Hepatitis C status awareness and test results confirmation among people who inject drugs in Ukraine

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HEPATITIS C STATUS AWARENESS AND TEST RESULTS CONFIRMATION AMONG
PEOPLE WHO INJECT DRUGS IN UKRAINE

by

Olena Iakunchykova

A Thesis
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ABSTRACT

Background. Hepatitis C virus (HCV) positivity is frequently found in people who inject drugs (PWID). The prevalence of HCV in this population in Ukraine is estimated at 71%. As treatment for HCV infection becomes more available, it is important to know what modifiable factors are related to testing, linkage to care and treatment.

Methods. Cross-sectional survey data were used to assess the association between participation in opioid agonistic therapy (OAT) and positive HCV status awareness and confirmation in the sample of 1002 HCV positive PWID in Ukraine. The predictors of receiving HCV testing ever in life and in the past 12 months were also assessed in the total sample of 1,613 PWID, stratified by positive HIV status awareness.

Results. Current and previous participation in OAT was associated with HCV positive status awareness (prevalence ratio [PR] = 1.52, 95% CI 1.34-1.73 for current vs. never OAT; PR = 1.30, 95% CI, 1.13-1.50 for previous vs. never OAT). Current, but not previous, OAT participation was independently related to HCV status confirmation (PR = 1.55, 95% CI 1.28-1.88). HCV testing any time in life was related to OAT only among those participants who were not aware of their HIV positive status. Other factors related to HCV positive status awareness were HIV positive status awareness, importance of religion, living with a spouse or partner, and hazardous alcohol use. HCV status confirmation was associated with HIV status awareness, importance of religion, gender, income and current anti-retroviral treatment.

Conclusions. Encouraging PWID to participate in OAT may be an effective strategy to diagnose and link PWID who are HCV positive to care. More studies are needed to assess HCV treatment utilization among PWID in Ukraine and OAT as a possible way to retain them in treatment.
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Chapter 1. LITERATURE REVIEW

1.1. Hepatitis C virus prevalence

**HCV prevalence in the world**

An estimated 185 million people are infected with hepatitis C virus (HCV) in the world and most of them are not aware of their status.\(^1\) There is evidence of a growing number of people with anti-HCV antibodies, from 2.3% (95% confidence interval [CI]: 2.1%-2.5%) and >122 million people in 1990 to 2.8% (95% CI: 2.6%-3.1%) and >185 million in 2005.\(^1\) Regional estimates of HCV prevalence indicate that Central and East Asia and North Africa/Middle East had high HCV prevalence; South and Southeast Asia, Andean, Central, and Southern Latin America, Australasia, Caribbean, Oceania, and Central, Eastern, and Western Europe, and sub-Saharan Africa had moderate HCV prevalence; and Asia Pacific, Tropical Latin America, and North America had low HCV prevalence in 2005.\(^1\) The regions with the highest estimated numbers of people with anti-HCV antibodies are South Asia (>50 million), East Asia (>50 million), North Africa/Middle East (>15 million), Southeast Asia (>11 million), and Western Europe (>10 million).\(^1\)

Another study presented a lower estimate of the global prevalence of anti-HCV antibodies: 1.6% (1.3-2.1%), corresponding to 115 (92-149) million past infections.\(^2\) Additionally, the viraemic (RNA positive) prevalence was predicted to be 1.1% (0.9-1.4%), corresponding to 80 (64-103) million viraemic infections.\(^2\)

**HCV prevalence in Ukraine**

Data about HCV prevalence in Ukraine are relatively less reliable than in North America and Western Europe. Anti-HCV prevalence of 2.7% was estimated for general population in Ukraine based on studies of blood donors.\(^3\) The population most affected by HCV is people who
inject drugs (PWID) due to frequent exposure via the parenteral route of transmission; because of the introduction of blood transfusion products testing, blood transfusion is no longer a major source of HCV infection.\textsuperscript{4} In European region, the prevalence of anti-HCV among PWID varied from 5\% to 90\%, while studies in Ukraine identified that 71\% of PWID have anti-HCV antibodies.\textsuperscript{3} With estimated numbers of PWID in Ukraine varying from 278,000 to 387,000,\textsuperscript{5} the number of PWID positive for anti-HCV antibodies approximates 266,300, and the number of PWID with chronic HCV infection approximates 197,000.\textsuperscript{3}  

\textit{Methodology to assess HCV prevalence}

As indicated above, the prevalence of anti-HCV antibodies from population-based studies is used to estimate global, regional and national levels of HCV infections. However, these estimates have limited validity because incidence and excess mortality are difficult to obtain due to a lack of clinical symptoms of HCV infection during many years after initial infection. Furthermore, poor surveillance systems for HCV infection worldwide limit researchers’ ability to estimate HCV burden. Disease modeling and meta-analysis are used to produce prevalence estimates and predict prevalence in countries where data are sparse or not available.\textsuperscript{1} In addition, the burden of HCV might be overestimated because most of the country level studies are conducted in the adult population and among people who inject drugs or blood donors with prevalence higher than population averages.\textsuperscript{2} Anti-HCV antibodies are indicative of previous encounter of organism with HCV. However, chronic HCV infection is detected by presence of HCV RNA in the blood.\textsuperscript{6} Therefore, anti-HCV antibody testing overestimates HCV prevalence because it doesn’t discriminate between chronic HCV infection and cured HCV free states.\textsuperscript{2} Despite these limitations in our understanding of the true prevalence of HCV worldwide and in specific countries, it is clear that HCV is highly prevalent among PWID, including in Ukraine.
1.2. Progression of hepatic disease caused by hepatitis C virus

The major routes of transmission for HCV are injection-drug use and receipt of a blood transfusion before 1990. The viral replication occurs in hepatocytes and, possibly, B lymphocytes, at a rate of 10 trillion virion particles per day, which is extremely robust.\(^7\) HCV infection is infrequently diagnosed during the acute phase of infection. Clinical manifestations can occur seven to eight weeks after initial infection, though symptoms are usually mild. The majority of adults with acute HCV (74 to 86 percent) develop chronic disease and persistent viraemia and can remain asymptomatic for a prolonged period.\(^7\) Spontaneous clearance of HCV RNA once chronic infection has been established is infrequent.\(^7\) Viraemic patients are infectious to others and are at risk of developing serious liver disease (hepatitis, cirrhosis or hepatocellular cancer).\(^8\) In most cases, chronic infection leads to hepatitis and some degree of fibrosis that presents with relatively nonspecific symptoms such as fatigue. Liver cirrhosis develops in approximately 15 - 20 percent of those infected and leads to severe complications and death.\(^7\) The time frame in which the sequence of liver damage develops varies: about one third of HCV-infected individuals are diagnosed with serious liver disease within 20 years of infection, while there is no progression in another third of persons for 30 years or longer.\(^9\) Clinical progression of liver disease is accelerated among men, in the presence of alcohol abuse, among those who were infected at older ages, and among those co-infected with HIV-1 or HBV.\(^9\) Once cirrhosis is established, the risk of hepatocellular carcinoma is approximately 1 to 4 percent per year.\(^10\) Although clinical progression does not occur among everyone with chronic HCV, the high prevalence of the disease translates into large numbers of persons with severe liver damage.

1.3. Current diagnostics

*Diagnostic tests for HCV infection*
Diagnostic tests for HCV infection are divided into serologic assays for antibodies and molecular tests for viral RNA. Persons with cleared HCV infection do not carry viral particles detectable in the blood, but usually remain positive for anti-HCV antibodies. The first diagnostic test to be performed to detect HCV infection is serologic assay, which is based on anti-HCV antibody detection and is not able to discriminate between chronic and cleared HCV infection. Serologic assays to detect anti-HCV antibodies are represented in two forms: rapid diagnostic test (RDT) or laboratory-based enzyme-immunoassay (EIA). Laboratory-based EIAs require existing laboratory infrastructure with high-volume throughput, that is accessible for individuals in need. So, when there is limited access to laboratory infrastructure and testing, RDT is recommended. Also, RDT can be a preferable strategy to facilitate linkage to care and treatment among certain high-risk groups (e.g., PWID, people in prisons and other closed settings, MSM and sex workers, and HIV-infected persons). The simplicity, relatively low cost and rapid turnaround time of RDTs lead to improved access to HCV testing, enhanced linkage to care and retention in care. RDTs can also be used in outreach programs for hepatitis C screening. RDT has high sensitivity (83% to 100%) and specificity (99% to 100%) in different settings and populations based on studies of different brands compared to reference EIAs.

Regarding test for viral RNA, qualitative PCR test is used universally nowadays for confirmation of chronic HCV infection. PCR assays are able to detect the presence of HCV RNA at broad range from 12 to 7,700,000 IU/ml, with analytical sensitivity as low as 5 IU/ml for qualitative HCV RNA tests. Both qualitative and quantitative assays are recommended, the sensitivity and lower cost of qualitative assays for HCV RNA makes them preferable for the confirmation of viremia and the assessment of treatment response.

*Proportion of people with HCV aware of their status*
In the United States only 50% of those who had ever been infected were diagnosed and aware of their HCV and 27% had HCV RNA confirmed.\textsuperscript{16} Available studies suggest that only 10% to 40% of people with HCV in Europe are aware of their infection.\textsuperscript{4} Screening campaigns in Ukraine were introduced among high risk groups since 2009. A survey of PWID in 2013 reported that 50% of PWIDs are aware of their HCV positive status in Ukraine.\textsuperscript{17} However, reliable data on the proportion of persons with anti-HCV antibodies who confirmed HCV RNA presence in their blood are not available for Ukraine.

**Awareness of HCV status and injection behaviors among PWID**

Awareness of HCV status is expected to influence injection behaviors among PWID. However, several studies conducted in different countries have failed to find the expected relation between these two characteristics. For example, a study of PWID in Montreal, Canada, showed that high levels of risky injection behaviors (borrowing drug preparation equipment, borrowing syringes) were associated with poor physical health and problems obtaining sterile equipment, but not with HCV status awareness.\textsuperscript{18} Similarly, a study from five U.S. cities showed no association between awareness of positive HCV status and safer injection practices.\textsuperscript{19} In addition, one study conducted in the U.S. among patients presenting for addiction treatment had conflicting results: participants who were aware of their positive HCV status exhibited some risk reduction behaviors more frequently than HCV negative/unaware (e.g., participating in syringe exchange programs, cleaning needles with bleach), but also were more likely to share needles.\textsuperscript{20} In an international longitudinal study, PWID who received positive HCV test results increased their frequency of alcohol use.\textsuperscript{21} Furthermore, both HCV negative and HCV positive groups didn’t change their drug injection behaviors post-notification.\textsuperscript{21}
This lack of the expected association between HCV status awareness and injection behavior in many studies may be explained by the extremely high prevalence of HCV among PWID, and hence, feelings of helplessness toward infection.\textsuperscript{22} Also, misperceptions of consequences of chronic HCV infection, confusion of HCV with other infectious diseases, and lack of access to counseling may account for the apparent lack of associations between awareness of HCV positive status and behaviors.\textsuperscript{22,23} Despite the uncertainty related to the effect of HCV testing on behavioral change among PWID, we argue in support of HCV screening as a means of engaging people with chronic infection into treatment and decreasing the population burden of HCV.

\textit{Factors related to HCV testing and confirmation}

Barriers to HCV testing that may be responsible for the low percent of the population with chronic HCV who are aware of their condition in low and middle income countries (LMIC): (1) discrimination and social marginalization of groups at the highest risk of acquiring HCV viral hepatitis (PWID, men who have sex with men (MSM), prisoners, and sex workers); (2) lack of health care infrastructure that would serve populations most affected with HCV and follow harm reduction approach; (3) lack of information about consequences of HCV infection, chronic hepatitis and treatment options among both health care providers and risk groups; (4) limited data on the epidemiological situation in the country to inform public health policy regarding hepatitis testing approaches; (5) scarce financial resources and lack of access to reliable low-cost HCV diagnostic tests, including rapid serological tests and viral RNA tests; (6) limited access to treatment for HCV, which is supposed to be the next step of HCV infection management; and (7) lack of political and financial commitment in governments.\textsuperscript{15,24}

\textit{Continuum of care}
The treatment cascade is an effective tool that is used by state and local agencies to identify gaps in the delivery of care, to prioritize and target resources, and to monitor the implementation of particular policies. According to proposed steps of the chronic hepatitis C care continuum (treatment cascade), people with detected anti-HCV antibodies need to be linked to care, confirm their chronic infection by HCV RNA detection and undergo liver fibrosis staging. At last, patients are prescribed antiviral treatment with the ultimate goal to achieve sustained virologic response (SVR). SVR is recognized as the best criterion of successful outcome after therapy for HCV infection; it is defined as an absence of detectable viral RNA in the blood with PCR test sensitivity of at least 50 IU/mL 6 months after completion of the treatment.

There are large gaps in the HCV treatment cascade, which indicate a number of opportunities to improve the continuum of care and achieve goals in treatment. Only 5–9% of all people with chronic HCV infection in the U.S. successfully progressed from detection of HCV infection to achievement of SVR. After treatment for chronic hepatitis caused by HCV becomes more convenient, effective, and safe, it is expected that the progression of HCV-infected individuals through the treatment cascade will improve.

1.4. Treatment for people with HCV

When treatment schemes with interferon were still used, liver functioning evaluation and liver fibrosis staging was done before making a decision about treatment considering possible complications and side effects. Some patients were reluctant to accept treatment for HCV due to low effectiveness, often complications, long duration, and high cost of schemes with interferon. In 2013, direct antiviral treatment (DAT) was approved for treatment of HCV. The regimens with DAT are more effective, cause less side effects, and require less time to achieve SVR. Still, lack of awareness of HCV status and poor accessibility due to high cost of treatment seem to be the
main restraining factors against universal treatment of chronic HCV. Access to chronic hepatitis C treatment is limited in most countries. In the U.S., treatment was prescribed in only 16% of those with chronic HCV, and 9% achieved SVR. In Ukraine, treatment with peg-interferon and ribavirin was introduced in 2013, and treatment with direct antiviral drugs was supported for 1,500 patients from risk groups (mostly PWID) in 2015-2016. In a cross-sectional survey conducted in 2013, 9.4% of HCV positive PWID reported receiving some treatment. While opportunities for better coverage with treatment in Ukraine are being explored, it is critical for program planners to obtain information about factors related to hepatitis C testing among PWID. It is also important to increase linkage to care and HCV status confirmation.

1.5. HCV and HIV co-infection

Clinical progression of HCV infection is considerably accelerated in HCV/HIV co-infected persons. Due to common routes of transmission of HCV and HIV, co-infection in PWID is high. For example, in Ukraine, co-infection with HIV was found in 26% of PWID with anti-HCV antibodies. As highly active antiretroviral therapy (HAART) for HIV treatment has become more widely available, the progression of comorbid conditions has become among the causes of morbidity and mortality among PLWH. Liver disease caused by HCV is the second leading cause of death among those with HIV infection in the U.S. after HIV/AIDS.

From the perspective of health care delivery, HIV testing became available to the general population and groups at risk for HIV earlier than HCV testing. HCV testing is still not widespread and available in LMIC. So, PWID are more likely to be diagnosed HIV positive and linked to care for HIV before getting HCV test.

1.6. Opioid agonistic therapy for opioid dependence
Opioid agonist therapy (OAT) has recognized effectiveness to reduce opioid use among persons with opioid addiction. In addition, it has a documented effect on HIV and HCV transmission, HIV risk behaviors, retention on ARV therapy and achievement of viral suppression. In Ukraine, buprenorphine maintenance treatment became available to a limited number of patients in 2004, and OAT using methadone was introduced in 2008. As of 2015, 8,400 opioid-addicted patients are receiving OAT through the medical care system in Ukraine. However, a lot of structural and individual level barriers hinder OAT treatment utilization and scale up in Ukraine despite high levels of need. Since the first OAT programs in Ukraine were launched, several studies have been published that reported their outcomes. There is evidence that OAT leads to a decrease in illicit opioid use, reduction of self-reported injection risk behaviors and criminal activity, and also improvement in physical and mental health outcomes. OAT integrated into inpatient TB treatment improved tuberculosis treatment outcomes. Health-related quality of life and quality of health care indicators were shown to be better in patients receiving integrated and collocated services. Participation of PWID in OAT programs proved to be effective in strengthening the response to HIV infection and improving continuum of care outcomes for people who live with HIV (PLWH). As such, OAT may be an effective way to address hepatitis C epidemics among PWID in Ukraine. To our knowledge, no studies to date have addressed the influence of participation in OAT on HCV testing, confirmation, or treatment.

1.7. Study significance and objectives

The primary objective of HCV testing is to identify individuals with anti-HCV antibodies and direct them to further confirmation of chronic infection and treatment. Timely identification and linkage of infected individuals to care ensures they receive appropriate diagnosis and treatment with direct-acting antiviral therapy. Therapy can stop progression of liver disease, reduce HCV-
related mortality and prevent spread of the virus to partners.\textsuperscript{45} Therefore, treatment of infected individuals, if widely implemented, may reduce population levels of HCV over time.\textsuperscript{46} Furthermore, HCV testing represents an opportunity to provide preventative interventions aimed at reduction of transmission or acquisition. While evidence linking the effect of HCV testing to safer injection behavior among PWID is inconclusive, additional prevention services provided along with testing may bring change.\textsuperscript{18, 20, 21} Another reason for testing among PWID is surveillance for acute and chronic hepatitis C in this high-risk group, monitoring of trends in incidence and prevalence, and planning of further public health actions.\textsuperscript{47} In conclusion, testing is a crucial component of the response to the hepatitis C epidemic.

While low and middle income countries (LMICs) are affected with HCV disproportionately, only a small fraction of the affected population is aware of anti-HCV antibody status and has access to confirmation of chronic HCV infection with RNA test.\textsuperscript{4} Even those with confirmed diagnoses have limited linkage to care and access to treatment, due to structural barriers and treatment cost. Participation of PWID in OAT may be associated with higher uptake of HCV testing, confirmation, and treatment. The present study is aimed to give preliminary conclusions regarding the association between receiving OAT and HCV testing, diagnosis confirmation and HCV status awareness among PWID in Ukraine. Because PWID who are HIV positive and aware of their status are expected to have more contacts with the health care system, OAT enrollment may not have particularly high association with HCV testing in this group. So, the study presents the analysis of association between OAT enrollment and HCV testing for two separate groups of PWID: those who are aware of their positive HIV status, and those who are HIV negative or unaware of their HIV status.

The study objectives are:
1. to report the proportion of PWID in 5 Ukrainian cities who have ever been tested for anti-HCV antibodies.

2. to report the proportion of anti-HCV antibody positive PWID who are aware of their positive hepatitis C status and have undergone confirmatory HCV testing.

3. to explore the differences in HCV continuum of care outcomes (i.e., being aware of positive HCV status and undergoing confirmatory testing) relative to OAT enrollment and other predictors.

4. to measure the strength of association between OAT enrollment and HCV testing in persons aware of their positive HIV status and others.
Chapter 2. JOURNAL ARTICLE “Hepatitis C status awareness and test results confirmation among people who inject drugs in Ukraine.”

BACKGROUND

An estimated 185 million people are infected with hepatitis C virus (HCV) in the world.\textsuperscript{1} There is evidence of a growing number of people with anti-HCV antibodies, from 2.3\% (95\% confidence interval [CI]: 2.1\%-2.5\%) and >122 million people in 1990 to 2.8\% (95\% CI: 2.6\%-3.1\%) and >185 million people in 2005.\textsuperscript{1} Another study presented a lower estimate of the global prevalence of anti-HCV antibodies: 1.6\% (1.3\%-2.1\%), corresponding to 115 (92-149) million past infections. Data about HCV prevalence in Ukraine are relatively less reliable than in North America and Western Europe. Anti-HCV prevalence of 2.7\% was estimated for the general population in Ukraine, based on studies of blood donors.\textsuperscript{3} The population most affected by HCV is people who inject drugs (PWID) due to frequent exposure via parenteral route of transmission; because of the introduction of blood transfusion products testing, blood transfusion is no longer a major source of HCV infection.\textsuperscript{4} In WHO European region the prevalence of anti-HCV among PWID varied from 5\% to 90\%, while studies in Ukraine identified that 71\% of PWID have anti-HCV antibodies.\textsuperscript{3} With estimated numbers of PWID in Ukraine varying from 278,000 to 387,000,\textsuperscript{5} the number of PWID positive for anti-HCV antibodies is approximately 266,300, and the number of PWID with chronic HCV infection is approximately 197,000.\textsuperscript{3}

The majority of adults with acute HCV (74\%-86\%) develop chronic disease and persistent viraemia and can remain asymptomatic for prolonged periods.\textsuperscript{7} Spontaneous clearance of HCV RNA once chronic infection has been established is infrequent.\textsuperscript{7} Viraemic patients are infectious to others and are at risk of developing serious liver disease (hepatitis, cirrhosis or hepatocellular
The global viraemic (RNA positive) prevalence was predicted to be 1.1% (0.9-1.4%), corresponding to 80 (64-103) million viraemic infections.²

Most individuals infected with HCV are not aware of their status.⁴ In diagnosing HCV, serologic assays are first used to detect anti-HCV antibodies. This test is not able to discriminate between chronic and cleared HCV infection. Persons with cleared HCV infection usually remain positive for anti-HCV antibodies, although not all of them.⁷ To confirm chronic HCV infection, the RNA of HCV is detected using a qualitative PCR test.⁶ In the United States, only 50% of those infected were diagnosed and aware of their HCV and 27% had HCV RNA confirmed.¹⁶ Available studies suggest that only 10% to 40% of people with HCV in Europe are aware of their infection.⁴ Screening campaigns in Ukraine were introduced among high risk groups since 2009. A survey of PWID in 2013 reported that 50% of PWIDs are aware of their HCV positive status in Ukraine.¹⁷ However, reliable data on the proportion of persons with anti-HCV antibodies who confirmed HCV RNA presence in their blood are not available for Ukraine.

According to proposed steps of chronic hepatitis C care continuum (treatment cascade),¹⁶ people with detected anti-HCV antibodies need to be linked to care, confirm their chronic infection by HCV RNA detection and undergo liver fibrosis staging. Finally, patients are prescribed antiviral treatment with the ultimate goal to achieve sustained virologic response (SVR). Before the direct antiviral treatment became available, liver functioning evaluation was used to make a decision about treatment, considering possible complications and side effects. Nowadays, lack of awareness and availability along with high cost of treatments seem to be the main restraining factors against universal treatment of chronic HCV. Access to chronic hepatitis C treatment is limited in most countries. In the United States, treatment is prescribed in only 16% of cases, and only 9% achieved SVR.¹⁶ In Ukraine, treatment with peg-interferon and ribavirin was introduced in 2013, and
treatment with direct antiviral drugs was supported for 1,500 patients from risk groups (mostly PWID) in 2015-2016. In a cross-sectional survey conducted in 2013, 9.4% of HCV positive PWID reported receiving some treatment. While opportunities for better treatment coverage in Ukraine are being explored, it is critical for program planners to obtain information about factors related to hepatitis C testing among PWID. It is also important to increase linkage to care and HCV status confirmation.

Clinical progression of HCV infection is considerably accelerated in HCV/HIV co-infected persons. Due to the common means of transmission, HCV/HIV co-infection in PWID is high. In Ukraine, co-infection with HIV was found in 26% of PWID with anti-HCV antibodies. From the perspective of health care delivery, HIV testing became available to general population and groups at risk for HIV earlier than HCV testing. So, PWID are more likely to be diagnosed HIV positive and linked to care for HIV before getting HCV test.

Opioid agonist therapy (OAT) has recognized effectiveness to reduce opioid use among persons with opioid addiction. In addition, it has a documented effect on HIV and HCV transmission, HIV risk behaviors, retention on anti-retroviral (ARV) therapy and achievement of viral suppression. In Ukraine, buprenorphine maintenance treatment became available to a limited number of patients in 2004 and OAT using methadone was introduced in 2008. As of 2015, 8,400 opioid-addicted patients are receiving OAT through the medical care system in Ukraine. However, many structural and individual level barriers hinder OAT treatment utilization and scale up in Ukraine despite high need. Among them are compulsory drug user registration, law enforcement policies and practices in Ukraine, waiting lists and limited number of treatment slots, negative perceptions and attitudes toward OAT in PWID community. Also, inconvenient hours and treatment site locations, complex regimens, rigid drugs dispensing guidelines, and ill-
treatment medical staff, misaligned treatment goals between clients and providers affected OAT retention.38 Since the first OAT programs in Ukraine were launched, several studies have been published that reported their outcomes.41 There is evidence that OAT lead to decreases in illicit opioid use, reduction of self-reported injection risk behaviors and criminal activity, and improvement in physical and mental health outcomes.37, 42 OAT integrated into inpatient TB treatment improved tuberculosis treatment outcomes.43 Health-related quality of life and quality of health care indicators were shown to be better in patients receiving integrated and collocated services.44 The association between receiving OAT and HCV testing, diagnosis confirmation and HCV status awareness was not assessed.

This study aimed to quantify the proportion of PWID in OAT programs who have ever been tested for HCV, are aware of their positive hepatitis C status and have undergone confirmatory HCV testing. Differences in HCV continuum of care outcomes were explored relative to the enrollment in OAT and other predictors. Because PWID who are HIV positive and aware of their status are often linked to care and have more contacts with health care system, the OAT enrollment may not have particularly high association with HCV testing. So, the study presents the analysis of association between OAT enrollment and HCV testing for two separate groups of PWID. The first group includes those who are aware of their positive HIV status and the second group includes those who are HIV negative or unaware of their HIV status.

METHODS

Data collection

A cross-sectional survey was conducted among 1,613 PWID in 5 cities in Ukraine (Kiev, Odesa, Mykolaiv, Dnipro, Lviv). Three groups of opioid dependent PWID were the participants of the study, specifically: (1) never on OAT; (2) previously on OAT; (3) currently on OAT.
Recruitment occurred between 2014 and 2015 and took approximately 60-90 days in each city. A computer-assisted, self-administered instrument (CASI) using Qualtrics® was completed by all participants. HIV and HCV testing using rapid tests (CITO TEST HIV 1/2/0, Pharmasco and CITO TEST HCV, Pharmasco) along with pre- and post-test counseling was performed by medical staff.

**Sampling and eligibility criteria**

Two sampling methods were used to recruit participants to the study: respondent driven sampling (RDS) and random sampling. Eligibility criteria were: more than 18 years old, met ICD-10 criteria for opioid dependence, lived/worked in the city where the survey was conducted, provided informed consent, and agreed to undergo rapid HIV and HCV testing. RDS was used to recruit PWID who had never been on OAT. “Seeds” for RDS were recruited at community outreach sites and in each city and included at least one: female, individual age 18-25, and individual with less than 2 years of injecting history. Random sampling procedures were used for recruitment of PWID who had ever been on OAT or were currently receiving OAT, because pre-existing lists were available of OAT patients.

**Measures**

**Outcomes:** Four Hepatitis C status awareness and testing outcomes were assessed using self-reported data, as well as rapid testing:

1. had ever been tested for hepatitis C;
2. had been tested for hepatitis C during the last 12 months preceding the interview;
3. are aware of positive hepatitis C status (among HCV positive);
4. have received confirmatory HCV testing (among HCV positive).
Participants were asked to provide the date and result of their last hepatitis C test (N = 1,613). This information was used to identify participants who: (1) had ever been tested for hepatitis C and those who: (2) had been tested during the last 12 months preceding the interview. Those who didn’t return for result were reclassified as being not tested. Date of last test was missing for 18 participants; they were excluded from analysis (for second outcome).

Hepatitis C rapid tests performed during the study were positive for 1002 PWID. Two outcomes that constitute “cascade” of care were created: “percent of hepatitis C positive who were diagnosed and aware of their status” and “percent of hepatitis C positive who have undergone confirmatory testing and received the results” for this sample of participants who were anti-HCV antibody positive (N = 1002). These measures are the remaining outcomes of interest: (3) those PWID who correctly reported their positive hepatitis C status in the questionnaire were classified as aware of their hepatitis C; and (4) those participants who were anti-HCV positive according to the rapid test and who responded yes to the following question: “Have you undergone confirmatory testing in a medical institution where they drew your blood and confirmed your hepatitis C test?”, were considered to have received confirmatory results.

**Exposures:** The main exposure of interest was participation in OAT based on the initial recruitment criteria: (1) never on OAT; (2) previously on OAT; (3) currently on OAT. Self-report was used to confirm if each participant’s group status was classified correctly. If the participant confirmed use of OAT during the last 10 days, he was classified as currently on OAT. If the participant reported ever using OAT, but not in the last 10 days, he was classified as a previous OAT patient. The analysis was based on self-reported measure.

**Other covariates:** The questionnaire measured a wide spectrum of socio-demographic characteristics, addiction history, alcohol and illicit drug use, HIV testing and HIV status
awareness, and risky sexual and injection behaviors. Some of these variables were assessed as potential confounders of the relationship between receiving of OAT and study outcomes: gender (male/female), age, living with a spouse or partner, having children, city of residence, importance of religion (not important, fairly important and extremely important), employment status (permanent job, temporary job, not employed), duration of injection drug use, median number of days injected any substance in the last 30 days, HIV status from rapid testing conducted in the study, and current antiretroviral treatment based on self-report. Awareness of positive HIV status was determined from the participant’s response to the question: “What was the result of your last HIV test?” Income level was categorized into: <1200 UAH (150 USD), 1200-3500 (150-437 USD) and >3500 (437USD) based on minimum poverty level and average monthly wage for Ukraine in 2014. Education level was categorized as (1) didn’t complete high school, (2) completed high school (including vocational school), (3) had incomplete or complete college education. Alcohol use was assessed using the AUDIT, with score >=8 for men and >=4 for women defining alcohol use disorder. Addiction severity was measured using the DUST-10. Scores <=5 were indicative of low to moderate addiction, whereas scores >5 indicated substantial to severe addiction. Depression was assessed using the CES-D-10, with scores >= 10 classified as moderate to severe depression.

Statistical analysis

Analyses aimed to assess if current or previous participation in OAT is associated with the four main study outcomes controlling for other covariates. First, we examined the frequency distributions of categorical variables and mean (or median) of continuous variables. Then, we conducted bivariate analyses of the associations between the exposure, outcomes and other variables. Pearson’s Chi-square tests were used to assess the statistical significance of associations
between two categorical variables, while t-tests were used to compare mean values of continuous variables. Univariate modified Poisson regression models with robust error variances\textsuperscript{52} were used to estimate unadjusted prevalence ratios (PR) for the association between OAT (currently on OAT/ previously on OAT / never on OAT) and outcomes: aware of positive hepatitis C status, ever undergone confirmatory testing for HCV in a medical institution, been tested for hepatitis C, and been tested for hepatitis C during last 12 months preceding the interview. A multivariate modified Poisson regression model with robust error variances was fit for each of the outcomes to compute the adjusted PR.\textsuperscript{52} Variables with associations at p-value<0.2 in bivariate analyses were initially put into multivariate regression models. A backward elimination approach was used to determine the final set of variables in each model. A significance level of p<0.05 based on Wald test results was chosen as a cut-off to keep each variable in the model. To further verify that no important covariates were missing, variables that were discarded with p>0.05 were put back into the model and retained if the exposure effect estimate changed by >=10%. An interaction term for exposure and being aware of positive HIV status was tested using QIC fit criteria. Where model fit with interaction term was better, separate models were specified for the two levels of effect measure modifier: “aware of positive HIV status” and “HIV negative or unaware of HIV status.”

**Ethical approval**

The study was approved by the institutional review boards at Yale University and the Gromashevsky Institute at the National Academy of Medical Sciences, Kyiv, Ukraine.

**RESULTS**

More than half of PWID in the study 1011 (62.7\%) reported having ever been tested for HCV, and 578 (35.8\%) were tested during the last 12 months. All PWID were tested for HCV using rapid tests in the study: 1002 (62.1\%) tested anti-HCV antibody positive. In this anti-HCV
antibody positive subsample, 568 (56.7%) were aware of their positive HCV status and 346 (34.5%) had received confirmatory testing. The percent who were aware of their positive HCV status and who had received confirmatory testing was 71.7% and 48.3% among current OAT patients, 62.4% and 33.9% among previous OAT patients, and 44.7% and 26.2% among PWID who had never been on OAT (Figure 1).

The characteristics of the total sample of PWID and anti-HCV antibody positive subsample are presented in Table 1. Most participants were male (76.4%) and had completed high school (63.1%). A substantial proportion of the sample was not employed (37.6%), lived with a spouse or partner (35.6%), and had previously (55.8%) or currently (26.9%) received OAT. The mean age was 36 years old; mean duration of drug injection was 17 years. Almost half of the sample (46.9%) were classified as hazardous drinkers, and the majority had moderate to severe addiction (85.3%). In total, 668 (41.4%) were tested HIV positive in the study (using rapid test), and 573 (35.5%) were previously diagnosed with HIV and aware of their HIV positive status.

**Association between OAT and awareness and confirmation of positive HCV status**

The association between OAT and awareness and confirmation of positive HCV status was analyzed in the subsample of PWID who tested anti-HCV antibody positive in the study. In the bivariate analysis, both previous and current OAT were positively associated with awareness (PR = 1.40 [95% CI 1.21-1.61] and PR = 1.60 [95% CI 1.42-1.81], respectively) and confirmation of positive HCV status (PR = 1.30 [95% CI 1.02-1.64]) and PR = 1.85 [95% CI 1.53-2.23], respectively) (Figure 1 and Table 2). In the multivariate analysis controlling for other covariates, the PRs were slightly attenuated (Table 2). The proportion of those previously on OAT who were aware of their positive HCV status was 1.30 (95% CI 1.13-1.50) times the proportion aware among those who
had never been on OAT. Furthermore, among those previously on OAT, the prevalence of HCV confirmatory testing was 1.08 (95% CI 0.85-1.36) times the prevalence of HCV confirmatory testing among those never on OAT. Those currently on OAT had 1.52 (95% 1.34-1.73) times the prevalence of positive HCV status awareness and 1.55 (95% 1.28-1.88) times the prevalence of HCV confirmatory testing, compared to those never on OAT.

PWID who were aware of their HIV positive status were 1.63 (95% 1.46-1.81) times more likely to know that they are HCV positive and 1.52 (95% 1.20-1.94) times more likely to receive confirmatory HCV testing. Duration of injection was associated with being aware of HCV status and confirmatory testing (PR = 1.01 [95% CI 1.00-1.01] and PR = 1.02 [95% CI 1.01-1.03], respectively).

PWID in Odessa had 1.23 (95% CI 1.07-1.43) times and PWID in Lviv had 0.59 (95% 0.47-0.74) times the prevalence of HCV status awareness compared to Kyiv. PWID living in Dnipro were less likely to confirm their HCV status compared to other cities (PR = 0.68, 95% CI 0.53-0.87, compared to Kyiv).

Living with a spouse or partner and hazardous alcohol drinking were each associated with slightly higher prevalence of being aware of HCV status (PR = 1.15 [95% CI 1.05-1.28] and PR = 1.17 [95% 1.05-1.29], respectively). PWID who mentioned that religion is fairly or extremely important had ~30% higher prevalence of being aware of HCV testing (PR = 1.23 [95% CI 1.05-1.43] and PR = 1.23 [95% 1.23 (1.02-1.48)], respectively, compared to religion not important).

Women had a higher prevalence of confirmatory HCV testing then men (PR=1.26, 95% CI 1.07-1.50). Income was also associated with confirmatory testing (PR = 1.21 [95% CI 1.01-1.46], comparing middle to low income category, and PR = 1.39 [95% CI 1.11-1.75] comparing high to
low income category). Current ARV treatment was associated with confirmatory testing (PR = 1.69, 95% CI 1.36-2.09).

The association between OAT and HCV testing

To see if higher anti-HCV status awareness was due to better utilization of HCV testing in the OAT group, we conducted an analysis of the total PWID sample. We found a negative interaction between OAT and being aware of HIV status (p<.001). Therefore, separate regression models were fit for those who were aware of their HIV positive status and all others. Among PWID who were aware of their positive HIV status, previous and current OAT was not associated with lifetime HCV testing in the bivariate and multivariate analyses (Table 3). In this group, HCV testing was associated with harmful alcohol use (PR = 1.11, 95% CI 1.02-1.21), less addiction severity (PR = 0.85, 95% CI 0.76-0.95), importance of religion (PR = 1.18 [95% CI 1.03-1.36] fairly important compared to not important; PR = 1.16 [95% CI 1.01-1.34] extremely important compared to not important), and ART treatment (PR = 1.20, 95% CI 1.10-1.30). In the multivariate analysis, current OAT patients aware of their positive HIV status had 1.54 times the prevalence of HCV testing during the last 12 months (95% CI 1.22-1.94), compared to those who had never been on OAT.

Among PWID who were HIV-negative or unaware of their HIV status, previous and current OAT were positively associated with lifetime HCV testing and HCV testing during the last 12 months both in the bivariate and multivariate analyses (Table 3). Those previously on OAT had 1.69 (95% CI 1.46-1.97) times the prevalence of having ever been tested for HCV and 1.81 (95% CI 1.42-2.32) times the prevalence of being tested for HCV during the last 12 months, compared to those never on OAT. Those currently on OAT had 2.13 (95% CI 1.90-2.39) times the prevalence of having ever been tested for HCV and 2.91 (95% CI 2.44-3.48) times the
prevalence of being tested for HCV during the last 12 months, compared to those never on OAT. HCV testing in this group was also associated with living with a spouse or partner (PR = 1.14, 95% CI 1.02-1.26), harmful or hazardous alcohol use (PR = 1.21, 95% CI 1.08-1.34) and moderate to severe addiction (PR = 1.30, 95% CI 1.11-1.53). Among PWID who were HIV-negative or not aware of their HIV status, HCV testing during the last 12 months was also associated with female gender (PR = 1.45, 95% CI 1.23-1.72) and moderate to severe addiction (PR = 1.40, 95% CI 1.10-1.77).

The prevalence of HCV testing was higher in Odessa and lower in Dnipro and Lviv, compared to Kyiv, among both those PWID who were aware of their positive HIV status and the rest of the participants (Table 3).

DISCUSSION

This study presented a detailed analysis of the association between OAT and HCV positivity awareness, HCV confirmatory testing among PWID in Ukraine. Being the first report of factors associated with HCV status awareness and confirmation, this study lays the groundwork for future research of the HCV treatment cascade among PWID and program planning for HCV treatment scale up in Ukraine.

The characteristic of our study sample are comparable to characteristics of PWID sample in the nationwide cross-sectional study conducted in Ukraine using RDS methodology: most participants are male, aged more than 25 years old, have high school education, up to 40% live with sexual partner, and almost half have children. HCV prevalence among PWID in our study was somewhat higher compared to the HCV prevalence in the nationwide study (61.1% vs 55%). Additionally, the proportion of PWID aware of their positive HCV status was comparable in these studies (56.7% vs 50%).
The proportion of participants who were aware of their positive HCV status and with confirmed status was highest among those currently on OAT (71.7% and 48.3%, respectively), and lowest among those who were never on OAT (44.7% and 26.2%, respectively). The estimated association between OAT and HCV positive status awareness was significant for both current and previous OAT users. The stronger association for current OAT users may be explained by the recent increase in HCV testing availability. Only current OAT participation was independently related to HCV status confirmation. The proportion currently on OAT who were aware of their status was substantially higher than reported in a previous study, in which only about one-third (34.8%) of HCV positive heroin users in methadone maintenance treatment in Taiwan were aware of their infection. Similarly, in cross-sectional survey of PWID in Methadone Maintenance Treatment (MMT) clinic in Shanghai (China) only 30% of anti-HCV positive patients were aware of their status at admission. However, these studies didn’t assess HCV testing outside of OAT program.

Although the proportion of anti-HCV positive participants tested for anti-HCV antibodies in our study was rather high (68.4%), the proportion of those with confirmed status was lower (34.5%). This discrepancy can be explained by the limited availability of HCV treatment to both the general population and PWID in Ukraine and the low effectiveness of available treatment. Although HCV treatment generally has lower uptake among PWID, treatment outcomes in this group have been observed to be comparable to those among patients without history of drug use in other studies. Additionally, HCV treatment among PWID would reduce transmission by eliminating the potential source of infection. Therefore, increased access to HCV treatment among PWID is critical. In 2015, a short-term project was launched which was supposed to make direct antiviral HCV treatment available to high risk groups including PWID in Ukraine. Studies
which will assess effectiveness and barriers of HCV treatment among PWID in Ukraine are needed.

The higher prevalence of HCV diagnosis and HCV status confirmation in Odessa and lower prevalence in Lviv and Dnipro, in comparison to Kiev, may be explained by different availability of HCV testing in cities, and also different level of testing promotion. These disparities should be addressed by local providers of services.

Other factors that were related to both HCV diagnosis and confirmation were positive HIV status awareness and importance of religion. Indication that religion is important may be a marker of coping with addiction, which in turn can lead to better care of one’s health. Those PWID who had been previously tested HIV positive would be more likely to be linked to care, receive ART and so, also receive HCV test. HIV/HCV co-infection is prevalent among PWID and is associated with greater health risks compared to mono-infection with HCV or HIV. Following improved access to ART, liver cirrhosis and hepatocellular carcinoma became the leading causes of death among patients with HIV. Analysis of ART outcomes did not show full correction of the adverse effect of HIV infection on HCV prognosis, so HIV/HCV co-infected patients have faster progression of fibrosis and should consider earlier initiation of HCV treatment. In Ukraine, with estimated HIV prevalence of 26% among PWID with chronic HCV infection (estimated 197,000), an estimated total of 51,200 PWID with HIV/HCV co-infection would need treatment for both conditions.

Living with a spouse or partner or having alcohol use disorder was associated with HCV status awareness in this study. These results are in line with previous study which found increase of alcohol use among participants who were notified of their positive HCV status. However, HIV-positive patients with history of alcohol problems, who were told one had HCV, were more
likely to abstain from alcohol or not drink unhealthy amounts of alcohol.\textsuperscript{61} Females, those with longer duration of injection and earning higher income were also more likely to confirm their HCV status. This can be explained by the higher uptake of health care by women\textsuperscript{62} and high costs of PCR tests that are required to confirm chronic HCV. Although the constitution of Ukraine guarantees the free health care for all citizens, out-of-pocket payments are very common and often required to receive medical services.\textsuperscript{63, 64}

The sampling scheme used in this study doesn’t allow the obtained proportion of participants aware of their HCV and with confirmed status to serve as a valid estimate of the corresponding proportion in the total population of PWID in Ukraine. Still, estimates obtained in each sampling group (currently on OAT/ previously on OAT/ never on OAT) are useful for program planners, as proportion estimates for that group are generalizable to the five cities where the study was conducted. However, estimates for PWID never on OAT should be treated with caution because of the RDS recruitment scheme. In addition, the obtained proportion of the total sample of PWID participants who had ever received anti-HCV antibody testing cannot be used as a valid estimate of the population proportion because of oversampling of PWID who had ever been on OAT. Still, the coverage with HCV testing among PWID (62.7\%) was lower compared to estimates in studies in USA (74\%)\textsuperscript{65} and Canada (79\%)\textsuperscript{18}. Stratified analysis revealed that HCV testing was not related to current or previous OAT participation among PWID who were already diagnosed with HIV. However, current and previous OAT was a predictor of HCV testing among PWID who were not previously diagnosed with HIV. Probably, HIV positive PWID received HCV testing along with other services of HIV care continuum. That means that involvement of PWID who have not received HIV positive diagnosis into the OAT would likely improve HCV testing participation in that group.
We found some discrepancy in answers about HCV test results among PWID: 117 indicated that they had tested negative, when anti-HCV antibody test indicated positive result; and 121 indicated positive previous test, when rapid test was negative. This discrepancy may be explained by newly acquired infections or inaccurate self-report due to lack of knowledge about disease. Although the cross-sectional nature of the data did not allow us to establish temporality, reverse causality is unlikely and the strong association between current OAT and HCV testing during last 12 month supports the conclusion that OAT is an effective strategy to increase HCV testing among PWID.

One of the limitations of this study is lack of PCR testing to detect chronic HCV infection. The available rapid anti-HCV antibody test result was indicative both of the resolved and chronic infection. Also, confirmation of HCV status was obtained from self-report, which may not be the most accurate measure of this outcome. Participants could be not familiar with specifics of chronic hepatitis C infection and understand this question incorrectly. Despite these limitations, we believe that these data give valid estimates of the association between OAT and HCV testing, and also provide foundation for future research. Studies with longitudinal design, detection of chronic HCV infection and HCV treatment uptake among PWID are warranted.
Chapter 3. EPIDEMIOLOGICAL CONSIDERATIONS

3.1. Research methodology

Eligibility criteria

This study was conducted in 5 Ukrainian cities: Kyiv, Odesa, Dnipro (formerly Dnipropetrovsk), Mykolaiv, and Lviv. They are highly populated cities with high burden of addiction to opiates. Eligibility criteria were: more than 18 years old, met ICD-10 criteria for opioid dependence, lived/worked in the city where the survey was conducted, provided informed consent, and agreed to undergo rapid HIV and HCV testing.

Sampling

Two sampling methods were used to recruit participants to the study: respondent driven sampling (RDS) and random sampling. Random sampling procedures were used for recruitment of PWID who had ever been on OAT or were currently receiving OAT, because pre-existing lists were available of OAT patients.

RDS was used to recruit PWID who had never been on OAT. RDS is a sampling method that is used to recruit hard-to-reach populations in epidemiological and sociological studies, when probability sampling is inappropriate or impossible because subjects cannot be drawn from an existing sampling frame, have privacy concerns, and/or comprise a small part of the general population. RDS was first developed by Douglas Heckathorn in 1997, as part of a HIV-prevention research project targeting drug injectors in Connecticut (US). RDS is only suitable when members of the target population know one another and are part of a larger network. RDS includes two components: (1) a participant recruitment scheme in which long referral chains are obtained by offering incentives for peer recruitment and recruitment quotas; (2) and a model of the sampling process from which estimates of population parameters are computed. For the first
component, the Markov model provides a statistical model of the sampling process; for the second component, the homophily model accounts for bias due to the tendency of respondents to refer those who are similar. Estimates of population parameters are computed through adjustment for the size of participants’ social network and the sample’s different recruitment patterns.

The RDS recruitment process begins with a set number of individuals, called “seeds” with predetermined characteristics and selected from the target population. Seeds are asked to recruit certain number of individuals (“recruitment quota”) from their network of peers. Quotas are imposed so that no small subset of “seeds” recruits most of the sample; in this study, the quota was set at three recruits after the initial interview and each follow up interview. A second reason for introducing quotas was to prevent order effects in recruitment (i.e., first named persons have different characteristics compared to last named persons). If only three recruits are expected from each recruiter, all invited participants will appear near the beginning of the queue of potential recruits. Quotas on recruitment were implemented by distributing coupons, which recruiters are instructed to give their recruits. The coupon provides information about the interview site and contact information of the interviewer, and also has an unique serial number that links the recruiter and the recruit who returns it to the study team.

“Seeds” for RDS in this study were recruited at community outreach sites in each city and included at least one: female, individual age 18-25, and individual with less than 2 years of injecting history. These seeds’ characteristics were pre-defined to ensure the diversity of the sample. In total, 20 seeds were recruited, 4 in each city.

The recruits of the “seeds” are asked to continue the recruitment process and invite individuals from their social network. As the recruitment chains lengthen, the composition of the sample begins to reach a point of “equilibrium” whereby the composition of certain
characteristics (e.g., age group, gender, ethnicity, HIV prevalence) within the sample eventually stabilizes, indicating that the final sample is not biased by the purposeful selection of seeds. Long recruitment “chains” made up of several “waves” of recruits are considered preferable to short “chains” in order for the sampling methodology to reach its goals.

RDS has been employed widely to gather biological and behavioral data on at risk groups for HIV in different countries affected by HIV/AIDS epidemics. However, the effectiveness of RDS can differ in socio-cultural settings and among certain most-at-risk populations. Furthermore, there are debates ongoing about RDS methodology, the importance of statistical adjustment, and the method’s requirements. Also, the methodology that could incorporate Respondent Driven Sampling Analysis Tool (RDSAT) weighting based on network size and participant relatedness in multivariate analysis is not developed. Statistical software, which is used to analyze data gathered through RDS methodology doesn’t currently have capabilities for multivariate analysis. As a result, the RDS sampling design could not be incorporated into this analysis.

**Interviewing**

A computer-assisted, self-administered instrument (CASI) using Qualtrics® was completed by all participants. The survey lasted 45-90 minutes and covered a broad range of questions: demographic characteristics, addiction history (duration of injection, overdose experience, registration at state narcology clinics), inventory for drug use, standardized instruments for measuring alcohol (AUDIT) and drug (DUST-10) addiction, depression (CES-D-10), and quality of life (SF-12). Also, participants who are currently or were previously on OAT answered questions about their experiences with medication assisted treatment for addiction, their attitudes and beliefs about OAT, intentions to continue or resume treatment, barriers to
participation in OAT and reasons for interruption. The qualitative research that was conducted before this study informed questions asked in this study.\textsuperscript{40, 48}

**Testing for HIV and HCV in the study**

HIV and HCV testing using rapid tests (CITO TEST HIV 1/2, Pharmasco and CITO TEST HCV, Pharmasco) along with pre- and post-test counseling was performed by medical staff (nurse, physician or NGO staff with relevant certification). CITO TEST HIV 1/2 detects antibodies (IgG, IgM) to HIV type I and HIV type 2, CITO TEST HCV detects antibodies (IgG, IgM) to HCV of any type in whole blood, serum or plasma of human. Rapid tests were chosen because of high sensitivity (99.99\%) and specificity (99.99\%), they do not require storage of blood sample, are convenient to use in the study setting, and deliver results fast (15 minutes). Despite high sensitivity and specificity, the results of rapid HIV and HCV tests are not considered enough to make a final diagnosis. The final diagnosis of HIV infection can be given by a physician after additional confirmation with recombinant immunoblot assay or enzyme immunoassays. Chronic HCV needs to be confirmed with PCR test for HCV RNA. All participants with positive HIV and HCV test results in the study were referred to confirm their status.

**Regression modeling**

All four outcomes for this study [i.e., (1) had ever been tested for hepatitis C; (2) had been tested during the last 12 months preceding the interview; (3) aware of positive hepatitis C status; (4) had received confirmatory results] are binary categorical. In epidemiological studies, researchers are interested in the risk ratio as a measure of association between predictors and binary outcomes, or in the prevalence ratio in case of a cross-sectional study. Usually, the odds ratios obtained by exponentiation of logistic regression coefficients are used to estimate the risk ratio. However, in
the case of common outcomes (>10%), the odds ratio will overestimate the risk ratio. Relative risks may be estimated directly by log binomial regression, which belongs to a class of generalized linear models which combines a log link with binomial distribution. However, convergence problems often occur during the iterative estimation procedure for this model. To overcome this problem researchers suggested using a modified Poisson regression approach. This model also uses a log link but applies the Poisson distribution to the data. Since the variance under a Poisson model is larger than the variance under the binomial model in the case of a common outcome, robust variance estimation is used to avoid overestimating standard errors of parameter estimates. The modified Poisson regression model can be expressed as specified below.

Assuming that subject $i$ has an underlying risk that is a function $\pi(x_i)$:

$$\log[\pi(x_i)] = \alpha + \beta x_i.$$ (1)

The relative risk (RR) is then given by $\exp(\beta)$.

$$\hat{R}R = \exp(\hat{\beta}) = \frac{an_0}{cn_1},$$

(2)

where $n_0$ – total of unexposed; $n_1$ - total of exposed; $a$ – exposed with outcome; $c$ – unexposed with outcome;

with the estimated variance of RR given by

$$\text{var}(\hat{R}R) = \frac{1}{a} + \frac{1}{c}$$

(3)

Because of the error term misspecification in the case of binomially distributed data, the sandwich estimator (robust error estimator) is used for correction. The corrected variance is then estimated by

$$\hat{\text{var}}(\hat{R}R) = \frac{1}{a} - \frac{1}{a n_1} + \frac{1}{c} - \frac{1}{c n_0}.$$ (4)
Standard errors are corrected by using generalized estimating equations (GEEs).\textsuperscript{80} PROC GENMOD with the REPEATED statement can be used to obtain a robust error estimator with one observation available for each cluster. The modified Poisson model has been widely cited and used in a variety of observational and interventional studies.\textsuperscript{81}

3.2. Ethical considerations

The study protocol was approved by the Institutional Review Board at Yale University (USA) and by the Medical Ethics Committee of the “Institute of Epidemiology and Infectious Diseases named after Gromashevskiy L.V.” at the National Academy of Medical Sciences (Ukraine). All participants received an incentive of 100 UAH (~12 USD) for participation in the study. Additionally, 20 UAH (~2 USD) were paid for peer recruitment (up to 3 peers). Participants signed an informed consent that explained purposes and procedures of the survey, ensured confidentiality, and informed about the risks due to sensitive nature of questions. Also, participants were made aware of voluntary participation in the study and possibility to refuse to answer any specific question. Trained medical personnel at the study site conducted HIV and HCV testing and provided pre- and post-test counseling.

The data analysis for this thesis was approved as exempt from full IRB review by the Institutional Review Board of the State University of New York on March 3, 2017.

3.3. Study limitations

Selection bias

RDS is used to recruit hard-to-reach populations, like PWID, where enumeration is not possible. RDS is believed to give a representative sample of PWID and allows estimates of the prevalence of the characteristics in the population by applying the participant selection probability (RDS weights). However, there is divided opinion regarding the utility of such
weights in multivariate analysis and this paper didn’t use them in analysis. Oversampling of PWID who are more socially active, with larger personal networks is likely, but this doesn’t imply they are more or less likely to be tested for HCV. Therefore, although HCV prevalence estimates in this sample overall may not reflect the true prevalence among PWID in Ukraine, selection bias is unlikely to affect the measure of association between OAT enrollment and study outcomes.

**Measurement error**

This study used two types of instruments to measure its variables: survey and rapid tests for HIV/HCV infections. The sensitivity and specificity of rapid tests are high, 99.99% and 99.99% respectively. However, there were cases for which the result of the HCV test was considered inconclusive or not valid. This could happen due to number of reasons: not enough whole blood used for testing, the procedures were not followed as expected, non-optimal storage conditions for test kits, damaged test kits (according to manufacturer’s instruction), spontaneous clearance of HCV accompanied with loss of anti-HCV antibodies, or low immune status in some individuals with HIV. In these cases the testing was repeated and status verified with self-report of laboratory confirmed HCV test results.

Surveys are more prone to misclassification and measurement error. The outcome variable “aware of positive hepatitis C status” was constructed using both rapid test result for anti-HCV antibodies and self-reported HCV status. We found some discrepancy in answers about HCV test results among PWID: 117 indicated that they have tested negative, when anti-HCV antibody test indicated positive result; and 121 indicated positive previous test, when rapid test was negative. This discrepancy may be explained by newly acquired infections or inaccurate self-report due to lack of knowledge about disease.
Confirmation of HCV status was obtained from self report, which may not be the most accurate measure of this outcome. Participants could be not familiar with specifics of chronic hepatitis C infection and understand this question incorrectly.

The main exposure of interest was participation in OAT based on the initial recruitment criteria: (1) never on OAT; (2) previously on OAT; (3) currently on OAT. Self-report was used to confirm if each participant’s group status was classified correctly. If the participant confirmed use of OAT during the last 10 days, he was classified as currently on OAT. If the participant reported ever using OAT, but not in the last 10 days, he was classified as a previous OAT patient. The difference between initial recruitment assignment and self-reported treatment with OAT could arise due to respondent driven sampling which allowed recruitment of PWID who could be receiving OAT. However, the discrepancy was not substantial: 26 PWID recruited through RDS were re-classified as previously on OAT, and 9 were re-classified as currently on OAT based on the baseline survey.

The questionnaire measured a wide spectrum of socio-demographic characteristics, addiction history, alcohol and illicit drug use, and injection behaviors. Some of these variables were assessed using standardized instruments: alcohol use with the AUDIT, addiction severity with the DUST-10, depression with the CES-D-10.

The AUDIT is a screening instrument for hazardous and harmful alcohol consumption that was developed in WHO cross-national study and is available without copyright fee. It is a 10-item questionnaire which contains items about alcohol consumption (questions 1-3), dependence (questions 4-6), and alcohol-related problems (7-10), with a cut-point of 8 used to identify a potential alcohol problem. The psychometric properties of the AUDIT have been studied extensively: the median sensitivity was 0.86 and the median specificity was 0.89, and differed
within different age ranges, sexes, and ethnic groups.\textsuperscript{82} The AUDIT has been found to be internally consistent: the median reported Cronbach’s alpha was more than 0.80 with diverse samples and settings.\textsuperscript{82} Several studies identified factor structure of the AUDIT: one is drinking behavior itself and the other is adverse consequences of drinking, including alcohol dependence symptoms.\textsuperscript{82}

Although initially developed for early detection of hazardous and harmful alcohol use in primary health care settings, the AUDIT has also been widely used in epidemiologic research studies. For example, comorbid alcohol problems in various psychiatric samples were estimated with the AUDIT.\textsuperscript{83}

The DAST was developed and validated by Harvey A. Skinner and all instrument’s three versions (DAST-28, DAST-20, and DAST-10) are copyrighted but available for not-for-profit research.\textsuperscript{50} For DAST-10, which was used in this thesis, the cutoff score for abuse/dependence of 3 was recommended. The concurrent validity of the short versions of the DAST has been measured: DAST-20 and DAST-10 are highly correlated ($r = .97$) with each other.\textsuperscript{84} Internal consistency for DAST-10 was measured in several studies: Cronbach $\alpha$ was between 0.80 and 0.94; the test-retest reliability of DAST-10 was 0.71.\textsuperscript{50} One study identified three factors for DAST-10,\textsuperscript{84} but others give support for the unidimensional nature of DAST-10.\textsuperscript{85, 86} Discriminative validity has been confirmed by high values for both sensitivity (95\% to 41\%) and specificity (68\% to 99\%).\textsuperscript{50} Criterion validity has been shown by measuring correlation of DAST-10 and different other instruments that measure problematic drug use. Construct validity has been determined by measuring correlation of the DAST with measures of other psychiatric disorders (interpersonal problems, persecutory ideas, thinking disorder, depression, and hypochondriasis).\textsuperscript{50} In conclusion, DAST has satisfactory reliability and validity to be used as a research tool. However, being an instrument with high face validity, the DAST is susceptible to “faking good”.\textsuperscript{50}
That means, a test taker can easily guess what the test is measuring and is able to fake answers if he/she doesn’t want to be known as a problematic drug user.

The Center for Epidemiologic Studies Depression Scale (CES-D) is a common screening tests for identifying depressive symptoms.\textsuperscript{87} It was developed as a 20-item scale measuring individual’s depressive feelings and behaviors in the past week. Most common symptoms of depression are incorporated into the instrument: depressed mood, feelings of guilt and worthlessness, feelings of helplessness and hopelessness, psychomotor retardation, loss of appetite, and sleep disturbance.\textsuperscript{87} The scale is valid and reliable, and has been used in various epidemiological research. Despite established CES-D reliability, this 20-item measurement instrument is lengthy. A number of studies have shown that the CES-D could be reduced to 10 items with comparable reliability and validity to the original scale.\textsuperscript{51, 88, 89}

Most research on the validity and the reliability of the instruments (DAST-10, CES-D-10, AUDIT) is focused on their English versions in populations of North America and Western Europe. So, one cannot be sure about psychometric properties of versions translated into Russian or Ukrainian. However, we assume that these instruments have comparable reliability and validity if used to study Ukrainian PWID and don’t introduce considerable measurement error into our study.

The crude estimate of association between OAT and HCV testing, OAT and HCV awareness has not substantially changed after controlling for other covariates. The estimate of the association between OAT and HCV status confirmation was attenuated by controlling for awareness of positive HIV status, current ARV treatment, gender, duration of injection and treatment in the regression model. Although, we included many potential confounders in this analysis, residual confounding is still possible.
Generalizability of results

The sampling scheme used in the study doesn’t allow the obtained proportion of participants aware of their HCV and with confirmed status to serve as a valid estimate of the corresponding proportion in the total population of PWID in Ukraine. Still, estimates obtained in each sampling group (currently on OAT/ previously on OAT/ never on OAT) are useful for program planners as proportion estimates for that group are generalizable to the five cities where the study was conducted. However, estimates for PWID never on OAT should be treated with caution because no adjustment for the RDS recruitment scheme was done.

3.4. Public health and policy implications

This study presented a detailed analysis of the association between OAT and HCV positivity awareness and HCV confirmatory testing among PWID in Ukraine. Also, it gave estimates for the proportion of PWID in OAT programs who were aware of their HCV and with confirmed status in 5 Ukrainian cities with the greatest numbers of population affected by opioid addiction. These results will help program planners to track results of implemented programs and to adjust programs to increase access among groups of PWID with non-optimal HCV testing coverage. In particular, PWID living in Odessa with less duration of injection, HIV negative or not aware of their HIV status are groups that are under diagnosed. Also, males and HIV positive PWID not on ART need to be linked to care to confirm HCV. Finally, HIV-negative PWID who were never on OAT or discontinued their OAT should be encouraged to join OAT programs.

Increasing awareness of HCV among PWID in Ukraine is crucial to reduce HCV prevalence in Ukraine, because currently the transmission of virus predominantly occurs within this group. HCV testing and confirmation are first steps towards HCV treatment, which is supposed to reduce transmission by eliminating the potential source of infection.46
3.5. Further research directions

Being the first report of factors associated with HCV status awareness and HCV status confirmation, this study lays the groundwork for future research of HCV treatment cascade among PWID and program planning for HCV treatment scale up in Ukraine. Future research should be able to distinguish between cleared and chronic HCV. Also, studies that would gather data about the full cascade of HCV care among PWID are warranted. The agreement reached by the Ukrainian government and pharmaceutical company Gilead Sciences, Inc. has lead to the substantial reduction of prices for the original drugs for treatment of chronic HCV. With prices becoming more affordable, the Ministry of Health of Ukraine is in the process of implementing new policies regarding treatment of HCV. Research that would evaluate the effect of these policies on each step of the cascade of care will be necessary. The longitudinal study among PWID that would assess the effect of OAT on all steps of HCV care cascade (including testing, linkage to care, confirmation of chronic HCV, treatment, and SVR) will help to confirm and expand the results of this study.
REFERENCES


Fig. 1 The “cascade” of care for anti-HCV antibody positive PWID in the study
TABLE 1 Demographic characteristics and risk behaviors in the sample of PWID in five cities in Ukraine

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total sample (N=1613)</th>
<th>Anti-HCV antibody positive (N=1002)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>1233 (76.4)</td>
<td>766 (76.5)</td>
</tr>
<tr>
<td>Age - mean (SD)</td>
<td>36 (8.3)</td>
<td>36.8 (8.0)</td>
</tr>
<tr>
<td>Living with spouse/partner</td>
<td>574 (35.6)</td>
<td>370 (36.9)</td>
</tr>
<tr>
<td>Have children</td>
<td>840 (52.1)</td>
<td>542 (54.1)</td>
</tr>
<tr>
<td>Importance of religion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not important</td>
<td>354 (22)</td>
<td>207 (20.7)</td>
</tr>
<tr>
<td>Fairly important</td>
<td>783 (48.5)</td>
<td>499 (49.8)</td>
</tr>
<tr>
<td>Extremely important</td>
<td>476 (29.5)</td>
<td>296 (29.5)</td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>249 (15.4)</td>
<td>151 (15.1)</td>
</tr>
<tr>
<td>High school (including vocational schools)</td>
<td>1018 (63.1)</td>
<td>633 (63.2)</td>
</tr>
<tr>
<td>Some university education or higher</td>
<td>346 (21.5)</td>
<td>218 (21.8)</td>
</tr>
<tr>
<td>Employment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full time/part time permanent job</td>
<td>752 (46.6)</td>
<td>453 (45.2)</td>
</tr>
<tr>
<td>Temporary/ Seasonal/ Day laborer</td>
<td>254 (15.8)</td>
<td>152 (15.2)</td>
</tr>
<tr>
<td>Not employed</td>
<td>607 (37.6)</td>
<td>397 (39.6)</td>
</tr>
<tr>
<td>Income</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1200 UAH</td>
<td>551 (34.2)</td>
<td>354 (35.3)</td>
</tr>
<tr>
<td>1200-3499 UAH</td>
<td>746 (46.3)</td>
<td>456 (45.5)</td>
</tr>
<tr>
<td>&gt;=3500 UAH</td>
<td>316 (19.6)</td>
<td>192 (19.2)</td>
</tr>
<tr>
<td>City of residence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kyiv</td>
<td>413 (25.6)</td>
<td>356 (35.5)</td>
</tr>
<tr>
<td>Odessa</td>
<td>215 (13.3)</td>
<td>93 (9.3)</td>
</tr>
<tr>
<td>Mykolaiv</td>
<td>344 (21.3)</td>
<td>222 (22.2)</td>
</tr>
<tr>
<td>Dnipro</td>
<td>368 (22.8)</td>
<td>213 (21.3)</td>
</tr>
<tr>
<td>Lviv</td>
<td>273 (16.9)</td>
<td>118 (11.8)</td>
</tr>
<tr>
<td>OAT experience</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never on OAT</td>
<td>900 (55.8)</td>
<td>481 (48.0)</td>
</tr>
<tr>
<td>Previously on OAT</td>
<td>279 (17.3)</td>
<td>221 (22.1)</td>
</tr>
<tr>
<td>Currently on OAT (last 10 days)</td>
<td>434 (26.9)</td>
<td>300 (29.9)</td>
</tr>
<tr>
<td>Years of injection – mean (SD)</td>
<td>17 (9)</td>
<td>18.1 (8.6)</td>
</tr>
<tr>
<td>Addiction severity (moderate to severe)</td>
<td>1376 (85.3)</td>
<td>872 (87.0)</td>
</tr>
<tr>
<td>Moderate to severe depression (CES-D-10)</td>
<td>968 (60.0)</td>
<td>602 (60.1)</td>
</tr>
<tr>
<td>Harmful or hazardous alcohol use (AUDIT)</td>
<td>756 (46.9)</td>
<td>481 (48.0)</td>
</tr>
<tr>
<td>Aware of positive HIV status</td>
<td>573 (35.5)</td>
<td>395 (39.4)</td>
</tr>
<tr>
<td>Positive HIV test result (rapid test)</td>
<td>668 (41.4)</td>
<td>441 (44.0)</td>
</tr>
<tr>
<td>Current ARV treatment</td>
<td>314 (19.5)</td>
<td>218 (21.8)</td>
</tr>
<tr>
<td>Positive HCV test result (rapid test)</td>
<td>1002 (62.1)</td>
<td>1002 (100)</td>
</tr>
<tr>
<td>Have ever been tested for hepatitis C and received the result</td>
<td>1011 (62.7)</td>
<td>685 (68.4)</td>
</tr>
<tr>
<td>Have ever been tested for hepatitis C during the last 12 months preceding the interview</td>
<td>578 (35.8%)</td>
<td>384 (38.8)</td>
</tr>
<tr>
<td>Aware of positive hepatitis C status</td>
<td>-</td>
<td>568 (56.7)</td>
</tr>
<tr>
<td>Have undergone confirmatory testing for hepatitis C</td>
<td>-</td>
<td>346 (34.5)</td>
</tr>
</tbody>
</table>
TABLE 2 Predictors of being aware of HCV positive status and getting confirmatory HCV test, among anti-HCV antibody positive PWID (N=1002)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Aware of positive hepatitis C status</th>
<th>Have undergone confirmatory testing for hepatitis C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td><strong>Univariate modified Poisson regression model</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OAT experience</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never on OAT</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Previously on OAT</td>
<td>1.40 (1.21-1.61)</td>
<td>.001</td>
</tr>
<tr>
<td>Currently on OAT</td>
<td>1.60 (1.42-1.81)</td>
<td>.001</td>
</tr>
<tr>
<td><strong>Multivariate modified Poisson regression model</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OAT experience</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never on OAT</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Previously on OAT</td>
<td>1.30 (1.13-1.50)</td>
<td>.001</td>
</tr>
<tr>
<td>Currently on OAT</td>
<td>1.52 (1.34-1.73)</td>
<td>.001</td>
</tr>
<tr>
<td>City of residence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kyiv</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Odessa</td>
<td>1.33 (1.14-1.56)</td>
<td>.001</td>
</tr>
<tr>
<td>Mykolaiv</td>
<td>0.95 (0.83-1.09)</td>
<td>.466</td>
</tr>
<tr>
<td>Dnipro</td>
<td>0.90 (0.78-1.05)</td>
<td>.195</td>
</tr>
<tr>
<td>Lviv</td>
<td>0.72 (0.57-0.89)</td>
<td>.003</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>-</td>
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</tr>
<tr>
<td>Living with</td>
<td>1.15 (1.05-1.28)</td>
<td>.005</td>
</tr>
<tr>
<td>Income</td>
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</tr>
<tr>
<td>&lt;1200 UAH</td>
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</tr>
<tr>
<td>1200-3499 UAH</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>&gt;=3500 UAH</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Years of injection</td>
<td>1.01 (1.00-1.01)</td>
<td>.037</td>
</tr>
<tr>
<td>Harmful or hazardous alcohol use (AUDIT)</td>
<td>1.17 (1.05-1.29)</td>
<td>.004</td>
</tr>
<tr>
<td>Importance of religion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not important</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Fairly important</td>
<td>1.23 (1.05-1.43)</td>
<td>.01</td>
</tr>
<tr>
<td>Extremely important</td>
<td>1.23 (1.02-1.48)</td>
<td>.06</td>
</tr>
<tr>
<td>Aware of positive HIV status</td>
<td>1.63 (1.46-1.81)</td>
<td>.001</td>
</tr>
<tr>
<td>Current ARV treatment</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>
TABLE 3 Predictors of HCV test and HCV test during last 12 month among PWID aware of HIV positive status (N=573) and those who are HIV-negative or not aware of HIV positive status (N=1040)

<table>
<thead>
<tr>
<th>OAT experience</th>
<th>HIV-negative or not aware of positive HIV status</th>
<th>Aware of positive HIV status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Have ever been tested for hepatitis C</td>
<td>Have been tested for hepatitis C during last 12 months</td>
</tr>
<tr>
<td>PR (95% CI)</td>
<td>P-value</td>
<td>PR (95% CI)</td>
</tr>
<tr>
<td>Never on OAT</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Previously on OAT</td>
<td>1.81 (1.57-2.09)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Currently on OAT</td>
<td>2.14 (1.91-2.39)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Univariate modified Poisson regression model

<table>
<thead>
<tr>
<th>City of residence</th>
<th>HIV-negative or not aware of positive HIV status</th>
<th>Aware of positive HIV status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Have ever been tested for hepatitis C</td>
<td>Have been tested for hepatitis C during last 12 months</td>
</tr>
<tr>
<td>PR (95% CI)</td>
<td>P-value</td>
<td>PR (95% CI)</td>
</tr>
<tr>
<td>Kyiv</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Odessa</td>
<td>1.23 (1.07-1.43)</td>
<td>.004</td>
</tr>
<tr>
<td>Mykolaiv</td>
<td>0.97 (0.86-1.10)</td>
<td>.662</td>
</tr>
<tr>
<td>Dnipro</td>
<td>0.82 (0.69-0.98)</td>
<td>.026</td>
</tr>
<tr>
<td>Lviv</td>
<td>0.59 (0.47-0.74)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Living with spouse/partner</td>
<td>1.14 (1.02-1.26)</td>
<td>.016</td>
</tr>
<tr>
<td>Harmful or hazardous</td>
<td>1.21 (1.08-1.34)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Alcohol use (AUDIT)</td>
<td>1.30 (1.11-1.53)</td>
<td>0.001</td>
</tr>
<tr>
<td>Addiction severity</td>
<td>Not important</td>
<td>-</td>
</tr>
<tr>
<td>Importance of religion</td>
<td>Fairly important</td>
<td>-</td>
</tr>
<tr>
<td>Current ARV treatment</td>
<td>Extremely important</td>
<td>-</td>
</tr>
</tbody>
</table>

Multivariate modified Poisson regression model