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Review

High hepatitis C virus prevalence among drug users in Iran: systematic review and meta-analysis of epidemiological evidence (2001–2012)

Mohsen Malekinejad [a,b,*], Soodabeh Navadeh [b,c], Ali Lotfizadeh [a], Afarin Rahimi-Movaghar [d], Masoumeh Amin-Esmaeili [e], Alireza Noroozi [c]

[a] Phillip R. Lee Institute for Health Policy Studies, University of California, San Francisco, California, USA
[b] Global Health Sciences, University of California, 3333 California Street, Suite 265, San Francisco, CA 94118, USA
[c] Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
[d] Iranian National Center for Addiction Studies (INCAS), Iranian Institute for Reduction of High-Risk Behaviors, Tehran University of Medical Sciences, Tehran, Iran
[e] Iranian Research Center for HIV/AIDS (IRCHA), Iranian Institute for Reduction of High-Risk Behaviors, Tehran University of Medical Sciences, Tehran, Iran

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SUMMARY

Objective: Drug users, particularly drug injectors, are at elevated risk of blood-borne diseases. This study systematically reviewed the prevalence of hepatitis C virus (HCV) mono-infection and its co-infections with human immunodeficiency virus (HIV) and hepatitis B virus (HBV) in drug users in Iran.
Methods: Searches were conducted in international, regional, and Iranian databases. Documents were screened, data extracted, and pooled point prevalence and 95% confidence intervals (CI) were calculated.
Results: Overall, 13 821 subjects (87.4% male) with an average age of 32.4 years (95% CI 31–33 years) from 24 original studies were included in the analysis. The pooled HCV prevalence (95% CI) among drug users with and without an injection history was 45% (37–54%) and 8% (4–13%), respectively. The pooled HCV prevalences (95% CI) among individuals with vs. without a history of imprisonment and needle sharing were 58% (39–77%) vs. 44% (20–68%) and 56% (41–71%) vs. 49% (26–71%), respectively. The prevalence of HCV/HIV co-infection among injectors was 11% (95% CI 5–16%).
Conclusions: HCV prevalence is high in drug users in Iran, especially among those with a history of injection drug use, needle sharing, and imprisonment. Drug user-focused HCV prevention and treatment programs are urgently needed.

1. Introduction

There are currently more than 150 million persons worldwide who are infected with the hepatitis C virus (HCV),[1,2] a blood-borne virus causing several difficult-to-treat diseases, such as cirrhosis (5–20% risk in 20–30 years) and liver cancer (1–5% annual risk depending on the staging of liver fibrosis and cirrhosis).[3,4] No effective HCV vaccine is yet available. As a result, public health and behavioral interventions are the only means of preventing HCV infection, particularly among high-risk populations. People who inject drugs (PWID) are at an especially high risk of contracting HCV and other fatal blood-borne diseases, including those caused by the human immunodeficiency virus (HIV) and hepatitis B virus (HBV).[5–7]

In 2012, it was estimated that there were nearly 12.7 million (95% confidence interval (CI) 8.9–22.4 million) PWID worldwide.[8] Access to HCV treatment for PWID has been limited due to a multitude of factors, including low HCV testing coverage and guidelines that recommend treatment only to drug-abstinent patients.[9] Thus, HCV prevention and treatment among PWID remains a major public health challenge globally, especially in countries with high rates of injection drug use such as Iran.[10–13]

The recreational use of opium smoking in Iran has been widespread for centuries. Over the past three decades, opium consumption in the country has been greatly influenced by its geographic proximity to neighboring Afghanistan, the world's largest opium producer.[8,14] In recent decades, there has been a shift in the patterns of opiate use from smoking opium to injecting

* Corresponding author. Tel.: +1 (510) 8168555; fax: +1 (415) 4760705.
E-mail address: MMalekinejad@ucsf.edu (M. Malekinejad).

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heroin.[15] According to the only national Iranian household survey, conducted in 2011, 6.2% of people aged 15–64 years (nearly 3.5 million people) reported using an illicit drug in the last 12 months, 5.2% reported using an illicit opioid, and 0.5% reported using heroin.[16] Varying sources place the number of PWID in Iran at between 200 000 and 300 000, with nearly 100 000 of these residing in Tehran.[17,18]

Since 2002, to curb the blood-borne epidemic among PWID, Iran has adopted and rapidly rolled out harm reduction policies promoting opioid substitution treatment (OST), needle and syringe programs (NSP), and outreach and prison-based programs.[19] Nevertheless, the HCV epidemic continues to pose an emerging public health threat in Iran.[20] While there have been several sporadic HCV serological surveys among PWID in the last decade, a systematic approach to assess HCV distribution and trends in various sub-populations in Iran is lacking. The objective of this study was to systematically compile and synthesize the epidemiological evidence on the prevalence of HCV infection and its co-infection with HIV and HBV among drug users outside of prison in Iran. This information could assist policy-makers in public health decision-making with regard to interventions targeted at reducing the burden of HCV.

2. Methods

2.1. Overview

A systematic review was conducted to identify studies reporting the prevalence and incidence of HCV infection and its co-infections with HIV and HBV among drug-using populations in Iran. The following four steps were undertaken: (1) searches to identify scientific documents, (2) screening of documents to identify eligible studies, (3) data extraction from the studies included, and (4) data organization, pooling, and analysis. Details of these steps are provided below.

2.2. Conducting searches and identifying scientific documents

This step included three components. First, the strategy employed in another systematic review conducted recently by this study team[21] was used to search several international (PubMed, Web of Science, CINAHL, PsycINFO), regional (IMEMR), and Iranian (Iranmedex, Iranpsych) databases. Given the scarcity of data related to Iran, a broad search was conducted using keyword combinations for geographic location (i.e., country and province names) and diseases (i.e., HCV, HIV, and HBV). The search parameters were not limited to a specific sub-population (e.g., drug users), language, or time interval. Instead, the documents retrieved were screened manually and all that met the eligibility criteria, as described below, were included. For Iranian databases, both Persian and English keywords were used. Since the use of combinations of keywords was not possible for these databases, a single broad search term was used to yield a more sensitive search. All citations identified through international databases were imported to an Endnote library and duplicate citations were removed. For Iranian databases, retrieved citations were reviewed in Microsoft Word and eligible titles were entered manually into the Endnote database, as the automatic export of citations to Endnote was not available for these databases. Second, the reference sections of relevant review articles (i.e., review studies with similar eligibility criteria and scope as the present review) and national program reports were hand-searched to identify studies with original data. Third, researchers in the field of drug use and infectious diseases in several academic and public health organizations in Iran and internationally were contacted and asked for additional reports of original data that may have been missed in this search.

2.3. Screening of scientific documents

2.3.1. Eligibility criteria

The objective of screening was to identify scientific documents with epidemiological evidence on the prevalence and/or incidence of HCV infection and its co-infection with HBV or HIV among drug-using populations who were not in a correctional facility (including prison) or inpatient healthcare facility during or immediately before the time of the survey. The following five eligibility criteria were used in the selection of relevant studies: document type, study design, disease area, geographic setting, and population.

With respect to the document type, all scientific documents reporting original data (i.e., gathered directly by conducting surveys and laboratory tests on specimens), in the form of a peer-reviewed manuscript, progress report, abstract, technical report, or substantive scientific commentary, were included. Documents not reporting epidemiological data (e.g., legal cases, legislation) and those not reporting original data (e.g., data simulation), as well as documents lacking scientific and methodological details needed for the assessment of the validity of findings (e.g., media reports) were excluded. Documents that were self-described as 'systematic reviews' or 'meta-analyses' (scientific documents such as peer-reviewed manuscripts or abstracts summarizing results from a group of epidemiological studies) were retained for hand searching of the references.

All study designs reporting data on the prevalence and incidence of disease, including cross-sectional studies, cohort studies, and even experimental studies (e.g., randomized controlled trials) in which a biological survey was conducted to test for HCV prior to the introduction of the intervention (baseline) were included. Case reports, case series, and qualitative studies were excluded. Studies with a sample size less than 20 were considered to be underpowered and also prone to a wider range of biases due to a narrow implementation scale and thus were also excluded.

For the disease area, studies with biological evidence on mono-infection with HCV and/or its co-infection with HBV or HIV were included. Self-reported data on the above diseases were excluded.

The geographic scope was limited to studies conducted within Iran; studies conducted among Iranian populations residing outside of Iran were not included.

For the study population, studies conducted in human subjects who self-identified as current or former drug users and at the time of the study were not hospitalized or in prison (i.e., facilities under the direct supervision of the Prison Organization, which may contain a mix of drug- and non-drug-related offenders) were included. Studies on populations who were in short-term mandatory drug treatment and rehabilitation detention centers were included. Studies in non-human subjects, blood donors, hospitalized patients (regardless of injection drug use status), dialysis patients, pregnant women, families or sexual partners of HCV/HBV patients, and populations with other chronic diseases (e.g., studies reporting HCV among people with liver cancer) were excluded. No limits were set on study implementation or publication age.

2.3.2. Screening process

Studies were screened in a stepwise fashion. First, one of the co-authors (SN) carefully reviewed and excluded studies that clearly did not meet the eligibility criteria solely based on the title (e.g., not related to HCV, HBV, HIV, not conducted in Iran, conducted among specific groups such as blood donors). Subsequently, at the abstract level, two co-authors (SN and AL) independently screened citations to identify eligible studies. Citations included by either of the two reviewers were put forward for full-text review. At the full-text level, two reviewers (SN and AL) screened studies independently and included studies that provided relevant data on the

prevalence and/or incidence of mono-infection with HCV, and its co-infection with HBV or HIV. Citations for which there was disagreement were discussed by the two reviewers until consensus was reached; a third co-author provided input as needed.

2.4. Data extraction

Two of the co-authors (SN and AL) independently extracted data from the selected studies using structured sheets in Microsoft Excel. Disagreements were discussed with a third co-author (MM) when required. The following data were extracted: authors (or principal investigator), publication year, publication type, language of the publication, study implementation year, study setting (e.g., drug treatment clinic, drop-in center (DIC), community), study scale (clinic, city, province, national), study target population (including eligibility criteria and history of drug use), sample size and sampling methods, number of recruitment sites, geographic location (urban vs. rural), key socioeconomic indicators (age, sex, marital status, employment status, housing status, education level), outcome measurement (specimen type, laboratory test), outcome including prevalence of HCV mono-infection (overall and broken down by history of incarceration, needle sharing, tattoos), and prevalence of HCV co-infection with HIV or HBV.

If information was missing from a study, the study authors were contacted for further clarification. For research studies reported in multiple formats (i.e., technical report, peer-reviewed paper, and conference abstract), the most comprehensive and accessible format was considered and the other documents used to supplement missing information. The original databases of one of the studies were obtained and used for a secondary data analysis (Malekinejad, 2008).

2.5. Assessment of the risk of bias

An existing and validated risk of bias assessment tool was adapted and used to rate the quality of evidence included in the meta-analysis.[22] In brief, the modified tool consisted of eight domains, three focusing on external validity and five on internal validity of the data. The external validity domains included the following: (1) relevance of the target population (i.e., was the study target population a close representation of Iranian drug users), (2) appropriateness of the sampling method (i.e., was some form of random sampling or other innovative method used to select the sample), and (3) likelihood of non-response bias (i.e., was there a high response rate or an analysis indicating that responders and non-responders were similar). The internal validity domains included the following: (1) directness of data collection from subjects (i.e., were the data collected directly from the subjects or by proxy), (2) acceptability of the case definition (i.e., was the case definition for HCV acceptable), (3) reliability and validity of laboratory tests (i.e., were the laboratory tests used for HCV diagnosis shown to be valid and reliable), (4) consistency of data collection methods for all subjects (i.e., were the methods employed for collecting data among different participants consistent), and (5) appropriateness of the numerator and denominator of the parameters (i.e., were the numerator and denominator used for the calculation of HCV prevalence appropriate). Two co-authors (AL and SN) independently rated studies on the eight domains; disagreements were resolved by discussion, and when needed, the third co-author (MM) made tie-breaking decisions.

Each domain was ranked as a high or low risk of bias domain. On aggregate, a three-tier ranking system (high, moderate, low) was used to rank the selected studies as follows: (1) high risk of bias: studies with two or more high risk of bias domains; (2) moderate risk of bias: studies with only one high risk of bias domain; (3) low risk of bias: studies without any high risk of bias domain. For studies presenting duplicate data, the version providing the most comprehensive and complete information allowing the appraisal of data points was reviewed.

2.6. Data synthesis

Tables were created in Microsoft Excel to organize and synthesize the data. Studies were categorized based on self-reported drug injection behaviors of the participants. Studies in which participants reported no history of drug injection were defined as 'never injector' (NI). Those in which subjects reported injecting drugs at least once in the year prior to the survey, or the subjects self-identified as current injectors and had injection marks, were defined as 'recent injector' (RI). Finally, those studies in which participants reported some history of drug injection but the timing of drug injection was not defined were considered as 'ever injector' (EI). If a study had both RI and EI populations, it was categorized as an EI study. Studies reporting on a combination of NI and EI or NI and RI were listed twice and prevalence data for each population were presented separately. Summary point estimates and 95% confidence intervals (CI) were calculated for HCV, HCV/HIV, and HCV/HBV weighted by inverse of variance, using a random-effects meta-analysis model in Stata version 13 with the metan command. Data for the above sub-populations were presented in the form of forest plots wherever such data were available. The meta-analysis was also repeated on a sub-set of studies that were ranked as low or moderate risk of bias studies. In circumstances where the distribution of the pooled prevalence was not normal or the pooled prevalence was close to 0 or 100 and the sample size was small, using a traditional meta-analysis command (metan command in Stata) would have resulted in CIs smaller than zero or larger than 100. To address this issue, the prevalence and CI were first transformed into the logit scale in order to generate a distribution closer to normal, and meta-analyses were then performed on the transformed values. Overall pooled prevalence and CIs were derived by back-transforming the estimates and CIs using the 'invlogit' function. In a few cases, the CI of pooled prevalence data remained smaller than zero or larger than 100 even after using the logit transformation. For these data points, CIs for the original data were calculated using the exact binomial and score test with the metaprop command in Stata.

3. Results

Of the total 3401 scientific documents retrieved from the electronic searches (after de-duplication), hand-searching of review studies and reports, and contacting experts, 32 relevant scientific documents were identified and included. A total of 24 experts were contacted, 11 of whom responded, yielding a total of 18 new documents. Four new documents sent by the research experts met the eligibility criteria and were included in the 32 documents for final assessment and potential data extraction. The 14 other documents were eliminated because the subjects were prison inmates (Figure 1).

From the final list of 32 documents, 23 (72%) were in English[23–45] and nine (28%) were in Persian.[46–54] Thirty documents were peer-reviewed articles[23–52,54] and two were technical reports.[53] Of the 32 documents included, eight reported the same data as other studies (six duplicates and one triplicate); hence there were 24 original studies. The eight duplicate studies were not included in the final meta-analysis but were used to complete key information when data points were missing from the original document reporting on the same study.

Table 1 presents the characteristics of the research studies included in the review. Of the 24 original studies, nine (37.5%)

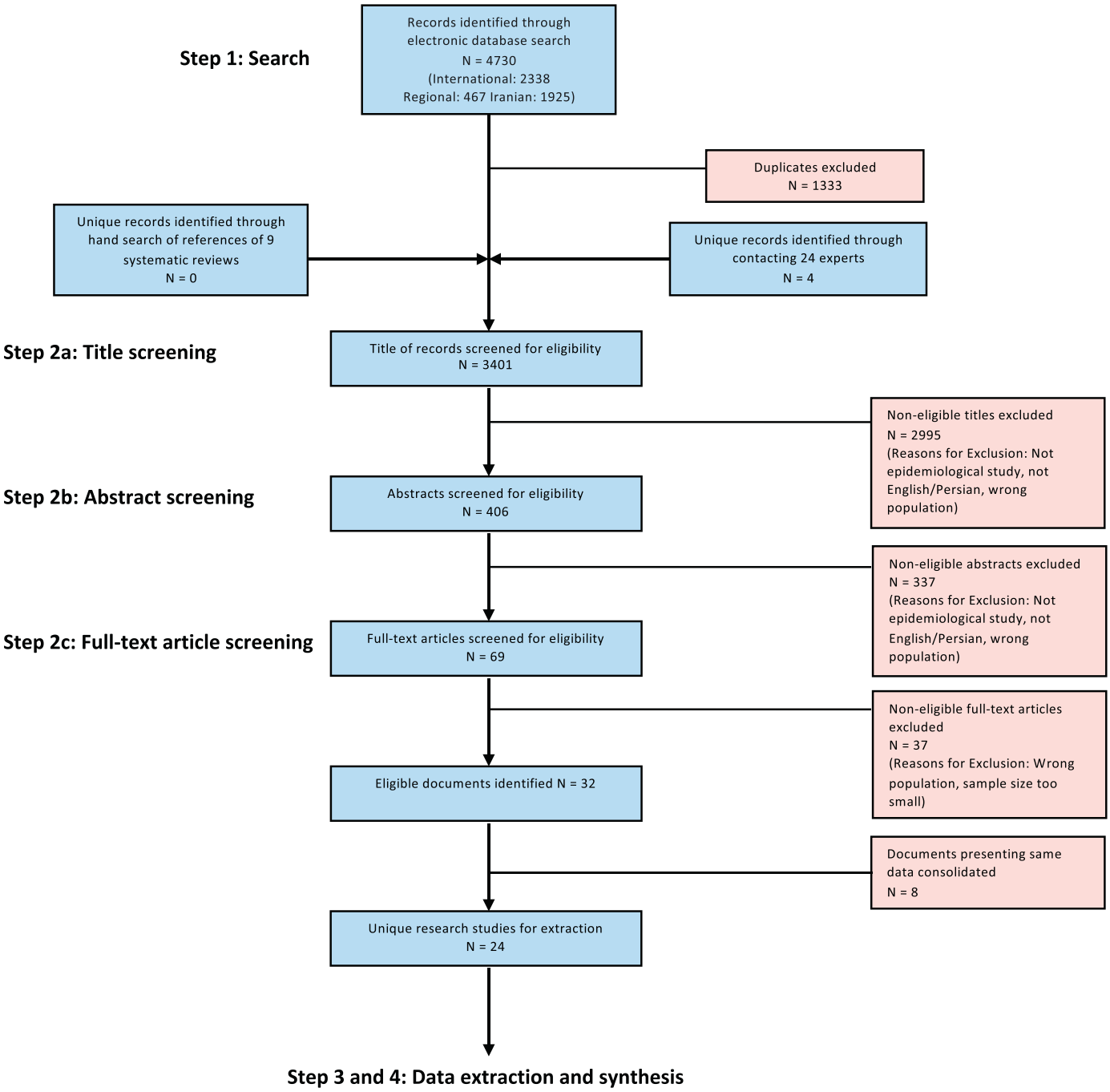


Figure 1. Search results: number of studies identified at each step of the search, screening, and data extraction process.

were studies on RI,[23–26,32,40,44,45,53] 10 (41.7%) were studies on EI,[29–31,33,35–37,41,46,54] and one (4.2%) was a study on NI.[43] Another four (16.7%) studies reported on both EI and NI.[27,42,47,50] These four studies are presented twice in Table 1, once among the EI population and a second time among the NI population. The studies included were carried out within an 11-year time span (2001–2012), with more than half being implemented between 2006 and 2012. With respect to the geographic location, eight (33.3%) studies were conducted only in Tehran (the capital city),[24–26,31–33,43,44] 12 (50.0%) in a city other than Tehran,[27,29,30,36,37,40,42,45–47,50,54] and four (16.7%) in multiple cities.[23,35,41,53] All studies implemented cross-sectional designs and two applied respondent-driven sampling (RDS) for participant recruitment.[32,45] With respect to study setting, three (12.5%) recruited subjects from DIC,[23,35,37] seven (29.2%) from drug treatment clinics,[25,29,31,33,40,47,50] two (8.3%) from the community,[36,46] one (4.2%) from homes,[42] four (16.7%) from health facilities including voluntary HIV counseling and testing (VCT) sites,[27,30,43,54] one from a detention center (4.2%),[26] and five (20.8%) from a mix of settings.[24,32,44,45,53] One study did not report the recruitment setting.[41] All studies used whole blood, except for one that used saliva[44] and one that used dried blood samples.[53]

Table 2 presents a summary of the demographic and socioeconomic characteristics of the 13 821 study subjects. The overall weighted mean age of subjects was 32.4 years (95% CI 31–33 years). Among all subjects, 87.4% (95% CI 82–92%) were male, 53.9% (95% CI 47–60%) were unmarried, 54.6% (95% CI 42–66%)

Table 1
Characteristics of the populations and studies included in the systematic review

Author/principal investigator, publication year, and language	Characteristics of the population			Characteristics of the study					
	Age, years, mean (SE) min–max	% Male	Sample, SES[a]	Study year and location	Scale and number of sites	Study setting[b]	Biological test[c]	Sampling method	Sample size[d]
Recent IDU									
Alipour 2013 (English)	36.4[e]	84%	Unmarried: 44.8% Under-educated: 74.2%	Tehran, Mashad, Shiraz (2010)	City (multiple)	DIC	HCV: ELISA and WB HIV: ELISA and WB HBV: ELISA	Convenience	268
Amin-Esmaeili 2012 (English) Rahimi-Movaghar 2010 (English)	33.9 (±9.4) 16–65	95.80%	Unmarried: 70.8% Under-educated:53.4% Homeless: 38.8% Unemployed: 64.1% Imprisoned: 70.9%	Tehran (2006)	City (multiple)	Mixed (drug treatment clinic, DIC, community)	HCV: ELISA HIV: ELISA and WB HBV: EIA and IEMA Well	Purposive and snowballing (community) Convenience (drug treatment centers)	904
Amini 2005 (English)	NR	NR	NR	Tehran (2002)	City (single)	Drug treatment clinic	HCV: EIA HIV: EIA HBV: EIA	Convenience	34
Eskandarieh 2013 (English)	28.78 13–62	96.50%	Unmarried: 76.2% Under-educated: 70.4% Homeless: 37.0% Unemployed: 14.8% Imprisoned: 72.7%	Tehran (2008)	City (single)	Detention center (Shafagh)	HCV: NR HIV: ELISA and WB	Convenience	402
Malekinejad 2008[f] (English) Rahnama 2014 (English)	36.5 (±9.2) 20–70	99.40%	Unmarried: 46% Under-educated: 45.7% Homeless: 34.9% Unemployed: 45.8% Imprisoned: 83.2%	Tehran (2007)	City (multiple)	Mixed (hospital, DIC)	HCV: ELISA HIV: EIA HBV: NR	Respondent-driven	564
Noroozi 2011[f] (Persian)	35.96 (±8.03) 20–54	95.3%	Unmarried: 29.7% Under-educated: 62.5% Homeless: 10.4% Unemployed: 32.8%	Karaj, Isfahan, Gorgan (2011)	City (multiple)	Mixed (drug treatment clinic, DIC)	HCV: ELISA	Convenience	192
Ramezani 2014[f] (English)	Median 33.3 17–58	100%	Unmarried: 67% Under-educated: 70% Unemployed: 17% Imprisoned: 73%	Arak (2012)	City (single)	Drug treatment clinic	HCV: ELISA HIV: ELISA and WB HBV: ELISA	Convenience	100
Zamani 2007 (English)	38.3 (±11.9) 15–64	97%	Unmarried: 41.1% Under-educated: 75.2% Homeless: 32.2% Unemployed: 65.8%	Tehran (2004)	City (multiple)	Mixed (DIC and community)	PA assays	Convenience	202
Zamani 2010 (English)	29.0 (±6.6)	97.40%	Unmarried: 69.2% Under-educated: 54.7% Unemployed: 42.7%	Foulad-shahr (2008)	City (multiple)	Mixed (NEP, MMT, community, DIC)	HCV: ELISA HIV: EIA HBV: NR	Respondent-driven	118
Ever IDU									
Ataei 2011 (Persian)	NR	NR	NR	Golpayegan[h] (2007)	City (multiple)	Community	HCV: ELISA	Convenience	136
Azizi 2011[i] (Persian)	31.82 (±9.18)[g]	NR	Unmarried: 51% Under-educated: 66.5% Unemployed: 14.8%	Kermanshah (2008)	City (single)	Drug treatment clinic	HCV: ELISA	Convenience	263

Table 1 (*Continued*)

Ever IDU									
Honarvar 2013[i] (English)	32.3 (±7.33) 19–59	98.3%	Unmarried: 70.8% Under-educated: 14.2% Unemployed: 26.6%	Shiraz (2012)	City (multiple)	VCT	HCV: ELISA and WB HIV: ELISA and WB HBV: ELISA	Convenience	569
Fadaei Nobari 2012 (English) Fadaei Nobari 2011 (Persian)	35 (±9.4) 17–64	NR	NR	Isfahan Province[h] (2008)	Province (multiple)	Community	HCV: ELISA	Convenience	1747
Imani 2008 (English) Imani 2006 (Persian)	31.3 (±7.1) 18–65	98.40%	NR	Shahr-e-Kord (2004)	City (multiple)	Drug treatment clinic	HCV: ELISA	Convenience	133
Keramat 2011 (English)	29.7 (±9.5) 13–80	71.50%	Imprisoned: 52.5%	Hamadan (2005)	City (single)	VCT	HCV: ELISA and WB HIV: ELISA and WB	Convenience	379
Kheirandish 2009 (English) Hosseini 2010 (English)	33.7 (±10.2) 17–70	100%	Unmarried: 60.4% Under-educated: 81.1% Imprisoned: 75.3%	Tehran (2006)	City (single)	Drug treatment clinic	HCV: EIA HIV: ELISA and WB	Convenience	454
Khodadadi-zadeh 2006[i] (Persian)	29.3 (±5.3)	95.50%	NR	Rafsanjan (2003)	City (single)	Drug treatment clinic	HCV: ELISA HIV: ELISA and WB HBV: ELISA	Convenience	180
Mirahmadizadeh 2009 (English)	33.1 (±8.97) 15–63	96.10%	Unmarried: 64.9%	Multiple cities (2005)	National (multiple)	DIC	NR	Systematic, random	1531
Mir-Nasseri 2008 (English) Mir-Nasseri 2011 (English) Mir-Nasseri 2005 (Persian)	33 (±8.66) 19–54	98%	NR	Tehran (2001)	City (multiple)	Drug treatment clinic	HCV: ELISA HIV: NR HBV: EIA	Convenience	132
Nokhodian 2012 (English) Meshkati 2011 (Persian)	31.77 (±8.51) 19–62	94.70%	Unmarried: 47.6% Under-educated: 19.9%[f] Unemployed: 44.1%	Isfahan (2008)	Province (multiple)	DIC	HCV: ELISA	Convenience	539
Rostami Jalilian 2006 (Persian)	27.7 (±7.6) 16–54	NR	NR	Isfahan (2002)	City (multiple)	VCT	HCV: ELISA	Convenience	148
Sarkari 2012 (English)	NR	66.40%	Unmarried: 39.7%	Yasuj, Gachsaran, Dehdasht, Kohgilooye Province (2009)	Province (multiple)	NR	HCV: ELISA	Convenience	158
Sayad 2008[i] (English)	32.7 (±12.5)[e] 15–64	49.60%	Unmarried: 38.5% Under-educated: 54.7%	Kermanshah (2006)	City (multiple)	Home-based	ELISA and WB	Systematic and cluster	1721
Never IDU									
Azizi 2011[i] (Persian)	31.82 (±9.18)[g]	NR	Unmarried: 51% Under-educated: 66.5% Unemployed: 14.8%	Kermanshah (2008)	City (single)	Drug treatment clinic	HCV: ELISA	Convenience	263
Honarvar 2013[i] (English)	28.49 (±7.72) 13–56	75.90%	Unmarried: 63.7% Under-educated: 11.3% Unemployed: 25.6%	Shiraz (2012)	City (multiple)	VCT	HCV: ELISA and WB HIV: ELISA and WB HBV: ELISA	Convenience	569

Table 1 (*Continued*)

Never IDU									
Khodadadi-zadeh 2006[i] (Persian)	29.3 (±5.3)	95.50%	NR	Rafsanjan (2003)	City (single)	Drug treatment clinic	HCV: ELISA HIV: ELISA and WB HBV: ELISA	Convenience	180
Sayad 2008[i] (English)	32.7 (±12.5)[e] 15–64	49.60%	Unmarried: 38.5% Under-educated: 54.7%	Kermanshah (2006)	City (multiple)	Home-based	ELISA and WB	Systematic and cluster	1721
Talaie 2007 (English)	37.9 (±14.95) 16–87	91.60%	NR	Tehran (2004)	City (single)	Health care facility	HCV: EIA HIV: EIA HBV: EIA	Convenience	214

DIC, drop-in center; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, intravenous drug user; IEMA, immunoenzymometric assay; MMT, methadone maintenance treatment; NEP, needle exchange program; NR, not reported; PA, particle agglutination; SE, standard error; SES, socioeconomic status; VCT, voluntary counseling and testing center; WB, Western blot.

[a] Socioeconomic status defined by marital status, employment status, history of imprisonment, homelessness, and education level. Under-educated defined as having less than a high school diploma.

[b] Description of the various study settings: drug treatment clinic = MMT or drug treatment center; DIC = NEP or harm reduction program for active drug users; health care facility = VCT or hospital; community = community or park or detention center (a place where drug users are detained after being arrested by police; the main detention center in Tehran is called Shafagh); home-based = conducted at home; mixed = two of the above categories.

[c] WB was used for confirmation when the initial test was positive.

[d] Sample size is the overall number of subjects recruited for the study.

[e] Imputed data.

[f] Includes unpublished data.

[g] Reported age distribution is a mixture of IDU and non-IDU.

[h] Mixture of urban and rural.

[i] Studies reporting on both 'ever injector' (EI) and 'never injector' (NI).

were under-educated (defined as having lower than a high school diploma), 30.3% (95% CI 17–42%) were homeless (data available only for RI), 34.1% (95% CI 23–45%) were unemployed at the time or within the year prior to the study, and 71.3% (95% CI 63–79%) reported ever being imprisoned.

As shown in Figure 2, the overall pooled HCV prevalence among all injection drug users (IDU) (RI and EI combined) was 45% (95% CI 37–54%).[23–27,29–33,35–37,40–42,44–47,50,53,54] The HCV prevalence among RI was 53% (95% CI 37–70%)[23–26,32,40,44,45,53] and in EI it was 40% (95% CI 30–50%).[27,29–31,33,35–37,41,42,46,47,50,54] The prevalence of HCV among NI was 8% (95% CI 4–13%)[27,42,46,47,50] (Figure 3).

Among the 24 original studies, 15 (63%) had a high risk of bias, seven (29%) had a moderate risk of bias, and two (8%) had a low risk of bias (Table 3). After excluding the 15 studies with a high risk of bias, the overall pooled HCV prevalence among all IDU was 53% (95% CI 38–68%).[31,33,35,42,44,45,47,54,55] The HCV prevalence among RI was 65% (95% CI 43–88%)[44,45,55] and among EI was 46% (95% CI 27–65%).[31,33,35,42,47,54] The HCV prevalence among NI was 6% (95% CI 3–9%).[42,47]

The pooled prevalence of HCV co-infection with HIV and HBV in all IDU was also examined. In total, 2615 individuals were tested for both HCV and HIV, while 1996 individuals were tested for HCV and HBV. The prevalence of HCV/HIV and HCV/HBV co-infection among IDU was 11% (95% CI 5–16%)[24,27,31–33,40,44,45] and 11% (95% CI 2–20%),[24,27,32,33,40,45] respectively (Figure 4).

With respect to the distribution of HCV infection among IDU by geographic location, pooled estimates of HCV prevalence in Tehran, cities other than Tehran, and a mix of Tehran and other cities were 55% (95% CI 35–74%),[24–26,31,33,44] 42% (95% CI 30–54%),[27,29,30,32,36,37,40–42,45–47,50,53,54] and 41% (95% CI 37–46%),[23,35] respectively. Further, when the distribution of infection by recruitment setting was assessed, the pooled HCV prevalences were as follows: 43% (95% CI 17–69%) among those recruited from drug treatment clinics,[25,29,31,33,40,47,50] 43% (95% CI 39–48%) among those recruited from DIC,[23,35,37] 48% (95% CI 32–63%) among those recruited from healthcare facilities,[27,30,54] 40% (95% CI 18–62%) among those recruited from the community,[26,36,46] 50% (95% CI 22–78%) among those recruited from the home,[42] and 52% (95% CI 27–77%) among those recruited from a mix of settings (Figure 5).[24,32,44,45,53]

As presented in Table 4, the pooled HCV prevalence was higher among IDU with a history of incarceration (58%, 95% CI 39–77%) as compared to those without such a history (44%, 95% CI 20–68%). HCV prevalence was also higher among those IDU with a history of tattoos (72%, 95% CI 55–88%) as compared to those without this history (55%, 95% CI 40–70%). Further, IDU who reported sharing needles in the past had higher rates of HCV (57%, 95% CI 41–71%) than those who reported not sharing needles (49%, 95% CI 26–71%). The differences in these three categories were not considered statistically significant.

4. Discussion

PWID are the main group affected by HCV infection worldwide.[56] This study examined the prevalence of HCV among drug users with and without a drug injection history. The results showed a high prevalence of HCV infection among PWID in Iran, which is consistent with world estimates of 52.0% in this population,[6] but still lower than the prevalence reported in certain other countries (e.g., Bulgaria, Estonia).[1] HCV infection can lead to serious and deadly liver diseases such as cirrhosis and hepatocellular carcinoma. The burden of hepatitis C attributed to injection drug use is high and was estimated to be 502 000 (286 000–891 000) disability-adjusted life-years globally in 2010.[57] Given that HCV prevalence in Iran is consistent with world estimates, HCV

Table 2
Summary of the demographic and socioeconomic characteristics of participants in the studies included, by pattern of drug injection

	Sample size	Age, years	Male	Unmarried	Under-educated	Homeless	Unemployed	Ever imprisoned
	N	Mean (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Recent IDU	2784	34.7 (32–37)	95.6 (93–97)	55.5 (43–67)	63.1 (54–71)	30.3 (17–42)	40.4 (23–57)	75.1 (68–82)
Ever IDU	8090	31.8 (30–32)	85.5 (76–94)	53.3 (42–64)	47.2 (22–72)	-	38.5 (12–44)	63.9 (41–86)
Any IDU (combined above)	10874	32.6 (31–33)	89.9 (85–94)	54.5 (46–62)	57.1 (44–69)	-	36.8 (24–49)	71.3 (63–79)
Never IDU	2947	31.9 (29–34)	78.1 (54–100)	51.1 (33–68)	44.1 (10–77)	-	20.2 (9–30)	-
Overall	13821	32.4 (31–33)	87.4 (82–92)	53.9 (47–60)	54.6 (42–66)	30.3 (17–42)	34.1 (23–45)	71.3 (63–79)

CI, confidence interval; IDU, injection drug user.

likely contributes to a high burden of disease in Iran. Therefore, special emphasis must be placed on the control of HCV infection among PWID in Iran.

In 2002, Iran implemented harm reduction interventions including NSP and OST, primarily in response to the HIV epidemics among PWID. These programs have been scaled up at the national level since 2007.[19] Although there is ample evidence on the effectiveness of NSP and OST in the reduction of self-reported injecting risk behaviors,[58–60] evidence regarding the effectiveness of these programs in reducing HCV incidence is inconclusive.[58,59] HCV infection is transmitted more efficiently than HIV.[61–66] Modeling studies have shown that an individual who shares needles and syringes is at greatest risk of contracting HCV during the first year.[67,68] In addition, the risk of becoming infected

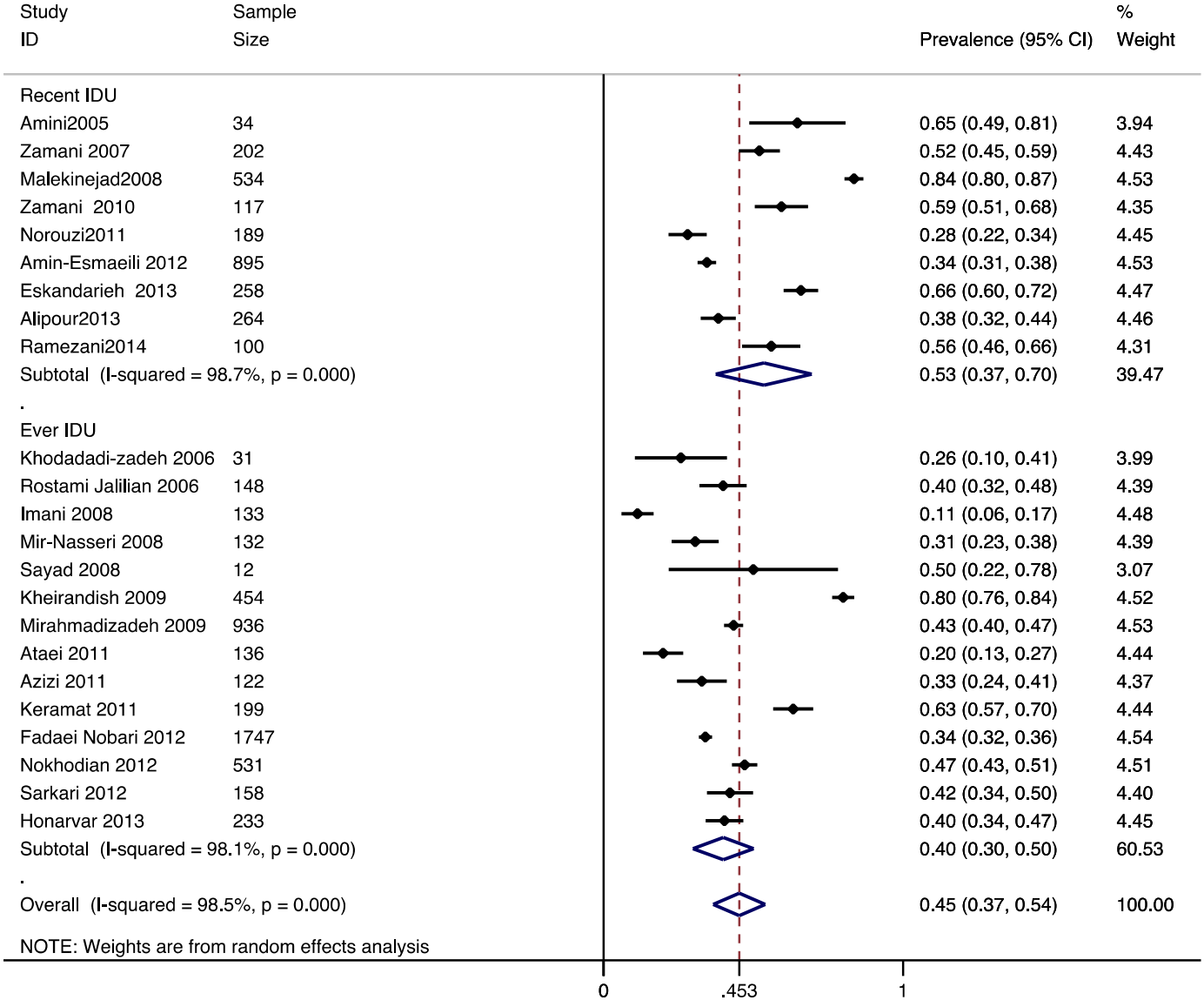


Figure 2. HCV prevalence in injecting drug users (IDU): summary estimate of HCV infection prevalence and 95% confidence interval among people who inject drugs, by timing of injection.

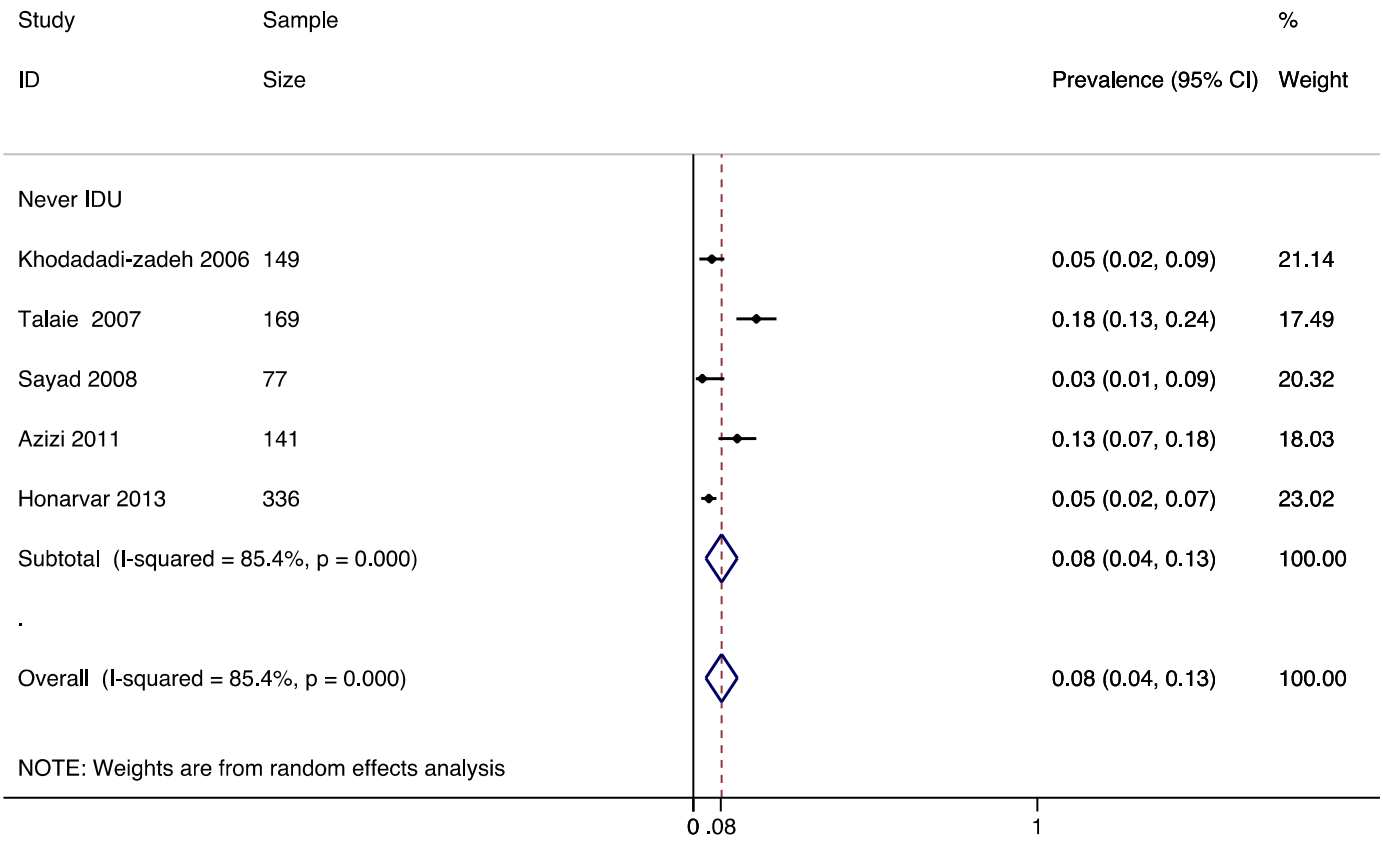


Figure 3. HCV prevalence in drug users who do not inject (non-IDU): summary estimate of HCV infection prevalence and 95% confidence interval among drug users who have never injected.

increases with injection duration.[69,70] In the Amsterdam Addiction Cohort study, the incidence of HCV infection among PWID who received both OST and high coverage NSP (i.e., sufficient numbers of syringes) was approximately one third lower than that of those who received either OST or NSP alone.[60] These studies suggest that a combination of harm reduction interventions need to reach PWID early on to be effective in reducing the risk of HCV transmission. This is especially applicable to Iran, since the overall coverage of the NSP and OST programs has remained insufficient among PWID[8,71] and many harm reduction facilities provide only one or the other.

In this study, the weighted pooled prevalence (11.3%) of HCV and HIV co-infection among PWID in Iran was also calculated. A recent systematic review of 22 European countries reported a median co-infection rate of 3.9%.[70] HIV co-infection accelerates disease progression in chronic hepatitis C and reduces the response rate to interferon-based therapy.[72] Further, there is a higher risk of hepatotoxicity among HIV-infected patients treated with antiretroviral therapy (ART) who are co-infected with HCV.[73–75] Direct-acting antivirals (DAA) are equally effective in HCV patients with and without HIV co-infection and may be a better treatment choice for this population.[76] However the cost of treatment limits their availably in Iran. It was not possible to provide a pooled prevalence of HCV and HIV co-infection among drug users who had never injected drugs, because only one study reported these data on NI.

In the study sample, non-IDU had a higher prevalence of hepatitis C (8.2%) than the general population (<1%).[20] Some studies on HCV infection among individuals with no reported history of blood transfusion and injection drug use have proposed sexual intercourse as the possible mode of HCV transmission.[77,78] The authors suspect that in this review, a high degree of mixing or bridging between IDU and non-IDU may have resulted in the high HCV prevalence. The higher than expected HCV infection among non-IDU may also be due to a multitude of other risk factors, such as unsafe tattoo procedures, body piercings, cocaine snorting, crack-cocaine use, herpes simplex virus (HSV)-2 infection, gonorrhea, HIV infection, and high-risk sexual activity.[78–83] HCV infection among non-IDU is likely also influenced by under-reporting of injection practices, as a result of the stigma attached to injection drug use, which leads to the misclassification of drug users.[84,85] Further studies are needed to determine the risk factors for HCV infection among non-IDU. Such studies should also focus on the extent to which the stigma associated with injection drug use may deter PWID from reporting injection behaviors.

It should be noted that studies that assessed HCV prevalence in incarcerated drug users were excluded from this review. HCV prevalence in this sub-population might be higher than in those out of prison. Nonetheless, more than 70% of drug users included in this review had a history of imprisonment in their lifetime. Although HCV prevalence was higher in those with a history of incarceration, the difference was non-significant. The Prison Organization in Iran launched small-scale programs to provide sterile needles and syringes to prisoners who inject drugs in a limited number of prisons, but these programs were not scaled up.[19] Another systematic review by our team is underway to determine the prevalence of HCV among incarcerated populations in Iran.

The sharing of injection equipment is the primary cause of HCV transmission;[2] however, no correlation was found between a self-reported history of needle sharing and HCV prevalence. Because many of the studies included in this review did not report information on the sharing of injection equipment other than

Table 3
Assessment of risk bias of studies included in the systematic review

Author and year	External validity			Internal validity					
	Relevance of target population	Appropriateness of sampling method	Likelihood of non-response bias	Directness of data collection from subjects	Acceptability of case definition	Reliability and validity of laboratory tests	Consistency of data collection methods for all subjects	Appropriateness of numerator and denominator of parameters	Overall risk of bias[a]
Alipour 2013	Low	High	High	Low	Low	Low	Low	Low	High
Amin-Esmaeili 2012	Low	High	High	Low	Low	Low	Low	Low	High
Rahimi-Movaghar 2010									
Amini 2005	High	High	High	Low	Low	Low	Low	Low	High
Eskandarieh 2013	High	High	High	Low	Low	Low	Low	Low	High
Malekinejad 2008	Low	Low	Low	Low	Low	Low	Low	Low	Low
Rahnama 2014									
Noroozi 2011	Low	High	High	Low	High	High	Low	Low	High
Ramezani 2014	High	High	High	Low	Low	Low	Low	Low	High
Zamani 2007	Low	High	Low	Low	Low	Low	Low	Low	Moderate
Zamani 2010	Low	Low	Low	Low	Low	Low	Low	Low	Low
Ataei 2011	Low	High	High	Low	Low	Low	Low	Low	High
Azizi 2011	High	Low	Low	Low	Low	Low	Low	Low	Moderate
Honarvar 2013	High	High	High	Low	Low	Low	Low	Low	High
Fadaei Nobari 2012	Low	High	High	Low	Low	Low	Low	Low	High
Fadaei Nobari 2011									
Imani 2008	High	High	High	Low	Low	Low	Low	Low	High
Imani 2006									
Keramat 2011	High	High	High	Low	Low	Low	Low	Low	High
Kheirandish 2009	Low	High	Low	Low	Low	Low	Low	Low	Moderate
Hosseini 2010									
Khodadadi-zadeh 2006	High	High	High	Low	Low	Low	Low	Low	High
Mirahmadizadeh 2009	Low	Low	High	Low	Low	Low	Low	Low	Moderate
Mir-Nasseri 2008	Low	High	Low	Low	Low	Low	Low	Low	Moderate
Mir Nasseri 2011									
Mir-Nasseri 2005									
Nokhodian 2012	Low	High	High	Low	Low	Low	Low	Low	High
Meshkati 2011									
Rostami Jalilian 2006	Low	High	Low	Low	Low	Low	Low	Low	Moderate
Sarkari 2012	Low	High	High	Low	Low	Low	Low	Low	High
Sayad 2008	Low	Low	High	Low	Low	Low	Low	Low	Moderate
Talaie 2007	High	High	Low	Low	Low	Low	Low	Low	High

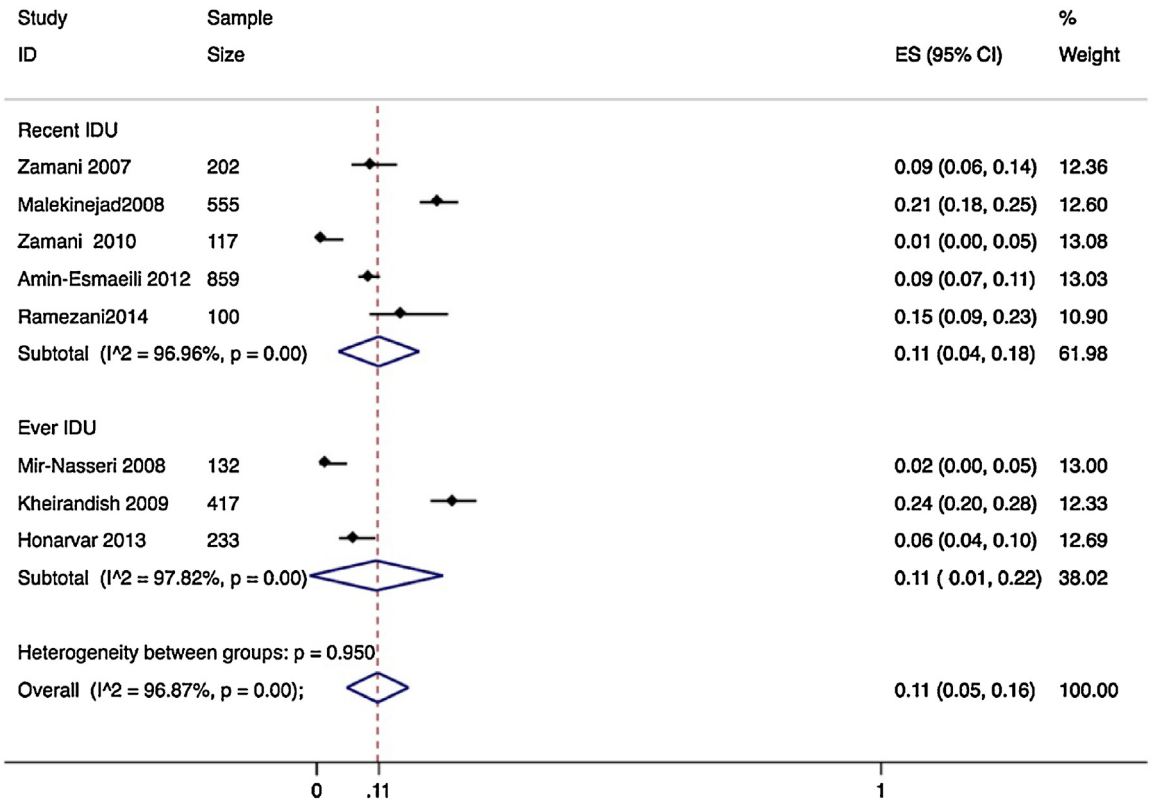
[a] Low: no high-risk domains; moderate: one high-risk domain; high: two or more high-risk domains.

needles, it was not possible to assess this correlation. It is noteworthy that a recent meta-analysis of the factors correlated with HCV transmission in China showed no significant difference between those who shared injection equipment and those who did not.[86]

Studies among Iranian PWID have shown that testing for blood-borne infectious diseases in this population is low.[53,71] Since there are multiple studies supporting the successful treatment of HCV among PWID,[87,88] easy access to testing services could be an initial step towards meeting the need for HCV infection treatment. In Iran, there is no publicly funded program for the treatment of HCV infection. Besides, insurance coverage for antiviral medications and the tests required are very limited. These issues negatively affect access to antiviral treatment for affected populations, particularly people who use drugs in Iran. Treatments may also have a positive impact on preventing HCV transmission. Modeling studies suggest that new-generation antiviral therapies could be a cost-effective and efficacious method of preventing HCV transmission among affected individuals while they are in treatment and once a sustained virological response has been achieved.[89,90]

Although the studies were heterogeneous with respect to the risk of bias, the overall quality of evidence was found to be low, with only two out of the 24 studies qualifying as low risk of bias studies. Nevertheless, the estimated pooled prevalence of HCV among all sub-populations of drug users (RI+EI, RI only, EI only, and NI) remained relatively stable (i.e., 95% CI overlapped significantly) after the 15 studies that were rated as having a high risk of bias were excluded from the meta-analysis. Although the prevalence remained relatively stable, this change resulted in a wider 95% CI for estimates as a result of a decrease in the number of subjects included in the model. For all drug-injecting sub-populations (RI+EI, RI, and EI), the distribution of the HCV prevalence shifted to the right (i.e., the prevalence increased), while among NI, the distribution shifted to the left (the prevalence decreased). In addition to heterogeneity with regard to the risk of bias, the studies included in this review were also heterogeneous with respect to study setting and the characteristics of the drug-using sub-populations. The wide confidence intervals around the pooled estimates generated by the random-effects model reflect the uncertainty around these estimates.

Given the present findings of high HCV prevalence in drug users, providing an appropriate response to HCV infection within this population in Iran is warranted. Such a response would likely require urgent implementation of a multi-pronged approach consisting of a combination of preventive measures, testing services, and antiviral treatment programs among drugs users, particularly PWID. Further studies are needed to provide evidence based on target coverage and a combination of harm reduction interventions to reduce HCV transmission among Iranian PWID.



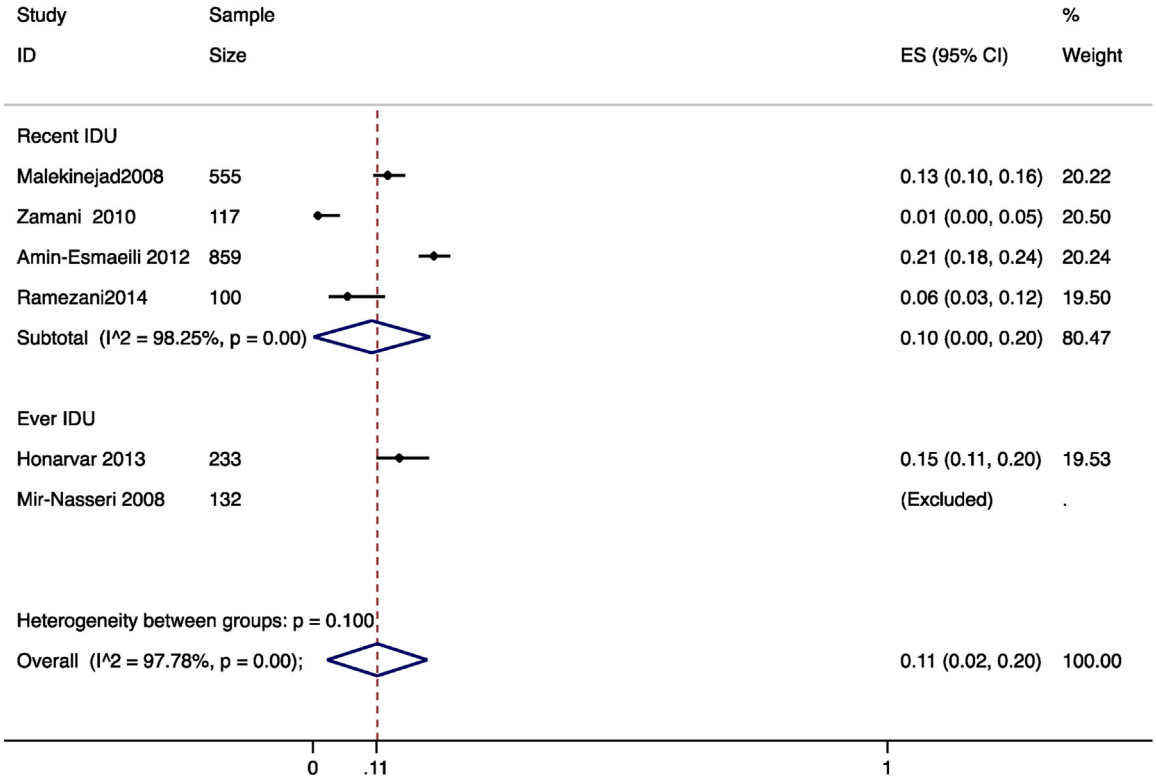
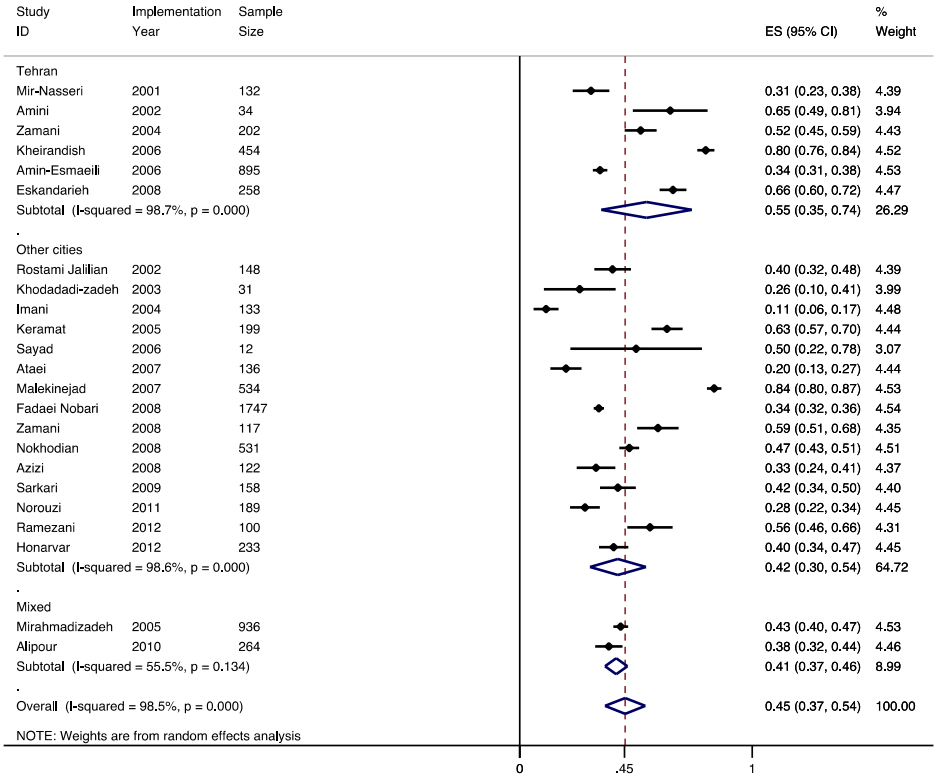


Figure 4. HCV co-infection prevalence: summary estimate of HCV/HIV (top) and HCV/HBV (bottom) co-infection prevalence and 95% confidence interval, by drug use pattern.



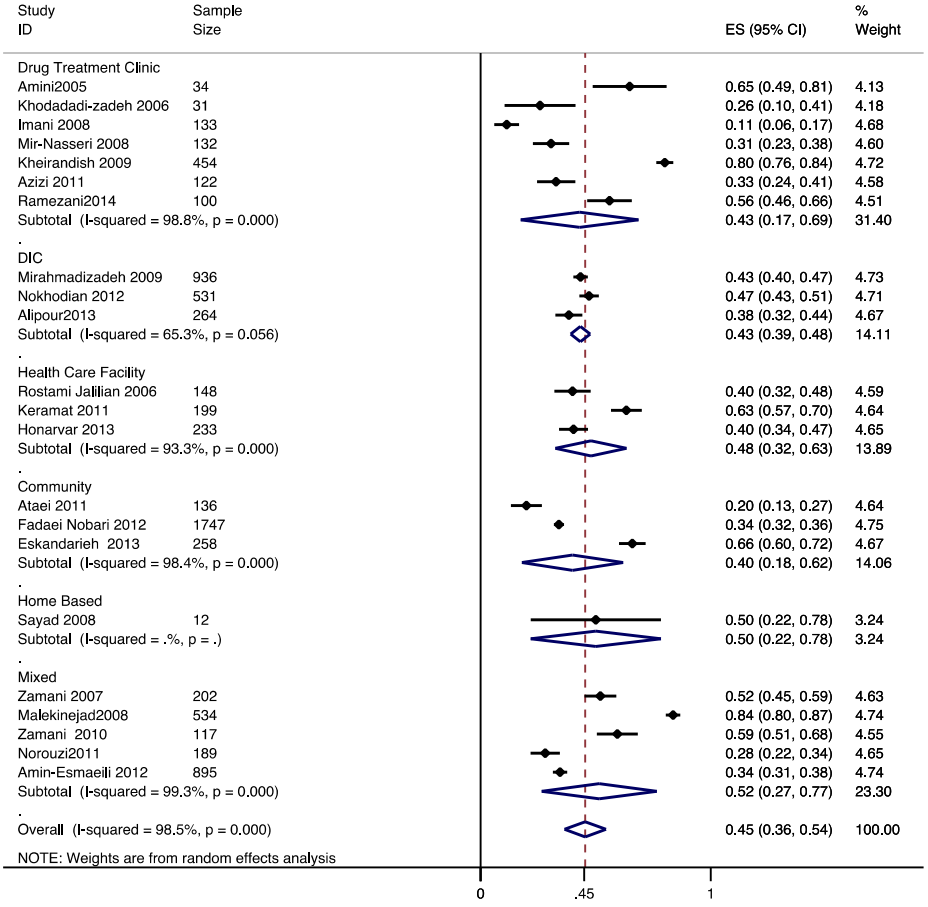


Figure 5. HCV prevalence in different cities/settings: summary estimate of HCV infection prevalence and 95% confidence interval among injection drug users, stratified by city (top) and study setting (bottom).

Table 4
Reported and pooled HCV infection prevalence and 95% confidence intervals by pattern of drug injection and risk factors

ID	Male	Female	Ever incarcerated	Never incarcerated	Ever shared needle/syringe	Never shared needle/syringe	Ever received tattoo	Never received tattoo
	n, % (95% CI)	*n*, % (95% CI)	*n*, % (95% CI)	*n*, % (95% CI)	*n*, % (95% CI)	*n*, % (95% CI)	*n*, % (95% CI)	*n*, % (95% CI)
Recent IDU (pooled)	1199, 44.6 (24–64)	81, 43.8 (30–57)	1160, 62.7 (30–95)	379, 35.2 (5–84)	820, 59.9 (35–84)	589, 56.0 (30–81)	285, 71.9 (44–88)	566, 60.1 (41–78)
Alipour 2013	226, 38 (20–60)	42, 36 (13–67)	-	-	-	-	-	-
Amin-Esmaeili 2012	859, 34 (30–37)	36, 44 (28–60)	631, 42 (38–46)	259, 14 (10–19)	566, 36 (32–39)	325, 32 (26–37)	-	-
Malekinejad 2008[a]	-	-	443, 86 (78–90)	89, 82 (39–100)	123, 79 (56–93)	76, 85 (77–93)	183, 94 (87–100)	349, 75 (69–83)
Zamani 2007	-	-	-	-	99, 53 (43–63)	103, 50 (40–60)	84, 58 (47–68)	118, 47 (38–56)
Zamani 2010	114, 60 (51–69)	3, 66 (20–93)	86, 59 (48–69)	31, 64 (47–81)	32, 71 (56–87)	85, 56 (45–67)	18, 83 (60–94)	99, 56 (46–66)
Ever IDU (pooled)	1875, 34.3 (21–47)	86, 28.5 (19–38)	720, 53.4 (23–83)	389, 35.1 (2–67)	399, 53.6 (30–76)	775, 41.7 (1–81)	660, 64.1 (50–77)	462, 48.3 (27–69)
Honarvar 2013	230, 40 (33–46)	4, 50 (1–98)	-	-	-	-	-	-
Imani 2008	131, 11 (6–16)	2, 0 (0–0)	47, 17 (6–27)	86, 8 (2–13)	26, 30 (13–48)	107, 6 (1–11)	-	-
Kheirandish 2009	-	-	342, 83 (79–87)	112, 69 (61–78)	58, 84 (72–92)	396, 79 (75–83)	125, 66 (41–86)	-
Mirahmadizadeh 2009	883, 44 (41–47)	48, 22 (11–34)	-	-	-	-	-	-
Mir-Nasseri 2008	128, 28 (20–35)	4, 25 (4–69)	-	-	60, 41 (29–54)	-	248, 71 (66–77)	220, 59 (52–65)
Nokhodian 2012	503, 47 (43–51)	28, 39 (21–57)	331, 58 (53–63)	191, 28 (21–34)	130, 76 (68–83)	263, 46 (40–52)	287, 55 (49–60)	242, 37 (31–43)
Sayad 2008	-	-	-	-	3, 100 (100–100)	9, 33 (2–64)	-	-
Azizi 2011	-	-	-	-	122, 32 (24–41)	-	-	-
Overall	3074, 37.9 (28–46)	167, 33.6 (25–41)	1880, 58.1 (39–77)	768, 44.2 (20–68)	1219, 56.5 (41–71)	1364, 49.1 (26–71)	945, 71.5 (55–88)	1028, 55.3 (40–70)

CI, confidence interval; IDU, injection drug user.
[a] Unpublished data.

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