferred reporting items for systematic reviews and meta-analyses) standards [32]. We searched the literature for all studies published between 2000 and January 1, 2021 that evaluated the prevalence of HCV among PWH in Iran. Two experienced investigators (A.A. and S.-K.R.-A.) independently identified potentially relevant studies by electronic searches of MEDLINE (via PubMed), SCOPUS, Embase, Google Scholar, and 2 Persian databases, including Scientific Information Database and Magiran. Keywords for the search included “HIV”; “AIDS” OR “Acquired Immunodeficiency Syndrome”; AND “HCV”; “hepatitis C” OR “hepatitis C antibodies”; AND “Iran”. No limitation regarding language was placed. To achieve all additional studies, manual searches were performed via the references section of eligible studies. We screened the article by first reading the title and abstract and then the full text. Conflicting results were resolved through joint discussion. In a joint discussion, each of the authors noticed convincing evidence regarding the strengths and weaknesses of the articles. All retrieved studies were collected in EndNote to identify duplication.

Eligible studies for our analysis met the following criteria: (1) studies with the cohort, clinical trials, cross-sectional, and case-control designs that assessed the prevalence of HCV in PWH in Iran; and (2) studies that diagnosed HIV and HCV with standard laboratory tests (enzyme-linked immunosorbent assay and molecular diagnostic assays). Exclusion criteria included the following: reviews, editorials, conference abstracts, theses, duplicates, studies with less than 5 PWH sample size, studies with no relevant data, and unclear serological assays.

Data Extraction

Data for the first author, year of study, setting of patients, city, type of HIV diagnostic test, HIV sample size, the median age of patients, male proportion, IDU proportion, type of HCV diagnostic test, and HCV/HIV coinfection size were separately extracted by 2 researchers (A.A. and S.-K.R.-A.). We reached out to the corresponding author of studies with unclear data or unavailable full text via E-mail.

The quality of eligible studies was independently evaluated by 2 authors (A.A. and S.-K.R.-A.) using the Joanna Briggs Institute (JBI) checklist [33]. The JBI critical appraisal checklist for systematic reviews assesses the quality of retrieved studies by examining 8 items to consider the risk of bias. A score less than 5 indicated insufficient study quality. Discrepancies were resolved through discussion.

Data Analysis

We used the Metaprop command using STATA version 14 (StataCorp, College Station, TX) for pooling the HCV coinfection among PWH. We estimated 95% confidence interval (CI) using the score statistic, the exact binomial method, and the Freeman-Tukey double arcsine transformation of proportions. Heterogeneity of the prevalence estimated between studies was assessed by Q statistic and I^2 index, assuming that I^2 values of 25%, 50%, and 75% represented low, medium, and high heterogeneity, respectively. Q statistic is a measure of weighted squared deviation on a standardized scale and compared with the expected sum of squares (on the assumption that all studies share a common effect) to yield a test of null and estimate excess variance. I^2 is the proportion of observed dispersion that is real, rather than spurious, and not dependent on the scale [34]. We assessed the quality of each study using JBI. Forest plots were drawn displaying the variation of the HCV Ab test
positivity rate among all PWH (HIV/HCV coinfection proportion) together with the pooled measure and subgroup analysis.

Egger's weighted regression method was used to test for publication bias, with \( P < .1 \) indicative of statistically significant publication bias. In the case of publication bias, we will report estimates after adjusting for publication bias using the trim-and-fill method.

We assessed the heterogeneity effect of several characteristics (age, male proportion, IDU proportion, and HIV and HCV route diagnostic tests) using meta-regression.

The pooled prevalence of HCV coinfection in PWH was reported for 5 subregions: (1) North-Central region: Tehran, Qazvin, Mazandaran, Semnan, Golestan, Alborz, and Qom province; (2) South-Central region: Esfahan, Fars, Bandar Bushehr, Chaharmahal and Bakhtiari, Hormozgan, Kohgiluyeh, and Boyer-Ahamd province; (3) Northwest region: East Azerbaijan, West Azerbaijan, Ardabil, Zanjan, Gilan, and Kurdistan province; (4) Southwest region: Kermanshah, Ilam, Lorestan, Hamedan, Markazi, and Khuzestan province; (5) East region: Razavi Khorasan, South Khorasan, North Khorasan, Kerman, Yazd, Sistan, and Baluchestan province.

**Patient Consent and Ethical Approval**

The design of the work was approved by the Ethics Committee of Mazandaran University of Medical Science. All procedures performed in studies are in accordance with the ethical standards of the institutional and/or national research committee of Iran.

### RESULTS

We identified 858 articles, 533 (62%) of which were duplicates and removed (Figure 1). We screened the title and abstract of 325 papers and read the full text of 84 articles. Of those, 16 articles were excluded for one of the following reasons: HIV–HCV coinfection was reported among HCV-positive individuals (5); the full text was not available (1); the sample size was less than 5 (4); insufficient statistics (6). Finally, we extracted data from 69 articles for analysis (Table 1). The 69 articles enrolled a total of 12 996 PWH, the majority from Tehran. As shown in Figure 2, the overall prevalence of HCV coinfection was 64.0% (95% CI, 58–69) among PWH. After the removal of 7 low-quality studies (total quality score below 5), pooling of these 62 studies (11 790 individuals) yielded an overall prevalence of HIV/HCV coinfection 64 (95% CI, .58–.71) per 100 PWH in Iran. Egger’s test indicated no publication bias (\( P = .19 \)).

**Meta-Regression Analysis**

Unadjusted meta-regression analysis showed that the prevalence of HCV coinfection increased by 1.4% (95% CI, 4–2.4; \( P = .007 \)) with each year increase in age and increased by 0.4% (95% CI, 2–6; \( P < .001 \)) with each 1% increase in the prevalence of injecting drug use among the study sample. Table 2 showed that after adjustment of other variables, the prevalence of HCV coinfection was associated with older age (\( P = .049 \)) and injecting drug use (\( P = .03 \)). Furthermore, we noticed a reduction in HCV-HIV coinfection over time. From 2015 (a year when the annual number of PWH and related deaths remained relatively constant [5]) to 2020, the coinfection was 11% lower than from 2000 to 2014 (\( P = .02 \)).

We observed that the prevalence of HCV coinfection was 61% and 69% among PWH with a mean age of less than 35 years and equal or more than 35 years (approximate combined mean), respectively (Table 3 and Figure 3).

The prevalence of HCV coinfection among PWH was 67% and 57% among PWH in the studies conducted in 2000–2014 and 2015–2020, respectively (Table 3 and Figure 4).

As shown in Table 3 and Figure 5, we found that the prevalence of HCV coinfection was 57% among PWH with IDU proportion of less than 75% and 77% among PWH with IDU proportion equal to or more than 75%.

Regarding the geographical disparities in HCV-HIV coinfection, the prevalence of HCV coinfection was 64% in North-Central, 75% in South-Central, 51% in Northwest, 61% in Southwest, and 59% in the East (Table 3 and Figure 6).

### DISCUSSION

To our best knowledge, this is the first systematic review and meta-analysis of the prevalence of HCV coinfection in PWH by the conditional probability method in Iran. Few studies measured the effect of confounding factors on HCV coinfection among PWH in Iran [29]. Based on the findings of our meta-analysis, we found that 64% of PWH in Iran are coinfected with HCV. In other words, 1 in 1.56 PWH is coinfected with HCV. With an estimated 54 000 PWH in Iran, we could expect 34 560 of these people to be infected with HCV [4]. The preliminary studies that were included have been conducted in only 15 (of 31 provinces of Iran) provinces. However, from each of the 5 regions of Iran, which are divided by the Ministry of Interior of Iran based on the proximity, geography, and cultural commonalities, we have identified several studies and examined them in this study.

In the current review, we estimated that the greatest burden of this coinfection is in the South-Central region (including the provinces of Isfahan and Fars), followed by the North-Central region (including Tehran, the capital of Iran). The lowest prevalence of HIV–HCV coinfection was observed in the Northwestern regions of Iran (including the provinces of East Azerbaijan, West Azerbaijan, and Kurdistan), corresponding to a prevalence of 51%. There is no geographical variability in antinarcotic law in Iran. However, it is consistent with other studies in terms of resource limitations and deaths due to the consumption of these substances [94].
Recent evidence indicated that during the years 2009–2017, the Central provinces of Iran always showed the highest incidence of HIV infection and the Western provinces (such as West Azerbaijan and Kurdistan) showed the lowest incidence of this infection [95]. Until 2015, the most important route of HIV infection in Iran was intravenous drug injection. Reports from the Ministry of Health of Iran showed that the transmission of infection by intravenous drug injection from 2000 to 2017 was evaluated at 67.6%, 67.3%, 70.4%, 69.6%, 78.1%, 84.5%, 75.4%, 77.3%, 74.9%, 71.1%, 66.6%, 62.6%, 57.8%, 50.4%, 47.7%, 43.4%, 43.4%, and 33.2%, respectively [4]. These numbers revealed that, until 2015, parenteral transmission remained the mainstay for contracting HIV infection in Iran, and simultaneously HCV infection could be considered probable.

In the current study, HIV/HCV coinfection was more common in older age. Numerous previous studies in Iran have shown that older individuals, especially older injecting drug users, are more vulnerable to being infected with HIV [4]. The higher prevalence of this coinfection in older PWH could result from the cumulative effects of HCV exposure in the elderly, the lack of coverage, and the impact of risk reduction

Figure 1. Flowchart of included studies. HCV, hepatitis C virus; HIV, human immunodeficiency virus; SID, Scientific Information Database.
| Author            | Year | City    | District       | HIV Sample Size (N) | Coinfection Sample Size (N) | Mean Age, Year | Male Proportion | IDU* % | HIV Test | HCV Test |
|-------------------|------|---------|----------------|--------------------|-----------------------------|----------------|----------------|--------|----------|----------|
| Ramezani et al    | 2012 | Arak    | Southwest      | 19                 | 15                          | 33.3           | 100            | 100    | ELISA    | Third-generation ELISA |
| Rahimi-movaghar et al | 2007 | Tehran  | North Central  | 52                 | 37                          | 33.87          | 95.77          | 100    | ELISA    | Third-generation ELISA |
| Rahimi-movaghar et al | 2007 | Tehran  | North Central  | 44                 | 41                          | 33.87          | 95.77          | 100    | ELISA    | Third-generation ELISA |
| Salem et al       | 2009 | Karaj   | North Central  | 12                 | 3                           | 34.6           | 100            | 41/8   | ELISA    | Third-generation ELISA |
| SeyedAlinaghi et al | 2005 | Tehran  | North Central  | 201               | 135                         | 36             | 85.57          | 33/3   | ELISA    | Third-generation ELISA |
| Sharif-Mood et al | 2005 | Zahedan | East           | 47                 | 19                          | 37.5           | 89.36          | 12/77  | ELISA and Western blot | Fourth-generation ELISA |
| Sofian et al      | 2009 | Arak    | Southwest      | 9                  | 8                           | 30.7           | 100            | 100    | ELISA and Western blot | Third-generation ELISA |
| Zahedi et al      | 2011 | Kerman  | East           | 165                | 122                         | 40.4           | 82.4           | 76.2   | ELISA and Western blot | Third-generation ELISA |
| Afhami et al      | 2005 | Tehran  | North Central  | 85                 | 58                          | 35/2           | 85.9           | 51/8   | ELISA    | Third-generation ELISA |
| Alavi et al       | 2006 | Ahwaz   | Southwest      | 18                 | 12                          | 26/3           | 91.5           | 100    | ELISA    | Third-generation ELISA |
| Rezaianzadeh et al | 2012 | Shiraz  | South Central  | 1338               | 1044                        | 36             | 84.75          | 73/8   | ELISA and Western blot | Third-generation ELISA |
| Ailpour et al     | 2013 | Shiraz  | South Central  | 1444               | 1132                        | 38.4           | 82.2           | 74.1   | ELISA and Western blot | Third-generation ELISA |
| Ataei et al       | 2007 | Isfahan | South Central  | 130                | 100                         | 50.23          | 98.5           | 83.5   | ELISA and Western blot | Third-generation ELISA |
| Babamahmoodi et al | 2010 | Sari    | North Central  | 80                 | 47                          | 37             | 82.5           | 81.5   | ELISA and Western blot | Third-generation ELISA |
| Bagheri Amiri et al | 2012 | Tehran  | North Central  | 20                 | 17                          | ...            | 90             | 90     | ELISA    | Third-generation ELISA |
| Etminani-Esfahani et al | 2012 | Tehran  | North Central  | 98                 | 54                          | 40.25          | 74             | 55.7   | ELISA    | Third-generation ELISA |
| Honavar et al     | 2013 | Shiraz  | South Central  | 23                 | 18                          | 30.4           | 85.06          | 40.94  | ELISA and Western blot | Third-generation ELISA |
| Hosseini et al    | 2006 | Tehran  | North Central  | 112                | 100                         | ...            | 100            | 100    | ELISA and Western blot | Third-generation ELISA |
| Javadi et al      | 2009 | Isfahan | South Central  | 6                  | 6                           | 35.1           | ...            | 100    | ELISA and Western blot | Third-generation ELISA |
| Keramat et al     | 2007 | Hamedan | Southwest      | 15                 | 13                          | 29.7           | 71.5           | 52.5   | ELISA and Western blot | Third-generation ELISA |
| Khoosravi et al   | 2010 | Shiraz  | South Central  | 101                | 87                          | 35             | 88.11          | 85.14  | ELISA and Western blot | Third-generation ELISA |
| Mansoori et al    | 2000 | Tehran  | North Central  | 44                 | 39                          | 38             | 91             | 75     | ELISA and Western blot | Third-generation ELISA |
| MirNasseri et al  | 2011 | Tehran  | North Central  | 70                 | 61                          | 35.24          | 89.5           | 88.8   | ELISA and Western blot | Third-generation ELISA |
| Mohammadi et al   | 2008 | Lorestan | Southwest      | 391                | 282                         | 40.5           | 91.6           | 51.6   | ELISA and Western blot | Third-generation ELISA |
| Davarpanah et al  | 2007 | Shiraz  | South Central  | 226                | 200                         | 35.6           | 94.7           | 79.2   | ELISA and Western blot | Third-generation ELISA |
| Majidpour et al   | 2008 | Tehran  | North Central  | 12                 | 9                           | 33.52          | 91.5           | 100    | ELISA and Western blot | Third-generation ELISA |
| Alavi et al       | 2003 | Ahwaz   | Southwest      | 104                | 77                          | 28             | 100            | 100    | ELISA and Western blot | Third-generation ELISA |
| Ramezani et al    | 2005 | Tehran  | North Central  | 95                 | 65                          | 33.8           | 83             | 55.33  | ELISA    | Third-generation ELISA |
| Moradmand Badie et al | 2009 | Tehran  | North Central  | 365                | 225                         | 30.5           | 79.7           | 50.9   | ELISA and Western blot | Third-generation ELISA |
| Author          | Year | City        | District       | HIV Sample Size (N) | Coinfection Sample Size (N) | Mean Age, Year | Male Proportion | IDU% | HIV Test                        | HCV Test                            |
|-----------------|------|-------------|----------------|--------------------|-----------------------------|----------------|-----------------|------|--------------------------------|-------------------------------------|
| Taeri et al [60] | 2007 | Isfahan     | South Central  | 106                | 90                          | 50.8           | 100             | 100  | ELISA and Western blot         | Third-generation ELISA               |
| Aminzadeh et al [61] | 2007 | Tehran      | North Central  | 21                 | 14                          | 34.4           | 100             | 100  | ELISA                           | Third-generation ELISA               |
| Azami et al [62] | 2010 | Tehran      | North Central  | 200                | 118                         | 36.5           | 76.5            | 56   | ELISA and Western blot         | Third-generation ELISA               |
| Khorvash et al [63] | 2005 | Isfahan     | South Central  | 9                  | 9                           | 31.7           | 96.91           | 100  | ELISA and Western blot         | Third-generation ELISA               |
| Tabarsi et al [64] | 2003 | Tehran      | North Central  | 15                 | 12                          | 36.9           | 87              | 87   | ELISA and Western blot         | Fourth-generation ELISA              |
| Ramezani et al [65] | 2005 | Tehran      | North Central  | 171                | 90                          | 37             | 80.7            | 68.4 | ELISA and Western blot         | Third-generation ELISA               |
| Ramezani et al [66] | 2014 | Tehran      | North Central  | 92                 | 63                          | 36.7           | 71.7            | 49   | ELISA and Western blot         | Third-generation ELISA               |
| Mozgani et al [67] | 2014 | Kashan      | South Central  | 63                 | 54                          | 34.91          | 96.8            | 100  | ELISA                           | Third-generation ELISA               |
| Donyavi et al [11] | 2018 | Tehran      | North Central  | 161                | 134                         | 38.9           | 95              | 100  | ELISA and Western blot         | Third-generation ELISA               |
| Jamshidi et al [26] | 2017 | Tehran      | North Central  | 190                | 85                          | 36.5           | 63.2            | 43.2 | ELISA and Western blot         | Third-generation ELISA               |
| Emamghani-Dehaj et al [69] | 2015 | Tehran      | North Central  | 140                | 62                          | 35.7           | 64.2            | 42.14| ELISA and Western blot         | Fourth-generation ELISA              |
| Teimoori et al [18] | 2016 | Ahwaz       | Southwest      | 390                | 229                         | 32             | ...             | 99.1 | ELISA and Western blot         | Third-generation ELISA               |
| Bokharaei-Salim et al [70] | 2014 | Tehran      | North Central  | 109                | 50                          | 35.2           | 61.5            | 41.3 | ELISA                           | Fourth-generation ELISA              |
| Sabouri et al [71] | 2009 | Tehran      | North Central  | 214                | 131                         | 36.52          | 80.8            | ...  | ELISA                           |                                   |
| Zayedi et al [72] | 2017 | Ahwaz       | Southwest      | 78                 | 25                          | 33.04          | 85.89           | 83.3 | Fourth-generation ELISA         |                                   |
| Moradi et al [12] | 2017 | 8 provinces | North Central  | 38                 | 17                          | 36             | 84              | 13.4 | ELISA and Western blot         | Third-generation ELISA               |
| Farhoudi et al [73] | 2013 | Tehran      | North Central  | 85                 | 50                          | ...            | ...             | ...  | ELISA                           |                                   |
| Doosti-Irani et al [27] | 2015 | Khorramabad | Southwest      | 20                 | 17                          | 35.9           | 100             | 38.76| ELISA                           |                                   |
| Hashemi-Shahri et al [74] | 2007 | Zahedan     | East           | 41                 | 13                          | ...            | 73.1            | ...  | ELISA                           | Third-generation ELISA               |
| Vaziri et al [75] | 2007 | Kermanshah  | Southwest      | 888                | 60                          | 30.7           | 97.9            | ...  | ELISA                           | Third-generation ELISA               |
| Saieh et al [76] | 2013 | Khorramabad | Southwest      | 50                 | 26                          | ...            | 49.5            | ...  | ELISA                           | Third-generation ELISA               |
| Haghighi et al [77] | 2012 | East Azerbaijan | Northwest    | 371                | 168                         | 30.8           | 91              | 59   | ELISA                           |                                   |
| Maracy et al [78] | 2014 | Isfahan     | South Central  | 205                | 97                          | 37.1           | 78              | 62   | ELISA and Western blot         | Third-generation ELISA               |
| Hassanzadeh et al [79] | 2011 | Shiraz      | South Central  | 180                | 47                          | ...            | 66.7            | ...  | ELISA                           |                                   |
| Advay et al [80] | 2015 | Sanandaj    | Northwest      | 165                | 121                         | 38.3           | 83              | 100  | ELISA and Western blot         | Third-generation ELISA               |
| Geibi et al [81] | 2017 | Shiraz      | South Central  | 1216               | 794                         | 34             | 74.2            | 67   | ...                             |                                   |
| Sani et al [82] | 2017 | Mashhad     | East           | 64                 | 53                          | ...            | 95.3            | 90.6 | ELISA and Western blot         | Third-generation ELISA               |
| Joulaei et al [83] | 2013 | Shiraz      | South Central  | 101                | 76                          | 39.1           | 70.9            | 17.1 | ELISA                           |                                   |
| Koochak et al [84] | 2009 | Tehran      | North Central  | 200                | 121                         | ...            | 72              | ...  | ELISA and Western blot         |                                   |
| Khazaee et al [85] | 2013 | Aabadan, khoramshahr | Southwest     | 366                | 172                         | ...            | 85.5            | 73.4 | ELISA and Western blot         | ELISA                             |
| Hajabdolbaghi et al [86] | 2010 | Tehran      | North Central  | 555                | 331                         | 36.59          | 84.9            | 75.1 | ELISA                           | ELISA                             |
A recent study by Bakhti et al. [92] in 2016 in Mazandaran North Central region showed 83 cases with a mean age of 41.7 years, male proportion of 85, 77.2% ELISA and Western blot, and 60.8% PCR. Shadmand et al. [93] in 2015 in Jahrom South Central area reported 73 cases with a mean age of 35 years, male proportion of 100, 80.8% ELISA and Western blot, and 56.2% PCR. Amini et al. [91] in 2016 in Sanandaj Northwest region reported 185 cases with a mean age of 39.26 years, male proportion of 100, 61.4% ELISA and Western blot, and 56.2% PCR. Foroughi et al. [90] in 2013 in Tehran North Central area reported 481 cases with a mean age of 15.62 years, male proportion of 95.55, 22.22% ELISA and Western blot, and 56.2% PCR. Khodadadi et al. [89] in 2010 in Sanandaj Northwest region reported 97 cases with a mean age of 34 years, male proportion of 100, 61.4% ELISA and Western blot, and 56.2% PCR. Pourahmad et al. [88] in 2003 in Esfahan, Chaharmahal Bakhtiyari, and Lorestan region reported 92 cases with a mean age of 8 years, male proportion of 100, 60.8% ELISA and Western blot, and 56.2% PCR. Table 1. Continued

| Author              | Year | City               | District                      | Sample Size (N) | Sample Size (N) | Mean Age, Years | Male Proportion | IDU% | HIV Test                  | HCV Test                  |
|--------------------|------|--------------------|-------------------------------|-----------------|-----------------|----------------|-----------------|------|--------------------------|--------------------------|
| Hosseini rad et al | 2014 | Tehran             | North Central                 | 481             | 356             | 41.7           | 85              | 77.2 | ELISA and Western blot   | Third-generation ELISA    |
| Pourahmad et al    | 2003 | Esfahan, Chaharmahal Bakhtiyari, and Lorestan | South Central, Southwest | 92              | 8               | ...            | 100             | 60.8 | ELISA and Western blot   | Third-generation ELISA    |
| Khodadadi et al    | 2010 | Sanandaj           | Northwest                     | 97              | 30              | 34             | 100             | 77.2 | ELISA and Western blot   | Third-generation ELISA    |
| Foroughi et al     | 2013 | Tehran             | North Central                 | 45              | 5               | 15.62          | 95.55           | 22.22| ELISA                    | Third-generation ELISA    |
| Amini et al        | 2016 | Sanandaj           | Northwest                     | 185             | 99              | 39.26          | 76.1            | 61.4 | ELISA and Western blot   | Fourth-generation ELISA    |
| Bakhti et al       | 2016 | Mazandaran         | North Central                 | 83              | 35              | ...            | 60.24           | ...  | PCR                      | ELISA                    |
| Shadmand et al     | 2015 | Jahrom             | South Central                 | 73              | 45              | ...            | 72.6            | ...  | ELISA                    | ELISA                    |

Abbreviations: ELISA, enzyme-linked immunosorbent assay; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injection drug user; PCR, polymerase chain reaction.

*aThe IDU refers to percentage of people with HIV who inject drugs.

strategies and other prevention programs in recent years in Iran [96]. In addition, we noticed that very low HCV coinfection in some studies was associated with a lower mean age of PWH [75, 88, 90].

Trends of shared injection and unprotected sexual contact have significantly increased in Iran. For 18 years from 2000 to 2017, the prevalence of sexual route of HIV infection in Iran has been estimated at 5%, 5.2%, 6.4%, 6.8%, 7.6%, 7.2%, 8.4%, 12.6%, 15.2%, 19.2%, 21.8%, 26.4%, 29.5%, 36.2%, 36.5%, 38.7%, 47.6%, and 46%, respectively [4]. We observed that coinfection prevalence has reduced to 11% among studies conducted after 2015 compared to those performed before 2015. Given the lower likelihood of transmitting HCV infection through sexual contact and the increasingly more effective coverage of national HIV programs implemented in Iran in recent years [14], we could expect a reduced prevalence of coinfection in studies conducted from 2015 onwards.

Based on the Iranian HIV Patient Registry System, at the end of 2019, of 22,054 cases, 14,311 (64.89%) and 6376 individuals (28.91%) were infected through intravenous injection and sexual contact, respectively [4, 97, 98]. Of special consideration, female partners of IDUs in Iran have always been considered one of the most high-risk groups for HIV in Iran. Previous studies have also shown a significantly higher risk of transmitting HCV infection within couples with at least 1 individual diagnosed with HIV [44, 99]. This information implies that we should ponder the likelihood of contracting these 2 infections simultaneously, either at the time of HIV infection or after its initial acquisition (individually or in dyads) as a crucial health issue. Because drug users are not prosecuted during the treatment period, according to the antinarcotics Law in Iran, there is a golden opportunity for these people for HIV and HCV infection screening.

In Iran, relatively good national programs for the prevention and management of HIV infection in 4 phases have been implemented since 2002. In the first phase (2002–2006), these programs focused on public awareness, risk reduction for injecting drug users, and mother-to-child transmission. Afterward, in the second (2007–2010) and third (2011–2015) phases, in addition to strengthening the first phase programs, the greatest concentration was placed on youth education. In the fourth phase (2016–2020), the main focus was on achieving the goals of UNAIDS and the 90-90-90 policy [4]. According to the 90-90-90 policy, by 2020, 90% of PWH will be aware of their HIV status, 90% of whom will receive ART, and 90% of PWH receiving antiretroviral therapy will have sustained viral suppression [100]. A recent study showed that 59,314 PWH live in Iran, 22,054 (37% of PWH) of whom were diagnosed with the infection. At the end of 2019, 25% of PWH received antiretroviral treatment. Furthermore, 11% of PWH achieved sustained viral load suppression by 2019. These reports clearly emphasized that further accurate programs are needed for prompt diagnosis of HIV infection in the general population and high-risk groups (especially PWID, their partners, and female sex worker groups) [101].

Our study had some limitations. First, we could not find a documented report to accurately estimate this coinfection in PWH from some provinces of Iran. However, the trim-and-fill analysis revealed that if reports were conducted in all Iran provinces, we would not have seen much change, and this simultaneous infection in PWH is approximately 58% (95% CI, 64–53). Second, different HIV and HCV diagnostic methods of
preliminary studies may be another limitation of our research, which may be one of the reasons for the observed heterogeneity. We made our best effort to reduce heterogeneity effects by performing stratified analysis. The correlation between the anti-HCV level and HCV ribonucleic acid (RNA) is another issue. However, in the literature, a positive correlation

| Study                  | ES (95% CI) | % Weight |
|------------------------|-------------|----------|
| Ramezani, A. et al.    | 0.70 (0.57, 0.87) | 1.44     |
| Rahimi-Movaghar, A. et al. | 0.71 (0.58, 0.82) | 1.62     |
| Rahimi-Movaghar, A. et al. | 0.65 (0.59, 0.69) | 1.59     |
| Saehr, F. et al.       | 0.35 (0.28, 0.43) | 0.31     |
| Seyedi-Moghadam, S. et al. | 0.57 (0.36, 0.77) | 1.71     |
| Shariati-Mir, B. et al. | 0.40 (0.29, 0.52) | 1.05     |
| Sokhan, M. et al.      | 0.50 (0.37, 0.63) | 1.21     |
| Zadeh, M. et al.       | 0.74 (0.67, 0.80) | 1.73     |
| Al-Hassan, S. et al.   | 0.65 (0.59, 0.70) | 1.66     |
| Alikhani, M. et al.    | 0.67 (0.44, 0.84) | 1.42     |
| Alikhani, M. et al.    | 0.62 (0.49, 0.73) | 1.62     |
| Rezaei-Pazand, A. et al. | 0.79 (0.76, 0.83) | 1.74     |
| Alipour, A. et al.     | 0.76 (0.73, 0.79) | 1.74     |
| Akbari, S. et al.      | 0.71 (0.65, 0.78) | 1.72     |
| Babasani-Moaddi, F. et al. | 0.50 (0.48, 0.53) | 1.65     |
| Bagheri-Amin, F. et al. | 0.88 (0.84, 0.91) | 1.45     |
| Emranzadeh, M. et al.  | 0.55 (0.45, 0.65) | 1.67     |
| Heravi, B. et al.      | 0.78 (0.78, 0.81) | 1.71     |
| Hossaini, M. et al.    | 0.85 (0.82, 0.87) | 1.68     |
| Jouhari, A. et al.     | 1.00 (0.96, 1.03) | 1.07     |
| Khadem, P. et al.      | 0.67 (0.62, 0.72) | 1.38     |
| Khodrav, A. et al.     | 0.86 (0.78, 0.92) | 1.82     |
| Moezoon, S. et al.     | 0.86 (0.78, 0.93) | 1.58     |
| Mir-Hassani, M. et al. | 0.87 (0.77, 0.95) | 1.65     |
| Mohammadi, M. et al.   | 0.72 (0.67, 0.78) | 1.72     |
| Dolehpoor-Afshari, M. et al. | 0.88 (0.84, 0.90) | 1.71     |
| Alkabi, S. et al.      | 0.74 (0.69, 0.80) | 1.68     |
| Ramezani, A. et al.    | 0.66 (0.62, 0.70) | 1.67     |
| Monemzadeh-Balali, B. et al. | 0.67 (0.62, 0.73) | 1.68     |
| Tofigh, K. et al.      | 0.85 (0.77, 0.93) | 1.68     |
| Amirozamani, Z. et al. | 0.67 (0.61, 0.73) | 1.48     |
| Khodrav, P. et al.     | 1.02 (0.95, 1.08) | 1.21     |
| Tabarsi, A. et al.     | 0.82 (0.76, 0.88) | 1.38     |
| Ramezani, A. et al.    | 0.63 (0.56, 0.71) | 1.79     |
| Ramezani, A. et al.    | 0.66 (0.60, 0.72) | 1.67     |
| Moosavifard, S. et al. | 0.54 (0.48, 0.63) | 1.61     |
| Afshar, H. et al.      | 0.86 (0.79, 0.94) | 1.64     |
| Dejnavi, F. et al.     | 0.82 (0.77, 0.88) | 1.79     |
| Jamshidi, S. et al.    | 0.45 (0.38, 0.51) | 1.71     |
| Delivani-Dalal, F. et al. | 0.44 (0.36, 0.52) | 1.68     |
| Tavangar, A. et al.    | 0.50 (0.44, 0.56) | 1.73     |
| Kohandel-Balali, F. et al. | 0.46 (0.37, 0.55) | 1.68     |
| Sabouri, S. et al.     | 0.61 (0.55, 0.67) | 1.71     |
| Zarei, S. et al.       | 0.50 (0.43, 0.57) | 1.66     |
| Moradi, G. et al.      | 0.45 (0.36, 0.53) | 1.57     |
| Derakhshani-Arani, A. et al. | 0.88 (0.84, 0.91) | 1.45     |
| Hashemi-Shafie, S. et al. | 0.32 (0.20, 0.47) | 1.58     |
| Vaeidi, S. et al.      | 0.57 (0.50, 0.63) | 1.73     |
| Salahi, F. et al.      | 0.82 (0.79, 0.86) | 1.61     |
| Heydari, B. et al.     | 0.48 (0.40, 0.57) | 1.72     |
| Nooray, N. et al.      | 0.56 (0.49, 0.64) | 1.71     |
| Agha, S. et al.        | 0.73 (0.69, 0.79) | 1.79     |
| Ghalb, Z. et al.       | 0.50 (0.36, 0.63) | 1.74     |
| Sami, A. et al.        | 0.82 (0.73, 0.92) | 1.84     |
| Hosseini, H. et al.    | 0.61 (0.54, 0.67) | 1.71     |
| Khazaei, S. et al.     | 0.47 (0.42, 0.52) | 1.72     |
| Hoseini, M. et al.     | 0.74 (0.70, 0.78) | 1.73     |
| Pourokhsh, M. et al.   | 0.09 (0.04, 0.16) | 1.67     |
| Khodadadi, L. et al.   | 0.31 (0.23, 0.41) | 1.67     |
| Farnahi, M. et al.     | 0.11 (0.03, 0.20) | 1.68     |
| Amiri, S. et al.       | 0.54 (0.48, 0.61) | 1.79     |
| Balavi, M. et al.      | 0.64 (0.58, 0.72) | 1.68     |
| Chavoshi (P2) (p = 0.07, 23.8%, p = 0.05) | 0.54 (0.58, 0.72) | 100.00   |

Figure 2. Prevalence of human immunodeficiency virus (HIV)-hepatitis C virus (HCV) coinfection in people with HIV in Iran. CI, confidence interval; ES, effect size.
Table 2. Meta-Regression Results for Univariate and Multiple (Adjusted Effect) Models Assessing the Effect of Age, Male Proportion, and IDU Proportion, Year of Study, HIV and HCV Route Diagnostic Tests on the Prevalence of HIV/HCV Coinfection in Iranian People

| Parameters                           | Unadjusted β (95% CI)     | P value | Adjusted β (95% CI)     | P Value |
|--------------------------------------|---------------------------|---------|-------------------------|---------|
| Age, year                            | 0.014 (0.001–0.018)       | .007    | 0.009 (0.004–0.024)     | .049    |
| Year (2015–2021 vs 2000–2014)        | −0.07 (−.18 to .05)       | .26     | −0.11 (−.19 to −.02)    | .02     |
| Male proportion                       | 0.004 (0.009)             | .12     | 0.002 (−0.003 to 0.006) | .41     |
| IDU proportion                        | 0.004 (0.002–0.006)       | <.001   | 0.003 (0.002–0.005)     | .03     |
| HIV route diagnostic test (ELISA vs ELISA and Western blot) | 0.1 (−.23) | .07 | 0.01 (−.11 to .13) | .83 |
| HCV route diagnostic test (Third generation vs fourth generation ELISA test) | −0.15 (−.31 to −.02) | .8 | −0.08 (−.22 to .07) | .28 |

Abbreviations: CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injection drug user; PCR, polymerase chain reaction.

Table 3. The Prevalence of HCV Coinfection in Different Subgroups of PWH

| Parameter                  | Number of Studies | HIV Sample Size | I², % | Overall Estimate (95% CI) |
|----------------------------|-------------------|-----------------|-------|---------------------------|
| Age, Year                  |                   |                 |       |                           |
| <35                        | 20                | 3948            | 98.54 | 61 (47–75)                |
| ≥35                        | 33                | 6814            | 93.39 | 69 (64–74)                |
| Year of Studies            |                   |                 |       |                           |
| 2000–2014                  | 47                | 8439            | 98.19 | 67 (59–75)                |
| 2015–2020                  | 15                | 3351            | 93.18 | 57 (50–64)                |
| IDU, Percentage            |                   |                 |       |                           |
| <75                        | 28                | 7448            | 96.38 | 57 (50–63)                |
| ≥75                        | 28                | 2866            | 91.05 | 77 (71–82)                |
| Geographic Areas           |                   |                 |       |                           |
| North Central              | 27                | 3250            | 92.14 | 64 (58–70)                |
| South Central              | 13                | 4959            | 96.94 | 75 (68–83)                |
| Northwest                  | 4                 | 818             | 94.2  | 51 (38–66)                |
| Southwest                  | 13                | 2408            | 98.78 | 61 (41–80)                |
| East                       | 4                 | 317             | 93.53 | 59 (35–80)                |

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injection drug user; PWH, people with HIV.

Figure 3. (A) Prevalence of human immunodeficiency virus (HIV)-hepatitis C virus (HCV) coinfection in people with HIV with mean age less than 35 years (A) and equal to or more than 35 years (B). CI, confidence interval; ES, effect size.
between serum anti-HCV level and HCV RNA supported the hypothesis that the positivity of HCV RNA can be anticipated by the anti-HCV status [102]. Third, HCV infection was detected by anti-HCV assays, so our results showed past exposure and may not reflect the active HCV infection among PWH.

Figure 4. Prevalence of hepatitis C virus (HCV) coinfection in people with human immunodeficiency virus (HIV) in years 2000–2014 (A) and 2015–2020 (B). CI, confidence interval; ES, effect size.

Figure 5. Prevalence of hepatitis C virus (HCV) coinfection among people with human immunodeficiency virus (HIV) with injection drug user (IDU) proportion less than 75% (A) and equal to or more than 75% (B). CI, confidence interval; ES, effect size.
CONCLUSIONS

Our study showed that PWH continues to have a high prevalence of HCV coinfection. Screening for HCV and treatment among PWH is required to avoid the future burden of HCV-related liver damage, cancer, and mortality. Further national standards should be carefully developed for HCV screening in PWH, provision of appropriate HCV care, and access to direct-acting antiviral treatment for those with chronic active infection. For this purpose, it is essential to build HCV surveillance and treatment strategies in Iran.

Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Author contributions. A. A. contributed to the study concept. A. A. and S.-K. R.-A. collected the data. A. A. performed the statistical analysis and data interpretation. S.-K. R.-A. and A. A. verified the data. A. A. drafted the manuscript and provided critical revision of the study. A. A. and S.-K. R.-A. revised the final version of the study.

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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Figure 6. Prevalence of hepatitis C virus (HCV) coinfection in people with human immunodeficiency virus (HIV) in Southwest (A), South-Central (B), Northwest (C), East (D), and North-Central Iran (E). CI, confidence interval; ES, effect size.
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