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**Intravenous Drug Use: the Predominant Risk Factors for Hepatitis C Virus Infection.**

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**Abstract:**

This manuscript provides a literature review of prevalence and routes of hepatitis C virus transmission, and prevention methods regarding its prevalence in different populations. There is a great difference in the frequency of hepatitis C virus infection of general population versus injection drug users. Even in developing countries with unsafe therapeutic injections and contaminated blood, the rate of disease is higher in injecting drug users. A literature review of published scientific reports on HCV epidemiology, prevalence, and its relation to addiction in some countries was performed. While different epidemiologic patterns of HCV infection exist with seroprevalence of 0.4% to 1.1% and 9.6% to 20% in general population in North America and some countries of North Africa; respectively, the frequency of HCV infection in injection drug users is 48% to 90%. Injection drug use seems the most important worldwide risk factor for hepatitis C virus infection. Substance abuse, HCV infection and mental illness frequently coexist and complicate HCV treatment. Implementing effective measures for preventing injecting drug use by effective drug education programs in school, research in behavioral/environmental addiction predispositions, implement strict drug abuse policy, regular estimation of addiction patterns, and to model prevention approaches according to every certain situation is necessary.

**Keywords: Hepatitis C virus; Global prevalence; Transmission; intravenous drug use**

**Introduction:**

It is estimated that approximately 130-170 million people worldwide are infected with hepatitis C virus (HCV). According to data from World Health Organization (WHO) community and blood donor surveys, the African and Eastern Mediterranean countries report the highest prevalence rates (>10%). The rates of infection in the general population and the incidence of newly-acquired cases indicate an appreciable change in the epidemiology of the infection in recent years. Prior to the widespread screening of blood donations, infected blood and blood products represented a common source of infection. Currently, the majority of such cases in North America and Northern Europe occurred among young adults and injected drug use is the most common risk factor. Other, less commonly reported modes of HCV acquisition are occupational exposure to blood, high-risk sexual activity, tattooing, body piercing and other forms of skin penetration. Finally, the overall rate of mother-to-child transmission from HCV-infected, HIV-negative mothers has been estimated at around 5%.<sup>(1)</sup> The wave of increased HCV-related morbidity and mortality that we are facing is due to the widespread availability of injectable therapies and the illicit use of injectable drugs.<sup>(2)</sup> More than 80% of hepatocellular (HCC) cases occur in developing countries, especially the Far East and Southeast Asia. Although immunization has been successful against hepatitis B virus (HBV), a changing disease burden of HCC has been observed in many parts of the world, but the shifting to HCV possibly because of the increasing prevalence of HCV infection in these countries.<sup>(3, 4)</sup> Intravenous

drug use (IDU) accounts for 75% of incident cases of HCV infection in the developed world.<sup>(4)</sup> The keys to a successful program appear to be appropriate patient selection as well as the delivery of care within an appropriate setting, preferably with a multidisciplinary team in a way that addresses the issue of addiction and other conditions simultaneously.<sup>(5)</sup>

Here we discuss about HCV epidemiology, and its association with addiction. Also need for implementing HCV awareness, screening for addiction and depression in primary care units, behavior therapy, and harm reduction therapy for addiction as routes for prevention HCV transmission is discussed.

**Methods:**

A review of literature was performed in 2009 to summarize scientific reports on epidemiology and transmission of the HCV infection and its association with addiction in Iran and some other countries. A search was performed on MEDLINE, EMBASE, PsycINFO databases, Iran Medex and other sources to identify published studies on social networks of. Articles published during recent years (1994-2009) were searched by using the following key words: Hepatitis C, epidemiology, prevalence, transmission, general population, addiction, intravenous drug users, and psychology. Country-specific information was searched by adding a country name to the search.

**Prevalence of hepatitis C infection in general population versus intravenous drug users**

Region-specific HCV prevalence estimates range from < 1.0% in Northern Europe to > 2.9% in Northern Africa.<sup>(2)</sup> The low-

est prevalence (0.01%-0.1%) has been reported from countries in the United Kingdom and Scandinavia; the highest prevalence (15%-20%) has been reported from Egypt.<sup>(6, 7)</sup> HCV infection is the most common chronic blood-borne infection in the United States. A national survey estimated 3.9 million US citizens (1.8%) have been infected with HCV, and injection drug use is currently the major risk factor for acute HCV infection.<sup>(8)</sup> In a survey in the USA, 48.4% of anti-HCV-positive persons between 20 and 59 years of age reported a history of injection drug use.<sup>(9)</sup> Evidence demonstrates that if the HCV disease is not contained in the USA, it will continue to spread and the death rate from hepatitis C will rise to a level far greater than that of AIDS.<sup>(10)</sup>

The most common risk factor for HCV infection in the Iran and many other countries in the world is illicit drug use, specifically intravenous drug use, although approximately one third to one half of cases has no identified risk factor.<sup>(11, 12)</sup> Of 965 subjects in the general population of Northern Italy, the prevalence of anti-HCV was 2.6%.<sup>(13)</sup> The HCV prevalence in 2200 of blood sample general population living in an urbanized region in of the Dutch population was 0.2%.<sup>(14)</sup> Of 1131 participants who had injected heroin or cocaine from Seville and Granada, Spain; Cologne, Germany; Vienna, Austria; Brussels, Belgium; Athens, Greece; Dublin, Ireland; London, England; Lisbon, Portugal and Perugia, Italy; 595 (52.6%) participants reported HCV-positive status. Multivariate analysis showed that women are at less risk than men, and longer drug use, injecting while in prison, sharing needles, and reported

positive status for tuberculosis, HBV, HIV or sexually-transmitted disease were positively associated with HCV.<sup>(15)</sup> In a study in France risk factors associated with HCV seroconversion were drug use (adjusted odds ratio [aOR] = 109.0; 95% confidence interval [CI] = 11.7-1015.8), digestive endoscopy (aOR = 5.7; CI = 1.4-23.8), and invasive radiology procedures (aOR = 11.6; CI = 1.7-78.5).<sup>(16)</sup> Of one hundred and eighty-two individuals attended in a drug addiction facility because of noninjecting drug use (NIDU) in Spain, HCV infection was detected in 23 (12.6%) of participants. Sharing the inhalation tube of crack cocaine [AOR 3.6, 95%; confidence interval (CI) 1.3-9.8, P=0.01], presence of tattoos (AOR 3.5, 95% CI 1.3-9.1, P=0.02) and age  $\geq 34$  years (AOR 3.9, 95% CI 1.3-11.6, P=0.01) were independently associated with HCV infection. The prevalence of HCV infection in NIDU is higher than in general population. This may be interpreted as inaccurate reporting of past intravenous exposure or as the presence of an unidentified source of HCV infection or have other risk factors such as sexual.<sup>(17)</sup>

Hepatitis B and C will remain for some time major health problems in Egypt and the entire continent of Africa.<sup>(18)</sup> During the 1970s the abuse of heroin and other opiates emerged as a serious problem of epidemic nature predominantly affecting young people in many countries of South-East Asia. Most recent studies have shown that heroin abuse has spread further in Asia, both socially and geographically, involving such countries as India and Sri Lanka, which had no previous experience with the problem. Studies have also shown that the abuse of manu-

factured psychotropic substances has been increasing.<sup>(19)</sup> In Taiwan, medical injections were found to be the main mode to sustain the persistent endemic state of HCV infection within a community. IDU is the predominant mode of HCV transmission in China. The pooled prevalence of HCV infection among IDUs in China was 61.4% (95% CI 55.7-67.2%), and the epidemic was most severe in Hubei, Yunnan, Guangxi, Hunan and Xinjiang. IDUs were 9.24 times more likely to be infected with HCV than non-IDUs, while non-IDUs were more likely to be infected with HCV than members of the general population and other risk populations.<sup>(20)</sup> A study in Thailand showed widespread opium addiction among the hill tribes. Over 90% of them were addicted to opium. About three-quarters of them used salicylate analgesics with opium. Illness, in particular abdominal pain, was the most frequent cause of their addiction.<sup>(21)</sup> In a study in St. Petersburg and Leningrad region of Russia, infection with hepatitis C among injection drug users was 85%.<sup>(22)</sup> Prevalence of hepatitis C in Iran ranges from 0.5% to 0.97% in blood donors<sup>(23)</sup>, 31.5% of drug abuser inmates in a prison of Hamadan<sup>(24)</sup>, and 88.9% of intravenous drug abusers of a prison in Guilan.<sup>(25)</sup> In a study in Tehran of Iran, 105 (52.0%) of 202 injecting drug users were positive for HCV-antibody. HCV infection was associated with length of drug injection (more than 10 years) [odds ratio (OR), 3.25; 95% confidence interval (CI), 1.43-7.38], length of lifetime incarcerations (OR, 3.44; 95% CI, 1.68-7.06), and a history of being tattooed inside prison (OR, 1.96; 95% CI, 1.06-3.62). High prevalence of HCV infection and its

association with incarceration-related exposures are important implications for harm reduction initiatives for drug using inmates in Iran.<sup>(26)</sup> A sample survey of 200 addicts attending the rehabilitation centre at Shiraz of Iran showed heroin use predominated among those who were urban residents, whilst villagers were more likely to be opium users.<sup>(27)</sup> The prevalence of substance dependency in 100 Iranian hemophilic patients was high in hemophilic patients (39%).<sup>(28)</sup>

#### **Co-morbidities in HCV-infected subjects with addiction/substance use**

HCV co-infection with the hepatitis B virus and other hepatitis viruses is common in individuals who inject drugs.<sup>(29)</sup> HCV co-infection with HIV ranges from 5% to more than 30%, depending on the overall prevalence of HIV in the area.<sup>(30)</sup> A study conducted in KwaZulu-Natal Province in South Africa where HIV is predominantly a sexually transmitted infection and intravenous drug use is rare in this region. The prevalence of HCV was 6.4% and that of HIV, 40.2%. There was a significantly higher prevalence of HCV among HIV infected patients as compared to HIV negative patients (13.4% vs. 1.73% respectively,  $P < 0.001$ ).<sup>(31)</sup> In a study of 250 IDUs from a de-addiction centre, one hundred and forty-nine (59.6%) IDUs were positive for HIV antibody, 226 (90.4%) were positive for anti HCV antibody and 27 (10.8%) were positive for HBsAg.<sup>(32)</sup> In a study among 266 drug users attending a drug-addiction treatment centre in Dhaka, Bangladesh, the seroprevalences of hepatitis B virus surface antigen (HBsAg), anti-HBc, anti-HBs, and anti-HCV antibodies among the IDUs were 8 (6.2%), 41 (31.8%), 15 (11.6%), and 32 (24.8%), and among

the non-IDUs were 6 (4.4%), 33 (24.1%), 9 (6.6%), and 8 (5.8%) respectively. The prevalence of HCV infection was significantly higher among the IDUs.<sup>(33)</sup> In a study of 973 inmates of eight Italian prisons, 30.4% were intravenous drug users. In this sample, high seroprevalence rates were found (HIV: 7.5%; HCV: 38.0%; anti-HBc: 52.7%; HBsAg: 6.7%). HIV and HCV seropositivity were associated strongly with intravenous drug use (OR: 5.9 for HIV; 10.5 for HCV). Tattoos were associated with HCV positivity (OR: 2.9). The number of imprisonments was associated with HIV infection, whereas the duration of imprisonment was only associated with anti-HBc.<sup>(34)</sup> On enrollment of 478 active opium or heroin users in rural parts of Iran, 108 (23%) reported injecting; 79 (73%) of them reported sharing needles. Of 65 participants tested for HIV, 46 (72%) were positive.<sup>(35)</sup> In a study of 103 former heroin addicted adults on methadone maintenance therapy in the USA, most methadone-maintained subjects had at least one marker for viral hepatitis. A quarter of subjects had silent HBV infection, defined as the presence of HBV DNA in the absence of HBsAg.<sup>(36)</sup> In a study in Switzerland, 78.3% of the 1035 patients entering heroin-assisted treatment, were HCV positive.<sup>(37)</sup> In a study of 433 subjects among a whole population of 900 inmates in the Prison of Bologna, Italia, 147 (33.9%) were intravenous drug users (IDU) and 286 were not addicts (66.1%). 12.5% of inmates were HIV positive, 8.1% HBV positive and 31.1% HCV positive.<sup>(38)</sup> The study conducted on a sample of 210 women from the Montreal detention center, showed that addicted inmates pre-

sent earlier onsets of both drug use and criminal behaviors compared to other female inmates.<sup>(39)</sup> In a study among 161 registered IDUs of a needle exchange and harm reduction programme in Karachi, Pakistan; number of drug injections per day was 2.3. Shooting drugs in group sharing syringes was reported by 128 (79.5%) of IDUs. Over half (58.3%) reported paying for sex and 64% reported never using a condom. Commercial selling of blood was reported by 44 (28%). The prevalence of hepatitis B was 12 (7.5%), hepatitis C 151 (94.3%) and syphilis 21 (13.1%).<sup>(40)</sup>

In 2856 consecutive HCV-infected patients, anti-HCV was detected in 2.1% of the members of their original families, and in 13.8% of 2662 sexual partners. The overall rate of infection for offspring was 2.3%, but the risk was significantly higher when the index case was female. Coinfection with HBsAg was recorded in 4.7%, and with HIV in 2.6% of the HCV-infected index cases. The risk for sexual partners was significantly higher when the risk factor for the index case was intravenous drug (IVD) use rather than blood transfusion. Logistic regression analysis showed that female gender and drug addiction in sexual partners of index case were independent factors significantly associated with HCV transmission to sexual partners. Sexual transmission may not be the main route of transmission though, since IVD use in the sexual partners themselves was independently associated with HCV infection.<sup>(41)</sup> Renal disease is a complication of heroin addiction. Of 19 patients with serological evidence of HCV infection, 68.4% were found to have membranoproliferative glomerulonephritis (MPGN).<sup>(42)</sup> Improved

detection of alcohol consumption in the context of HCV and opiate dependence would allow for earlier intervention in this population that is at particular risk of liver disease and fatal respiratory-depressed overdose.<sup>(43)</sup>

#### **Vulnerability to addiction and specific treatment modalities**

According to a study, high stress load in childhood and before puberty was related to negative affect in all participants. In patients, high stress load was related to depressive and posttraumatic symptoms, and the diagnoses of major depressive disorder and personality disorders.<sup>(44)</sup> Depression in older adults is a serious health problem with a poor prognosis. The different risk factors described in addiction could be related to a depressive dimension.<sup>(45, 46)</sup> Medications which bind to opioid receptors are increasingly being prescribed for the treatment of multiple and diverse chronic painful conditions. The psychological addiction that can occur with the use of these medications, abuse and diversion of these medications is a growing problem as the availability of these medications increases and this public health issue confounds their clinical utility.<sup>(47)</sup> Of 170 schools from seven countries (Austria, Belgium, Germany, Greece, Italy, Spain, Sweden) by European Drug Abuse Prevention trial (EU-Dap) study, 34.9% of students had smoked cigarettes, 24.7% had been drunk, and 8.9% had used cannabis at least once in life.<sup>(48)</sup> In Germany each general practitioner who has completed an additional training in addiction medicine is allowed to prescribe substitution drugs to opioid dependent patients.<sup>(49)</sup> In a study of 26 former male inmates who

had recently used drugs within correctional facilities in Vancouver, Canada showed the harms normally associated with drug addiction and injection drug use are exacerbated in prison. The scarcity of syringes has resulted in patterns of sharing amongst large numbers of persons. Continual reuse of scarce syringes poses serious health hazards and bleach distribution is an inadequate solution.<sup>(50)</sup> Harm reduction policies, such as needle exchange programs, injection centers, and substitution treatments, attempt to reduce the health and social damage associated with illegal drug use.<sup>(51)</sup> Since 1996 in France, IDUs have had greatly improved access to sterile syringes and substitution treatments. However, because of the persistent sharing and re-use of syringes and a remaining high HCV prevalence in IDUs, efforts to facilitate access to sterile syringes must continue, and targeting of at-risk groups must be improved.<sup>(52)</sup> Harm reduction can be understood as "policies and programs which are designed to reduce the adverse consequences of mood altering substances without necessarily reducing their consumption"; it is consistent with the best traditions of both medicine and public health.<sup>(53)</sup> Methadone pharmacotherapy has been the most widely used treatment for opioid addiction in injection drug users. Methadone has adverse drug-drug interactions with many antiretroviral therapeutic agents that can contribute to nonadherence and poor clinical outcomes in this high-risk population. Buprenorphine has a significant pharmacokinetic interaction with efavirenz but no pharmacodynamic interaction; therefore, simultaneous administration of these drugs is not associ-

ated with opioid withdrawal, as has been observed with methadone.<sup>(54)</sup> Injection drug use is the most significant risk factor for HCV infection in most western countries. The prevalence of HCV antibody is high in injection drug users (53-96%) and in patients enrolled in methadone maintenance programs (67-96%).<sup>(55)</sup>

Integrating services for hepatitis C, addiction, mental health, and psychosocial problems involves a collaboration of medical providers and peer educators and incorporates elements of other proven behavioural models, including self-help groups, therapeutic communities, and peer interventions.<sup>(56)</sup> According to a study, harm reduction programmes was associated with a lower incidence of HCV and HIV infection in ever-injecting drug users, indicating that combined prevention measures, but not the use of needle exchange programme or methadone alone might contribute to the reduction of the spread of these infections.<sup>(57)</sup> Cocaine injectors had the highest risk profile and the highest incidence of HCV (82.6 per 100 person years, 95% CI 52.0-131.0).<sup>(58)</sup> According to findings of a study took place in Granada of Spain, intravenous diacetylmorphine (DAM) could be safely delivered, and in physical health, HIV risk behavior, street heroin use, and days involved in crime, DAM plus methadone was more efficacious than methadone alone.<sup>(59)</sup> Screening for alcoholic beverage drinking should include measures of quantity-frequency, as well as screens for alcohol abuse or dependence.<sup>(60)</sup> The synthetic opioids are not routinely assessed in many screening procedures. If a drug screen is positive, but the patient denies drug use, the labo-

ratory should be asked to conduct a test using gas chromatography/massspectroscopy.<sup>(61)</sup>

Optimally, all patients with HCV should be screened for psychiatric and substance use disorders before initiation of antiviral therapy. Although interferon-based therapies can lead to severe neuropsychiatric adverse effects, including in rare instances suicide, evidence suggests that many patients with comorbid psychiatric and substance use diagnoses can be treated safely and effectively using comanagement strategies. The definition of HCV 'treatment' must expand to include treatment of the comorbid psychiatric and substance use disorders that accompany HCV infection and precede antiviral therapy.<sup>(61)</sup>

#### **Summary and conclusions:**

In a desk-based data on HCV prevalence among IDUs in 57 countries and in 152 sub-national areas reviewed literature released between 1998 and 2005, HCV prevalence of at least 50% among IDUs in 49 countries or territories was found. Available regional estimates varied widely, from 10 to 96% in Eastern Europe and Central Asia, from 10 to 100% in South and South-East Asia, from 34 to 93% in East-Asia and the Pacific, from 5 to 60% in North Africa and the Middle-East, from 2 to 100% in Latin America, from 8 to 90% in North America, from 25 to 88% in Australia and New Zealand, and from 2 to 93% in Western Europe. Only in Colombia and Lebanon were all HCV prevalence estimates below 20%. In China, Poland, Puerto Rico, Russia, Spain, Switzerland, Thailand and Viet Nam, estimates of the prevalence of

HIV/HCV co-infection among IDUs reached 90%.<sup>(62)</sup>

Addiction professionals belong in the forefront of prevention and management of this disease. We can assist HCV infected patients by helping them stabilize their lifestyles, teaching prevention and health maintenance, promoting access to diagnosis and treatment, monitoring for treatment side effects, and providing encouragement to remain in treatment.<sup>(63)</sup>

It seems due to insufficient preventive measures, transmission of HCV infection would be swifter in developing countries. Intravenous drug use is a major risk factor for hepatitis C virus infection. Control of addiction is an important measure for HCV transmission prevention. There is an urgent need to implement modern treatments for opiate dependence such as: effective drug education programs in school, research in behavioral/environmental addiction predispositions, implement strict drug abuse policy, regular estimation of addiction patterns, and to model prevention approaches according to every certain situation.

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