Alliance for Public Health

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Access to Innovative HCV Treatment for Key Populations

2018

Alliance for Public Health

REPORT ON RESULTS OF THE PROJECT

"Scaling Up Accessible and Effective Hepatitis C Virus Treatment

through Community-Based Treatment Model for Most Vulnerable Populations in the Resource-Constrained Ukraine"

2018

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The report outline the results of the project ***Scaling Up Accessible and Effective Hepatitis C Virus (HCV) Treatment Through Community-Based Treatment Model for Most Vulnerable Populations in the Resource-Constrained Ukraine , which was implemented by ICF Alliance for Public Health in the period of 2015 through 2018. Besides, the publication presents findings of the Effectiveness of the Hepatitis C Virus (HCV) Treatment Program for Vulnerable Populations in the Resource-Constrained Ukraine*** operational research (data collection lasted from May 2016 till July 2018).

The Project results and research findings will be of use for representatives of public authorities, public health centers, health care facilities, non-governmental organizations, and all those who may be involved in prevention, diagnosis, and treatment of hepatitis C virus.

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The successful implementation of the ***Scaling Up Accessible and Effective Hepatitis C Virus (HCV) Treatment Through Community-Based Treatment Model for Most Vulnerable Populations in the Resource-Constrained Ukraine Project and the Effectiveness of the Hepatitis C Virus (HCV) Treatment Program for Vulnerable Populations in the Resource-Constrained Ukraine*** operational research was possible due to joint efforts of a number of stakeholders: experts, analysts, health care professionals, NGO representatives, technical partners from different cities and regions of Ukraine.

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We express our special gratitude to the Ministry of Health (MoH) of Ukraine for their cooperation in adopting Order of the MoH of Ukraine No. 729 of July 18, 2016, which amended the Unified Clinical Protocol for Primary, Secondary (Specialized), and Tertiary (Highly Specialized) Medical Care "Hepatitis C Virus in Adults". Thanks to MoH important decision medicines procured with funds from the State Budget of Ukraine, were used for the treatment of Project's patients.

LIST OF ABBREVIATIONS

AF	alkaline phosphatase
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
AMA	anti-mitochondrial antibodies
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
AVT	antiviral therapy
CKD	chronic kidney disease
CMU	the Cabinet of Ministers of Ukraine
DAAct	direct antiviral action
DAAs	direct-acting antivirals
ELISA	enzyme-linked immunosorbent assay
GF	the Global Fund to Fight AIDS, Tuberculosis and Malaria
GFR	glomerular filtration rate
GGT	gamma-glutamyltransferase
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCF	health care facility
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	international charitable foundation
JFO	Joint Force Operation
KP	key population

MDT	multidisciplinary team
MoH	Ministry of Health
MPSS	medical and psychosocial support
MSM	men who have sex with men
NGO	non-governmental organization
OST	opioid substitution therapy
PCR	polymerase chain reaction
PPs	pharmaceutical products
PegIFN	pegylated interferon
PTI	prothrombin index
PWID	people who inject drugs
RBV	ribavirin
RNA	ribonucleic acid
SVR	sustained virologic response
SVR12	sustained virologic response 12 weeks after completion of hepatitis C virus antiviral treatment
SWs	sex workers
T3	triiodothyronine
T4	thyroxine
TTG	tyreotropic hormone
VL	viral load
WHO	the World Health Organization

SUMMARY

In 2015, the Alliance initiated the Scaling Up Accessible and Effective HCV Treatment Through Community-Based Treatment Model for Most Vulnerable Populations in the Resource-Constrained Ukraine Project (hereinafter – the Project), which was implemented till September, 2018.

The main purpose of the Project was to ensure access to effective innovative viral hepatitis C treatment with DAAs for key populations.

The Project started when DAAs were not yet registered in Ukraine and were not used for viral hepatitis C treatment. Focusing on scaling up access to comprehensive prevention, diagnosis, and treatment of HIV/AIDS, tuberculosis, viral hepatitis, the Alliance was the first in Ukraine to launch, in 2015, the modern treatment of HCV-infection with DAAs and made it accessible for the most challenging patients.

The Project was rolled out in three phases. Alliance provided a total of 1 907 DAA-based HCV treatment courses with (sofosbuvir and sofosbuvir/ledipasvir) for representatives of key populations throughout Ukraine. Out of 1 907 treatment courses, administered to key populations' representatives within the Project, 468 included combination of ledipasvir/soforbuvir, and 953 treatment regimens were interferon-free. 1,873 patients retained in the program and successfully completed full treatment course.

The Project beneficiaries were key population representatives, and patients with HIV/HCV co-infection, namely: PWID; OST clients; PWIDs' sexual partners; SW; MSM; individuals from KPs who were clients of HIV prevention, medical and psychosocial support projects. In 2017, during the third phase, ATO (now Joint Force Operation) veterans and NGO activists from KPs became eligible for enrollment on HCV treatment within the Project. More than 80% of Project participants were PWIDs, and 73% were HIV/HCV co-infected.

25 health care facilities in 19 regions of Ukraine and 19 local NGOs were providing HCV treatment and social support within the Project. Patients from several regions not covered by the Project were granted treatment in medical institutions of national level: SI "Gromashevsky Institute of Epidemiology and Infectious Diseases of the National Academy of Medical Sciences of Ukraine" and National Military Medical Clinical Center "The Main Military Clinical Hospital".

Before treatment started, the Alliance organized and conducted trainings for physicians and social workers involved in Project implementation.

The overall effectiveness of hepatitis C virus treatment within the Project was 95%.

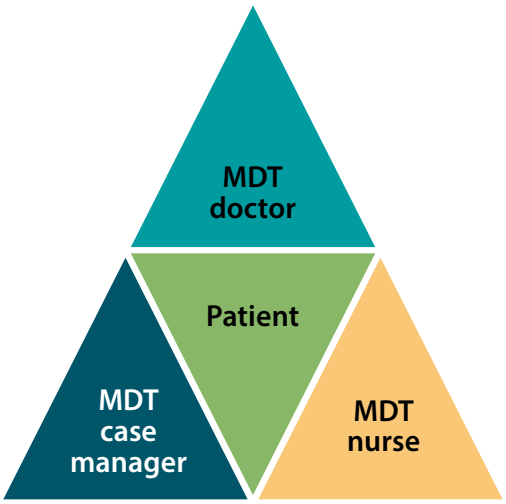
With this Project the Alliance has successfully implemented the community-based treatment model. Following patients centered approach community based treatment model was designed by Alliance to address patients needs. Information on the Project was communicated by local NGOs, KPs communities representatives, doctors involved into the Project. Before the start of HCV treatment, multi-disciplinary teams (MDTs) consisting of a physician, a nurse and social worker were set up at each health care facility. MDTs made joint recruitment decisions and provided medical and social support during treatment. Each Project patient was granted social support. Three sessions on possible ways of HCV reinfection and safe behavior were mandatory hold by case managers for the Project patients.

We really had intense meetings … We discussed patients after they had gone. We had time to talk…on patients' behavioral patterns, who needs more supervision, who needs none»

(doctor infectionist)

In result for the first time in Ukraine, the retention on treatment reached 98%.

Multi-purpose operational research was conducted to determine the most effective treatment model for viral hepatitis C among key populations using DAAs and to assess the risks of HCV reinfection and fibrosis regression factors after effective antiviral therapy. The key finding of the operational research was that patients in all the key populations showed a high level of satisfaction with MDT work and with the quality of Project services due to friendly attitude, no stigma or discrimination, comfort, attention to the patient's individual needs and provision of quality care services. Both patients and medical staff recognized social support as most valuable tool to achieve high treatment success and adherence to treatment.



Thank you for the treatment, for the chance to be included into the program and get cured. Thank you for the MDT approach, it was a very professional team! This is true, I have something to compare with, we work in similar projects ourselves. It's just great that there was this team.

(patient, Odesa)

As of reinfection rates, only 3% of successfully treated patients had detectable HCV RNA viral load at 48 weeks after achieving SVR12.

94% (based on the FIB4 index) of successfully treated patients with advanced liver disease before treatment, showed improvement in liver fibrosis at 48 weeks after achieving SVR12.

Success story

HENADIY (Luhansk Oblast)

"It so happened that since 1993 I have been injecting drugs, I learned after a while that I was infected with HIV and hepatitis C, I was treated at the clinic in Lavra, registered with the AIDS Center. In 2000, I returned to my homeland, to Luhansk, where I met my beloved Anyutka, who gave birth to my three wonderful sons... Periodically, this beast – HIV – would wake up in me, manifesting itself with various symptoms, so in 2007 I was hospitalized with severe bilateral lung inflammation. And in 2014, the war came to our home... We had to leave everything behind and flee. Friends helped us to settle in Kyiv. But my beast arose again – this time it was hepatitis... My condition began deteriorating, I was losing weight, the CD cell count dropped. I had a full examination at the Institute of Epidemiology, and the findings were disappointing – fibrosis grade 4, 1st genotype, CD4 – 123 cells. But I was so eager to live on...

I am a musician, a creative personality, but I turned into an unhealthy vegetable – irritable, yellow, and dried almost to the skeleton.

We were waiting for a chance to get on the program. For an entire year... It was not easy. Those regimens that were available could not be prescribed to me because of their possible side effects, that would just kill me, would undermine the already low immunity, there was a high risk of an opportunist appearance – tuberculosis or whatever. An entire board of doctors met to discuss my case. Reflected. Waited. I believed and trusted in God, that He would save me till the start of treatment. I completely trusted the doctors, I knew that they would make a right decision... And God heard my prayers. I received HCV treatment, and it turned out successful.

I just do not have the words to express my gratitude to the people who I met at certain moments of my life on my way... Thanks to everyone who helped me to be treated of hepatitis C."

1. Background

The International Charitable Foundation "Alliance for Public Health" (hereinafter referred to as the Alliance) is a leading non-governmental professional organization that, in cooperation with governmental partners and non-governmental organizations, effectively counteracts epidemics of HIV/AIDS, tuberculosis, viral hepatitis, and other infectious diseases by providing financial and technical support for the relevant programs, which, in particular, cover more than 314,000 representatives of the most vulnerable populations in Ukraine – which is the highest among European countries. In Ukraine, the Alliance is one of key implementers of the large-scale national HIV prevention, care, and support program, it implements opioid substitution therapy programs (most national coverage is by the Alliance and its partners); tuberculosis diagnosis among key populations, and the treatment of multi-resistant tuberculosis program (most national coverage), as well as programs for diagnosis and treatment of hepatitis C among key population representatives.

Viral hepatitis is a serious threat to public health. More than 300 million people globally are suffering viral hepatitis, among them more than 70 million people have hepatitis C. 1.3 million people die annually of complications that are directly related to these diseases [1]. Almost 14 million people in the WHO European Region are infected with hepatitis C virus, more than two thirds of them live in Eastern Europe and Central Asia [2]. Prevalence of hepatitis B and C virus varies from less than 0.5% in Western, Northern, and Central Europe to 3 to 8% in Eastern Europe and Central Asia [3]. Of the five major hepatitis viruses (A, B, C, D, and E) that lead to acute and/or chronic infection, hepatitis B and C are the cause of almost 98% of all deaths [4] in the European region associated with viral hepatitis. Since the course of the disease is often asymptomatic or paucisymptomatic ("the occult nature of the infection"), which causes late coming for treatment, chronic hepatitis C is the main cause of cirrhosis and primary liver cancer. The pressing nature of the problem of hepatitis C virus is determined by its significant prevalence, high rates of spreading, and the peculiarities of its clinical course, which condition late diagnosis of the disease – often at terminal stages.

According to WHO and national experts, HCV prevalence in Ukraine ranges from 3 to 5%, which implies that 1 to 2 million Ukrainians have viral hepatitis C and require treatment. However, dozens of times fewer people are aware of their disease, because, according to the MoH of Ukraine, approximately 53 thousand [5] patients are currently registered for treatment of viral hepatitis C. WHO data shows that Ukraine is the only country in the European region that is on the list of the 28 countries with the highest burden of viral hepatitis in the world [6].

1 *World Health Organization. Global hepatitis report 2017.*

2 *Ibid.*

3 *European Centre for Disease Prevention and Control. Systematic review on hepatitis B and C prevalence in the EU/EEA. Stockholm: ECDC; 2016.*

4 *World Health Organization, 2017 Action plan for the health sector response to viral hepatitis in the WHO European Region*

5 *http://moz.gov.ua/article/news/moz-ukraini-opriljudnilo-dlja-gromadskogo-obgovorennja-proekt-strategii-profilaktiki-diagnostiki-ta-likuvannja-virusnih-gepatitiv-v-ta-s-do-2030-roku*

6 *World Health Organization. Global hepatitis report 2017.*

People who inject drugs (PWID) are particularly vulnerable to infection with hepatitis C virus. Among the key populations (PWID, MSM, SW), HIV/HCV co-infection is common. As a result of the mutual influence of HIV and HCV in co-infected patients, serious clinical consequences are observed: rapid progression of liver fibrosis to cirrhosis and an increased risk of hepatocellular carcinoma at young age. HCV infection increases risks of hepatotoxicity of antiretroviral (ARV) medications, which may adversely affect antiretroviral therapy (ART) and requires careful selection of treatment regimens with minimal hepatotoxicity. According to findings of bio-behavioral research among key populations conducted by the Alliance for Public Health in 2017 and 2018, prevalence of hepatitis C among people who inject drugs is 63.9%. Prevalence of hepatitis C among PWID is 29.8% in the group under the age of 25, and 66.3% among those older than 25 [7].

In 2015, the Alliance initiated the Scaling Up Accessible and Effective HCV Treatment Through Community-Based Treatment Model for Most Vulnerable Populations in the Resource-Constrained Ukraine Project (hereinafter – the Project), which was implemented till September, 2018. The key prerequisites for the Project's implementation were: the hazardously unfavorable epidemic situation with regard to hepatitis C in Ukraine and, at the same time, the expanded hepatitis C infection treatment options globally, in particular, the emergence of direct-acting antivirals (DAAs) in the international clinical practice for HCV treatment. The widespread use of the innovative hepatitis C virus treatment with DAAs has opened up the possibility of obtaining over 95% effectiveness of treatment of HCV patients with an average treatment course of 12 weeks [8]. The new WHO Guidelines for the Care and Treatment of Persons Diagnosed with Chronic Hepatitis C Virus Infection, released in July 2018, recommend that all patients with chronic hepatitis C older than 12 years of age, regardless of the stage of their disease, were treated with DAAs [9]. Eradication of the hepatitis C virus from the organism makes it possible to reduce the risk of liver cirrhosis and primary liver cancer, as well as to reduce mortality resulting from terminal stages of liver disease and severe extra-hepatic HCV infection manifestations.

As of the start of the Project, DAAs were not yet registered in Ukraine and were not used for viral hepatitis C treatment. The national treatment standards were based solely on interferon regimens, which implied high costs, significant duration of treatment, relatively low effectiveness, high toxicity levels, and risks of serious adverse reactions and their consequences. The modern direct-acting antivirals, on the contrary, are characterized with high effectiveness and safety. In 2015, the HCV treatment with DAAs-based regimens cost dozens of thousands of dollars and was not affordable for most people, especially for key population representatives.

By focusing on expanding access to comprehensive measures for prevention, diagnosis, and treatment of socially hazardous diseases, the Alliance was the first organization in Ukraine that, in 2015, has introduced the modern treatment for viral hepatitis C with DAAs and made it accessible for the most challenging patients. HCV treatment with DAAs was made possible for representatives of key populations in Ukraine through the persistent work of the Alliance for Public Health. The Project implementation involved 19 non-governmental organizations (NGOs) and 25 health care facilities (HCFs) that provided services for diagnosis, treatment, and support of patients from key populations with hepatitis C virus for three years.

7 *Key findings of the bio-behavioral research among key populations. – K.: Alliance for Public Health, 2018. – Access mode: http://aph.org.ua/wp-content/uploads/2018/07/osnovni-rezultaty__A4__10.07.2018__Cajt.pdf*

8 *EASL Recommendations on Treatment of Hepatitis C 2015. – Journal of Hepatology. 2015. – vol. 63. pp. 199–236. – Access mode: http://www.easl.eu/medias/cpg/HEPC-2015/Full-report.pdf*

9 *Guidelines for the Care and Treatment of Persons Diagnosed with Chronic Hepatitis C Virus Infection. – World Health Organizations, 2018. – Access mode: http://apps.who.int/iris/bitstream/handle/10665/273174/9789241550345-eng.pdf?ua=1*

Objectives of the Project were to reduce the cost of DAA drugs for Ukrainian patients in general and to provide access for key populations not only to modern treatments, but also to screening, laboratory diagnosis, and follow-up services; to develop innovative community-based services, including medical and social support for persons subject to an increased risk and the highest incidence of hepatitis C virus. In 2015, due to the advocacy work held and the reduced price of the direct-acting antiviral drug ***sofosbuvir*** in Ukraine to USD 900 for a full 12-week treatment course, the Alliance got the opportunity to launch the country's first hepatitis C virus treatment program with DAA-based (sofosbuvir) treatment regimens. The initial procurements held by the Alliance with the financial support from the Global Fund to Fight AIDS, Tuberculosis and Malaria (GF) resulted in that the prices of DAAs in Ukraine constituted only 1% of the prices of the same medicines in the United States. Over the next two years, the price for public procurement was further unprecedentedly reduced – DAAs started being procured with funding from the state budget of Ukraine. This made it possible for more people to access free of charge efficient modern treatment of hepatitis C virus due to procurement of a greater number of treatment courses.

During the Project's implementation in 2015/2016, the Alliance carried out systemic work to advocate inclusion of treatment regimens based on DAAs – sofosbuvir and sofosbuvir/ledipasvir – into the Unified Clinical Protocol of the Primary, Secondary (Specialized), and Tertiary (Highly Specialized) Medical Care "Hepatitis C Virus in Adults" in Ukraine and to include these medications into the list of pharmaceutical products that can be procured by the Ministry of Health and health care facilities at the expense of the state and local budgets (the item "Procurement of medicines for patients with hepatitis B and C virus"). Active cooperation with the Ministry of Health and the Center for Public Health under the MoH of Ukraine, national and international experts was developed.

Scaled up access to HCV infection treatment among key populations required a particular approach, namely use of an effective social support model for the patients' retention in treatment; providing free laboratory testing to control treatment effectiveness; organizing a system of free and convenient for patients access to the antiviral drugs; taking effective measures to prevent HCV re-infection, in view of the challenges associated with the high prevalence of stigma and discrimination, as well as the risky behavior of key group representatives.

It should be noted that in the medical community there is some doubt about duration of the effect of HCV treatment using DAAs among key populations. The reason is the prevalence of risky behavior among these groups, which may adversely affect compliance with the prevention rules and result in HCV re-infection. In the framework of the Project's implementation, in 2018 it was possible for the first time, using the accumulated data, to explore the prevalence and possible factors of the increased risk of the HCV reinfection in our country. An acute problem in Ukraine is untimely diagnosis of viral hepatitis C, which results in the late start of patients' treatment at the stages of severe liver fibrosis or cirrhosis. In this case, HCV eradication reduces the level of de-compensation and mitigates, although does not eliminate, the risk of HCC development. Another important component of the Project was a study of liver fibrosis regression factors after effective antiviral HCV treatment using DAAs.

2. Key results of the Scaling Up Accessible and Effective HCV Treatment through Community-Based Treatment Model for Most Vulnerable Populations in the Resource-Constrained Ukraine Project implementation

KEY ACHIEVEMENTS OF THE PROJECT (2015 TO 2018):

- Treatment regimens using DAAs – sofosbuvir and sofosbuvir/ledipasvir were included into the Unified Clinical Protocol of the Primary, Secondary (Specialized), and Tertiary (Highly Specialized) Medical Care "Hepatitis C Virus in Adults" in Ukraine.
- The price of sofosbuvir for public procurement in Ukraine was reduced to USD 250 per month of treatment, and of sofosbuvir/ledipasvir – to USD 300 per month.
- In 2016, DAAs procurement with funds from the state and local budgets started in Ukraine.
- In 2015 and 2016, due to cooperation with the Ministry of Health of Ukraine, the medicines procured with funds from the State Budget of Ukraine were included into treatment regimens for the Project's patients.
- The Alliance provided 1,907 HCV treatment courses with DAAs (sofosbuvir and sofosbuvir/ledipasvir) for representatives of key populations in 19 regions of Ukraine.
- For the first time in Ukraine, high retention (98%) and treatment effectiveness (95%) levels for HCV treatment using DAAs were obtained among key populations.
- As part of the Project's implementation, the Alliance successfully implemented the community-based treatment model.
- An operational research was conducted to determine the most effective treatment model for hepatitis C virus among key populations using DAAs and to assess the risks of HCV reinfection and fibrosis regression factors after effective antiviral therapy.

The Project for hepatitis C virus treatment became a significant supplementary resource for improving performance of the State Targeted Social Program for Prevention, Diagnosis, and Treatment of Viral Hepatitis for the period till 2016, adopted by the Cabinet of Ministers of Ukraine (CMU Resolution of April 29, 2013 No. 637). The Project contributed to ensuring equal access for representatives of key populations to prevention, diagnosis, and effective treatment of hepatitis C virus; reduction of morbidity, disability, and mortality rates; improving quality of life, reducing stigma and discrimination of key populations.

In the process of the Project's implementation, the Alliance introduced the best practices of scaling up access to effective hepatitis C virus treatment for key populations using DAAs via community-based treatment models in the resource-constrained Ukraine.

The Project's results can be used to develop the evidence base for preparation and implementation of the national strategy for elimination of viral hepatitis, development of the health care system of Ukraine in the context of the further introduction of modern interventions, and community-based integration of the HCV infection treatment and social support model, ensuring modern and affordable laboratory diagnosis and treatment monitoring, both for key populations and for the general public.

Success story

OLEH (Lviv City)

"Since 2010, I have been aware about my HIV status, and at the same time I found out that I was infected with hepatitis C virus. In 2011, I became a client of an ST program, but the prospects for me were not very bright, because I knew that having these two severe infections, I was at a high-risk of rapid development of cirrhosis.

In March 2016, I found out that viral hepatitis C treatment options were available within the Alliance Project, and in May I started treatment with sofosbuvir, interferon, and ribavirin. The treatment was not easy – all through the three months I had unbearable headache, I could not sleep. But the idea that I would be free of at least one of the infections gave me the energy, and I did not give up. And I was glad that the treatment was supposed to last not a year, as before, but only three months. Literally a week after the last injection, all the side effects disappeared, I started feeling better.

Now I am full of energy and optimism. I have forgotten about that permanent fatigue. I work. Twelve weeks after the treatment I passed a final test – no hepatitis C virus was detected."

3. Key features of the Project to scale up accessible and effective hepatitis C virus treatment

3.1 THE TITLE AND IMPLEMENTATION PERIOD

The **Scaling Up Accessible and Effective Hepatitis C Virus Treatment Through Community-Based Treatment Model for Most Vulnerable Populations in the Resource-Constrained Ukraine** Project was implemented by the Alliance in the period **from April 2015 through September 2018.**

3.2 THE GOAL AND OBJECTIVES OF THE PROJECT

The main goal of the Project was to ensure access to effective and modern hepatitis C virus treatment with DAAs for key populations.

Project objectives:

- To scale up access of key populations to diagnosis and effective treatment of hepatitis C virus.
- To cover 1,500 representatives of key populations suffering from hepatitis C virus with DAA-based treatment.
- To pilot an effective medical and social support model for treatment of hepatitis C virus among KPs.
- To monitor and evaluate adherence of KP representatives to treatment and effectiveness of DAAs-based viral hepatitis C treatment.
- To analyze the prevalence and the factors of HCV re-infection, regression of liver fibrosis after effective treatment of hepatitis C virus using DAAs.
- To include modern highly efficient DAA-based hepatitis C virus treatment regimens into the standards of medical care in Ukraine and into national clinical practice.

3.3 THE GEOGRAPHY OF THE PROJECT

The Project was implemented in 19 regions of Ukraine, where 25 health care facilities and 19 non-governmental organizations were involved into implementation of its activities (see ***Fig. 1***).

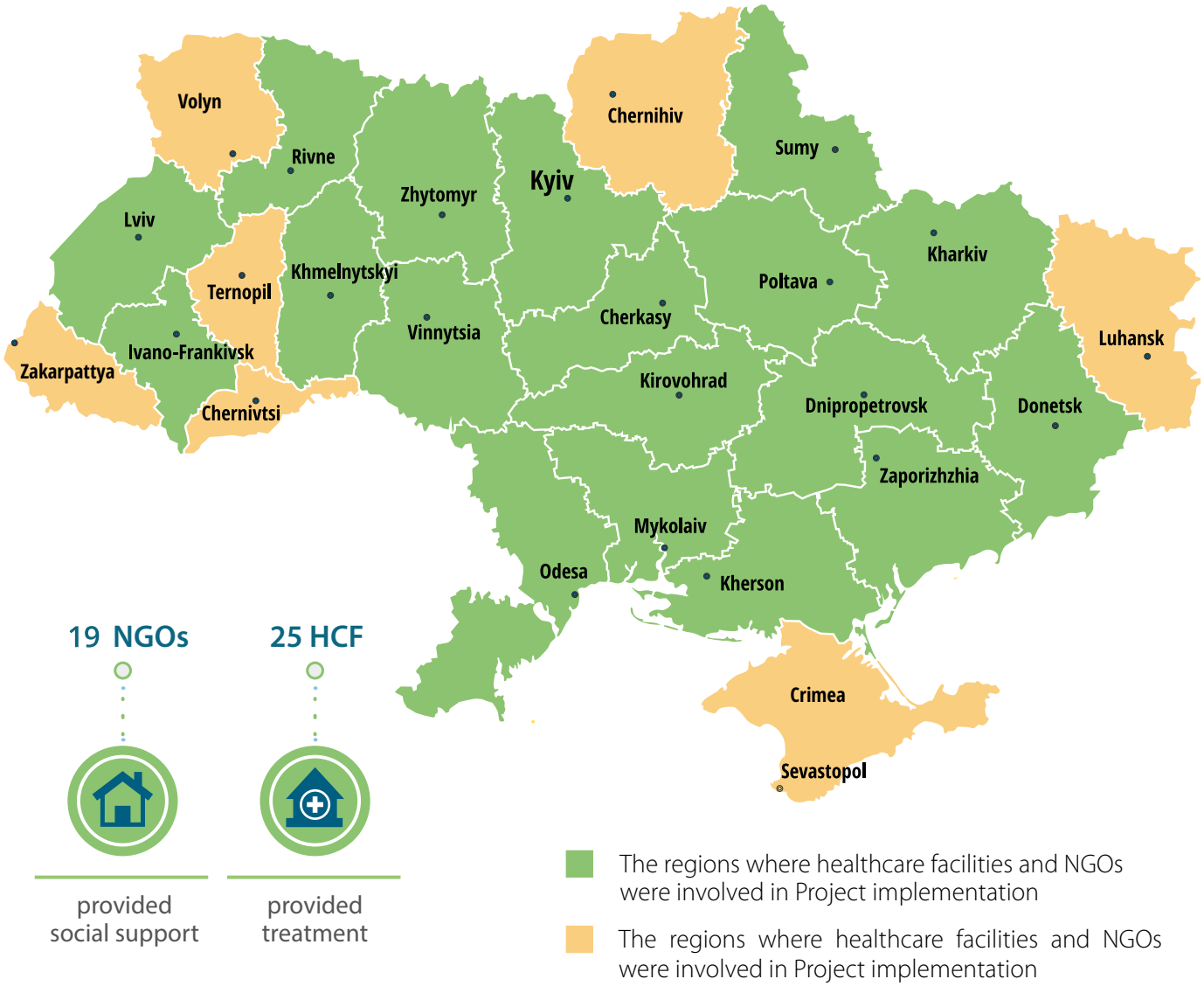


FIG. 1. The geography of implementation of the Project for treatment of hepatitis C virus among KPs in Ukraine, 2015-2018.

3.4 PHASES OF PATIENT ENROLLMENT TO PARTICIPATE IN THE PROJECT AND TREATMENT REGIMENS USED

Enrollment of patients was carried out in three steps:

I. June-December 2015 (450 patients).

II. January 2016 – February 2017 (763 patients).

III. March – December 2017 (694 patients).

At the first stage of treatment in the framework of the Project, only sofosbuvir was available among DAAs. Due to the fact that DAAs were not at that time registered in Ukraine, composing a full-fledged DAA combination for a 12-week course of treatment was virtually impossible for most patients (for example, for patients with the first and third HCV genotypes, which are the majority in Ukraine). As a result of consultations with the Project's International Advisory Board and its National Steering Committee, it was decided that at the first stage along with the ***sofosbuvir+ribavirin 24 weeks*** regimen of antiviral treatment, administration of the ***sofosbuvir+pegIFN+ribavirin 12 weeks*** AVT regimen will be initiated, i.e. ***the combination of the DAA drug sofosbuvir with pegylated interferon and ribavirin***. This made it possible to shorten the standard course of treatment for any genotype of hepatitis C virus to ***12 week SOF+pegIFN+RBV*** vs the ***24-week SOF+RBV*** AVT regimen. Thus, due to the combination of ***pegIFN and sofosbuvir DAA*** at the Project's first and second stages, a greater number of patients than planned accessed treatment. The patients with contraindications and interferon intolerance were prescribed with the AVT regimen ***sofosbuvir+RBV 12-24 weeks*** (standard 24 weeks for the 1st and 3rd HCV genotypes).

In addition to the above, the approach described allowed for more effective use of pegIFN procured with funds from the State Budget of Ukraine, since the combination of interferon, ribavirin, and sofosbuvir (DAA) made it possible to reduce the interferon AVT course from 24-48 weeks to 12 weeks, which in turn significantly contributed to increased effectiveness of treatment (from ~50% to 95%) and reduced cost per course of hepatitis C virus treatment. Thus, in 2015/2016, as a result of cooperation with the Ministry of Health of Ukraine, medicines procured at the expense of the State Budget were included into the Project's patient treatment regimens.

So, at the first stage of the Project's implementation, the actual patient coverage with treatment exceeded the planned targets by 80% (450 patients received access to treatment, while the plan was 250). At the second stage, access to treatment was provided for 11% more patients (763 patients vs 689 planned). At the third stage, the Alliance, for the first time in Ukraine, started HCV infection treatment with a combined DAA – ledipasvir/sofosbuvir – which made it possible to use 12-week interferon-free treatment regimens. Due to the significant increase in access to treatment at the first and second stages of the Project, only 93% of the planned number of patients (694 with 750 planned) were covered with treatment at the third stage (see ***Fig. 2***).

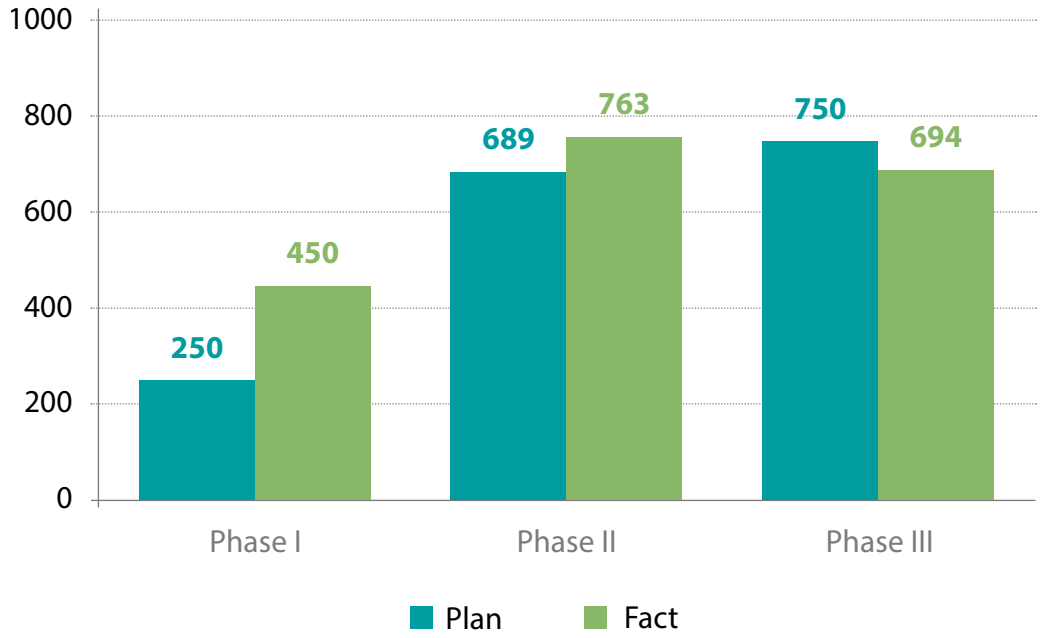


***FIG. 2.** The planned and actual coverage with hepatitis C virus treatment among KPs in the framework of the Project's implementation in Ukraine, 2015-2018*

In 2017, at the third stage of the Project, 468 patients started hepatitis C virus treatment with the combined ledipasvir/sofosbuvir DAA, and 226 patients continued receiving sofosbuvir.

In the process of increasing the number of patients enrolled, the number of HCFs involved into the implementation increased as well – while at the first and second stages their number was 15, in 2017, at the third stage of the Project's implementation, 25 health care facilities in 19 regions of Ukraine were involved.

3.5 CRITERIA FOR ENROLLING PATIENTS FOR TREATMENT

The clinical criteria for enrolling patients into the Project were:

- Active HCV infection.
- Fibrosis ≥ F2 based on METAVIR (prioritization – F3, F4, including compensated liver cirrhosis) or extrahepatic disease manifestations.
- No clinical contraindications for inclusion into the Project.

Clinical contraindications for inclusion into the Project, which depended on the hepatitis C virus treatment regimen, are listed in *Table 1*.

TABLE 1. *Clinical contraindications for inclusion into the Project, depending on the HCV infection treatment regimen*

Contraindication	Sofosbuvir / ribavirin	Sofosbuvir / peg-interferon / ribavirin	Sofosbuvir / daclatasvir	Ledipasvir / sofosbuvir
Pregnancy or planning it in the next 12 months	+*)	+	+	+
All forms of active tuberculosis	+	+	+	+
Chronic kidney disease with a significant decrease in GFR (creatinine clearance <50 ml/min)	+	+	+	+
Malignant neoplasms with an unfavorable prognosis for life	+	+	+	+
Decompensated liver cirrhosis (class B (B>7) and C by Child-Pugh score)	+ / – Requires thorough monitoring due to ribavirin administration	+	–	–
Severe depression with suicidal ideation/attempts (based on the specialist's opinion)	+ / – Depression must be compensated before starting the AVT	+	+ / – Depression must be compensated before starting the AVT	+ / – Depression must be compensated before starting the AVT
Decompensated type I diabetes mellitus or severe chronic and acute complications of any diabetes mellitus variant	+ / – Diabetes mellitus must be compensated before starting the AVT	Diabetes mellitus must be compensated before starting the AVT	–	–
Thyroid gland conditions in the decompensation stage, thyrotoxicosis	–	+	–	–
Any serious autoimmune diseases	–	+	–	–
Severe anemia	+	+	–	–

**) + a contraindication; – not a contraindication*

In the course of the Project's implementation, the number of contraindications for treatment was significantly reduced due to the transition to DAA combinations for hepatitis C virus treatment (without the use of interferon or ribavirin). Lots of diseases and conditions – such as decompensated liver cirrhosis, thyroid gland diseases in the stage of decompensation, thyrotoxicosis, any severe autoimmune diseases, severe depression, severe anemia – were no longer obstacles for patients' access to treatment of hepatitis C virus in case of using such antiviral therapy regimens as modern DAA combinations without interferon or ribavirin.

3.6 KEY POPULATIONS PARTICIPATION INTO THE PROJECT

The Project beneficiaries were key population representatives, patients with hepatitis C virus, and patients from KPs who had the HIV/HCV co-infection, namely:

- active PWIDs;
- PWIDs in remission;
- OST clients;
- PWIDs' sexual partners;
- SWs;
- MSM;
- individuals from KPs who were clients of HIV prevention, medical and psychosocial support projects;
- NGO activists from KPs;
- ATO (now Joint Force Operation) veterans diagnosed with "hepatitis C virus" or "HCV/HIV co-infection" (starting from the third stage of the Project).

All Project participants were to belong to the identified key groups and meet the clinical inclusion criteria.

GROUP DISTRIBUTION OF PROJECT PARTICIPANTS

TABLE 2. *Distribution of Project participants by the key group, 2015-2018*

PWIDs	1,531 (80.3%)
PWIDs' partners	152 (8.0%)
MSM	69 (3.6%)
SWs	82 (4.3%)
ATO (JFO) veterans	49 (2.6%)
Activists, etc.	24 (1.2%)

> For me as a key population representative, this Project is a triumph, a breakthrough. It is important that such needy populations had this chance and could be treated. And it's a big deal that prevention of reinfection was done, because it is in the interest of the entire society. ***Thanks to the Alliance, the donors, and everybody!***
>
> *(the Project's social worker)*

3.7 CRITERIA FOR SELECTION OF HEALTH CARE FACILITIES, HCF GEOGRAPHY

SELECTION OF HEALTH CARE FACILITIES WAS PERFORMED ACCORDING TO THE FOLLOWING CRITERIA:

1. Availability on the staff physicians of the corresponding profile (infectious disease doctors, gastroenterologists) who have the experience and skills of providing medical care to patients with hepatitis C virus.
2. Availability of a diagnostic laboratory or collaboration with a diagnostic laboratory that has the capacity to conduct diagnostic tests before the start of the course of hepatitis C treatment and to further monitor its effectiveness and safety.
3. Experience of collaboration with non-governmental organizations having the experience of and specialists for social support of KP representative patients receiving treatment for hepatitis C; readiness of the HCF to engage NGO staff into the process of joint decision-making on enrollment for treatment, distribution of treatment courses, and exchange of information about individuals from key populations in need of hepatitis C virus treatment.
4. Availability in the HCF of a storage facility for medicines in line with the rules for PPs storage stipulated in the national regulatory requirements.
5. Adherence to standards to ensure targeted use of the pharmaceutical products and maintenance of the respective medical and accounting documents.
6. Ensuring separate accounting for pharmaceutical products provided by the Alliance for the Project's implementation.
7. Opportunity to allocate pegylated interferon available to the HCF and purchased at the expense of the state or local budgets for treatment of KP representatives (optional).

A special evaluation form was developed for HCFs indicating the facility's capacity to enroll the required number of patients from the key populations for hepatitis C virus treatment. In addition to the aforementioned, every HCF held a preliminary self-assessment of its resources. Subsequently, monitoring visits to the HCFs were conducted for on-the-spot capacity check in the field. Based on findings of the monitoring, a regional plan for the Project's implementation was adopted indicating the number of courses and duration of hepatitis C virus treatment. The HCF selection was coordinated with the Project's National Supervisory Board, ensuring compliance with the principles of transparency and impartiality.

TABLE 3. *The list of HCFs selected for the Project's implementation*[10]

No.	Region	Health care facility
1	Vinnytsia Oblast	ME Vinnytsia Regional AIDS Prevention and Control Center
2	Dnipropetrovsk Oblast	ME Dnipropetrovsk Regional AIDS Prevention and Treatment Center
3	Dnipropetrovsk Oblast	ME Krivy Rih Infection Disease Hospital No.1 of Dnipropetrovsk Oblast Council
4	Donetsk Oblast	Mariupil AIDS Prevention and Control Center MH No. 4 named after I.K. Matsuk
5	Zhytomyr Oblast	Zhytomyr Regional AIDS Prevention and Treatment Center
6	Zaporizhzhya Oblast	MS Zaporizhzhya Regional AIDS Prevention and Treatment Center
7	Ivano-Frankivsk Oblast	Ivano-Frankivsk Regional Center for HIV Prevention and AIDS Control (Ivano-Frankivsk Oblast Clinical Infectious Disease Hospital)
8	The city of Kyiv	Kyiv City Clinical Hospital No. 5: Kyiv City AIDS Prevention and Control Center
9	The city of Kyiv	SI "Institute of Epidemiology and Infectious Diseases named after L.V. Gromashevsky, the National Academy of Medical Sciences of Ukraine"
10	Kyiv Oblast	ME of KRC Kyiv Regional HIV/AIDS Prevention and Control Center
11	The city of Kyiv	National Military Medical Clinical Center "The Main Military Clinical Hospital"
12	The city of Kyiv	Kyiv City Clinical Narcology Hospital "Sociotherapy"
13	Kirovohrad Oblast	ME Kirovohrad Regional AIDS Prevention and Control Center
14	Lviv Oblast	ME Lviv Regional AIDS AIDS Prevention and Control Center
15	Mykolaiv Oblast	Mykolaiv Regional AIDS AIDS Prevention and Control Center
16	Odessa Oblast	Municipal Institution Odessa Regional AIDS Prevention and Control Center
17	Poltava Oblast	MI Poltava Regional HIV Prevention and AIDS Control Center
18	Poltava Oblast	Poltava Regional Clinical Infectious Disease Hospital
19	Rivne Oblast	ME Regional AIDS AIDS Prevention and Control Center at Rivne Regional Council
20	Sumy Oblast	Oblast Municipal Institution Sumy Regional Infectious Disease Clinical Hospital named after Z.I. Krasovytsky
21	Kharkiv Oblast	MHCF Regional AIDS AIDS Prevention and Control Center
22	Kharkiv Oblast	LTD Kharkiv Medical Center "Alternatyva"
23	Kherson Oblast	Kherson Regional AIDS Prevention and Control Center
24	Khmelnytsky Oblast	Khmelnytsky Regional AIDS Prevention and Control Center
25	Cherkasy Oblast	Municipal Non-Commercial Enterprise Cherkasy City Infectious Disease Hospital, Cherkasy City Council

10 *The names of the HCFs are indicated as at the time of signing the cooperation agreements.*

4. Description of the HCV infection treatment model at the community level

Hepatitis C virus treatment model is schematically shown in ***Figure 3***.

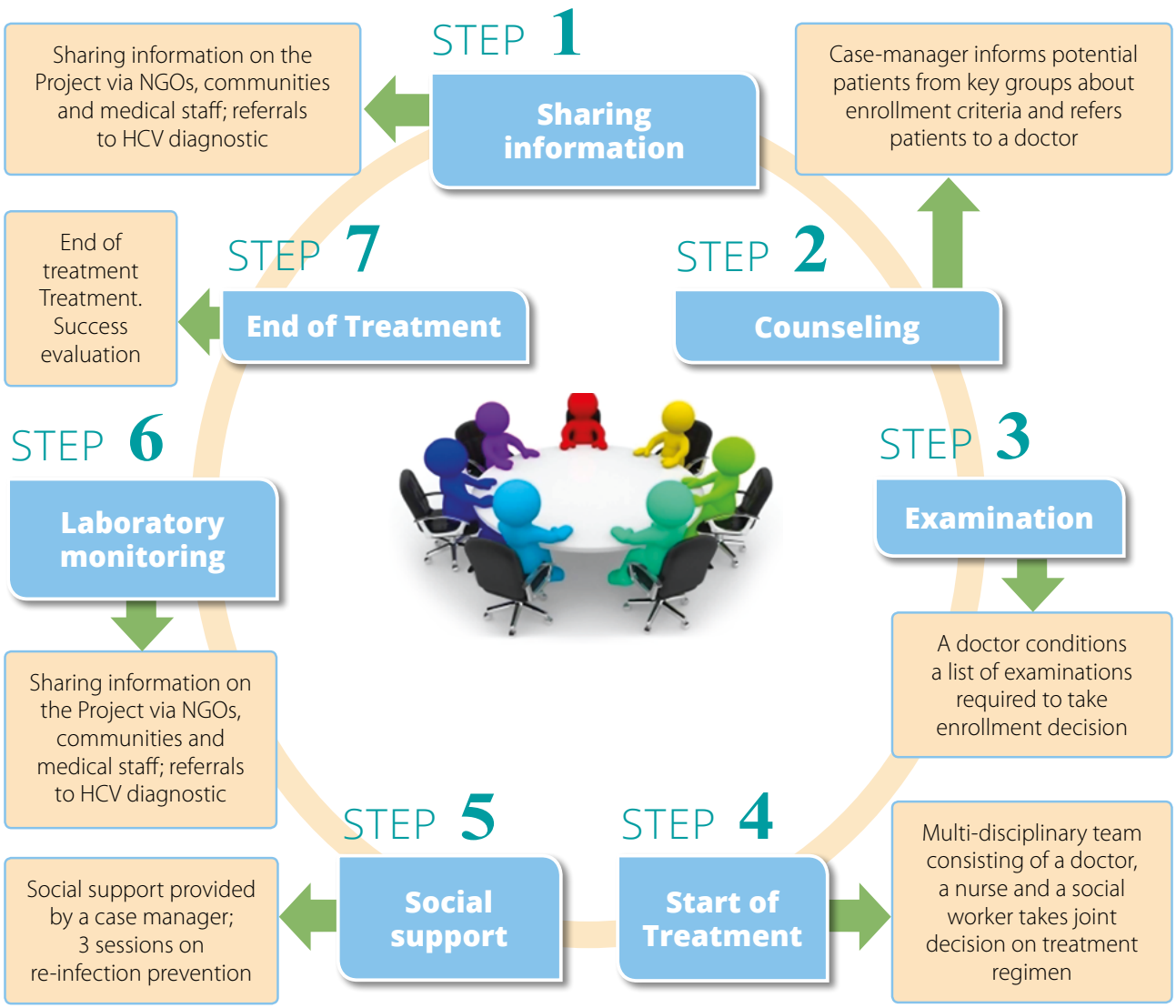


FIG. 3. *HCV infection treatment model at the community level*

4.1 DISSEMINATION OF INFORMATION ABOUT THE PROJECT PARTICIPATION PRINCIPLES

Information on the Project's terms and conditions, participant's enrollment criteria for the Project was duly published on the official website of the Alliance, as well as disseminated among HCFs and NGOs. Information was disseminated through local NGOs working with KPs; through communities representing KPs and HCF health professionals involved into hepatitis C virus treatment.

4.2 CONSULTATIONS FOR POTENTIAL PROJECT PARTICIPANTS

NGO and HCF staff in the field organized meetings with potential Project participants, provided consultations on participation terms and conditions and further medical examinations required for treatment prescription; informed individuals about possible side-effects of taking the medications. HCF medical staff, NGO case managers and social workers selected for the Project's implementation informed potential participants from the key populations about the inclusion criteria for the Project and referred them directly to the physician.

4.3 THE LIST OF MEDICAL EXAMINATIONS AND LABORATORY TESTS REQUIRED TO ENROLL PATIENT FOR HEPATITIS C VIRUS TREATMENT WITHIN THE PROJECT

During the entire period of the Project implementation, it was not possible to ensure free of charge access to laboratory and instrumental examinations for patient at state and municipally-owned HCFs. However, the Project participants received a 50% discount on the complex laboratory diagnostics at a chain of private laboratories. Prior to the start of treatment, patients were provided with special personalized forms that made it possible for them to pay only 50% of the cost of the required laboratory diagnostics at the private laboratory, including biochemical and general clinical tests.

The list of tests required for decision-making on enrollment into the Project was determined by the physician. It included a number of laboratory tests.

Tests required for all treatment regimens within the Project:

- total blood count (advanced);
- general urinalysis;
- biochemical blood test (ALT, AST, GGT, ALP, thymol test, total protein, albumin, bilirubin, creatinine, urea, PTI); serology HIV infection markets (ELISA), HBV (anti-HBcore, HBsAg), HCV (anti-HCV, HCV RNA – qualitative);
- HCV RNA viral load (quantitative) and HCV genotyping;
- *for patients with HIV co-infection:* the number of CD4 lymphocytes and HIV RNA viral load;

- *for women:* pregnancy test (3 to 7 days before the AVT start);
- clinical screening of symptoms raising suspicion of tuberculosis (cough, fever, night sweats);
- *in case of presence of tuberculosis-like symptoms, and/or if no thoracic organs X-ray examination was done during the previous 6 months:* X-ray examination of thoracic organs.

Additional tests for pegylated interferon treatment regimens:

- TTG, T3, T4, AMA;
- depression/anxiety assessment using Zigmond and Snaith Score;
- psychiatrist consultation (in case of severe depression);
- ECG;
- ophthalmologic examination to detect fundus pathologies.

It should be noted that in the process of the Project's implementation, as a result of transition to the DAA combination for hepatitis C virus treatment without use of interferon or ribavirin, the number of required laboratory tests before and during the treatment significantly decreased.

4.4 PRINCIPLES OF ESTABLISHMENT OF MULTIDISCIPLINARY TEAMS (MDTS)

Before the start of treatment, a MDT was set up at each HCF included into the Project, consisting of a physician, a nurse, a case manager and/or a social worker, who made decisions on participants' compliance with clinical and other inclusion criteria (individually in each case). MDT members jointly provided support for Project participants' treatment. The team's composition was approved by the HCF manager.

4.5 MDT FUNCTIONS

Each member of the multidisciplinary team performed activities in line with his/her professional duties and functions, as defined in the Project terms and conditions. Decisions on patient enrollment for treatment were made jointly, in line with the professional duties and competencies.

> I liked the fact that they [the physician, social worker] were not indifferent. It seems to me that they were more concerned about my health than I was, constantly monitoring the course of treatment, all the time offering their significant positive contribution. Thanks to the physician and the social worker!
>
> *(Patient, Poltava)*

4.5.1 FUNCTIONS OF THE PHYSICIAN:

- selection of patients for treatment;
- unbiased patient examination;
- ordering laboratory and instrumental tests and the respective treatment;
- maintaining patient medical records;
- assessment of the patient's condition in the course of treatment;
- follow up for adverse reactions and complications in the course of treatment and taking measures for their correction;
- prevention of adverse interaction of antiviral drugs with other medicines;
- control of targeted use of medicines;
- organization of collaboration with the nurse and the social worker;
- submission of information about the patient in the course of operational research;
- reporting to the Alliance.

4.5.2 FUNCTIONS OF THE NURSE:

- dispensing medicines;
- keeping a log for registration and dispensing of medicines;
- keeping a log for registration of receipt of medicines;
- organization of patient referral for examination;
- counseling patients on treatment side effects and complications;
- counseling on prevention of adverse interaction of antiviral drugs with other medicines;
- control of targeted use of medicines;
- organization of collaboration with the social worker;
- submission of information about the patient in the course of operational research.

4.5.3 FUNCTIONS OF THE SOCIAL WORKER/CASE MANAGER:

- patient social support;
- providing explanations and consultations for key population representatives on the possibility of receiving hepatitis C virus treatment;
- referring potential participants of the Project with positive HCV AB rapid test results to the HCF for further diagnosis of hepatitis C virus;

- providing patients with advisory, psychological, and practical assistance in the course of treatment;
- formation and support of patient's adherence to treatment;
- referring patients to the physician with the first signs of possible complications;
- monitoring patient visits to the physician and their receipt of medicines;
- counseling and follow up of patients to ensure targeted use of the prescribed medicines;
- informing the physician or the nurse about patients' possible non-compliance with the treatment regimen;
- advising Project participants on safety of the medicines' use;
- holding three sessions on prevention of re-infection.

> There was one complicated case when the fact of being acquainted with the patient's relatives turned out an important benefit. We joined efforts with the client's mother, started working together. I explained it to her that without her involvement it would be extremely hard, she should be available on the daily basis... We exchanged phone numbers, and I contacted both the client and the mother. Eventually, that was a success, and I'm very glad.
>
> ***(the Project's social worker)***

4.6 TRAINING OF HEALTH PROFESSIONALS AND SOCIAL WORKERS WITHIN THE PROJECT

As part of the Project's implementation, experts and medical advisers of the Alliance organized and conducted trainings for physicians and social workers. The key topics were: enrollment into the Project and the respective patient inclusion criteria; principles of MDT formation; clinical features of HCV infection treatment with DAAs and patient follow up. As part of the training, participants also received basic knowledge about hepatitis C virus, distribution of roles for each team member in execution of and support for treatment, HCV screening for KPs, diagnosis, selection criteria, and laboratory diagnostic tests prior to the start of treatment, monitoring of treatment, prevention of complications and their correction, DAA treatment regimens, social support for treatment, teamwork skills, prevention of HCV re-infection, and motivation to change risky behavior.

4.7 HCV TREATMENT REGIMENS PRESCRIBED FOR PROJECT PATIENTS

Patient distribution according to the treatment regimens is presented in ***Figure 4***.

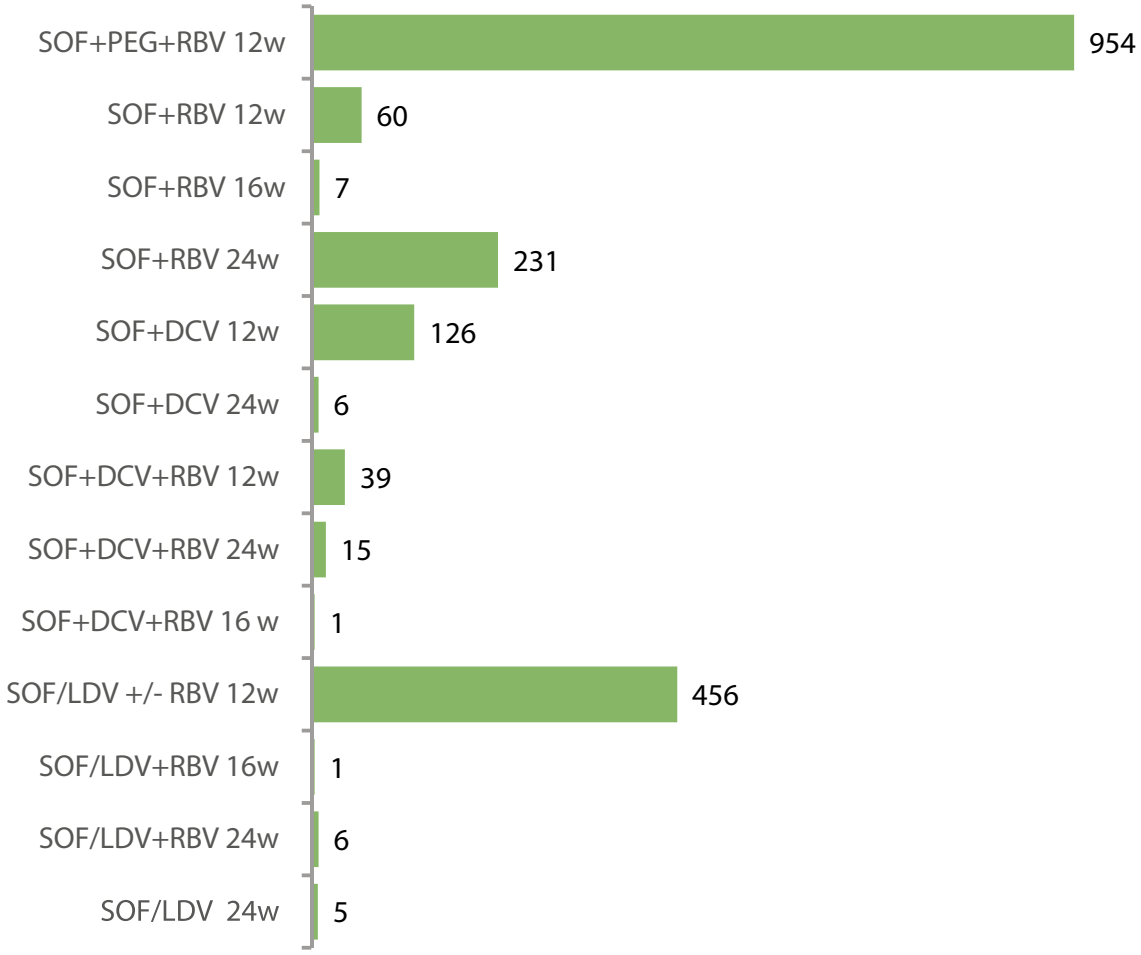


FIG. 4. *Project patient distribution according to HCV treatment regimens, absolute figures*

4.8 SOCIAL SUPPORT FOR PROJECT PATIENTS

4.8.1 STAGES OF ENGAGING SOCIAL WORKERS AND NON-GOVERNMENTAL ORGANIZATIONS FOR SOCIAL SUPPORT COMPONENT IMPLEMENTATION

In the first stage of the Project implementation, the case manager provided social support to each patient. In the second and third one, 19 non-governmental organizations were engaged to work with patients, who allocated specialists for social support. Selection of NGOs was based on assessment of their previous experience of collaboration with the HCFs that provided hepatitis C virus treatment for KP representatives.

4.8.2 THE LIST OF NGOs ENGAGED INTO PROJECT IMPLEMENTATION

TABLE 4. *The list of NGOs engaged into Project implementation*

No.	Region	NGOs
1	Vinnytsia Oblast	Vinnytsia Oblast Branch of Charitable Organization "All-Ukrainian Network of People Living with HIV/AIDS"
2	Dnipropetrovsk Oblast	"Doroha Zhyttya Dnipro"
3	Dnipropetrovsk Oblast	Charitable Organization Charitable Foundation "Hromadske Zdorovya", Kryvy Rih
4	Donetsk Oblast	NGO Mariupil Youth Union
5	Zhytomyr Oblast	Zhytomyr Oblast NGO "Perspectiva"
6	Zaporizhzhya Oblast	Charitable foundation "Spodivannya"
7	Ivano-Frankivsk Oblast	CF "Zahid Shans"
8	The city of Kyiv	NCO "Chas Zhyttya Plus"
9	Kyiv Oblast, Kyiv	National Charitable Organization "Convictus Ukraine"
10	Kirovohrad Oblast	Kirovohrad Oblast Branch of National Charitable Organization "All-Ukrainian Network of People Living with HIV/AIDS"
11	Lviv Oblast	Charitable foundation SALYUS
12	Odessa Oblast	Odesa Charitable Foundation for Rehabilitation and Social Adaptation of Homeless Citizens "Shlyah Dodomu"
13	Poltava Oblast	Charitable Association "Svitlo Nadii"
14	Rivne Oblast	Rivne Oblast Charitable Foundation "Nashe Maybutne"
15	Sumy Oblast	NGO "Shans" Club
16	Kharkiv Oblast	Charitable Organization 100 Percent of Life Network, Kharkiv
17	Kherson Oblast	Kherson Oblast Charitable Foundation "Mangust"
18	Khmelnytsky Oblast	Khmelnytsky Association for Drug Abuse and AIDS Combating Advancement "Viktoria"
19	Cherkasy Oblast	Charitable foundation "Insight"

4.8.3 SOCIAL SUPPORT COMPONENT

The key components of social support for the Project's patients:

- providing information on the conditions to access hepatitis C virus treatment in the framework of the Project;
- counseling, psychological and practical assistance in the course of treatment;
- support for adherence to treatment;
- monitoring patient visits and their receipt of medicines ;
- referring patients to the physician with the first signs of possible complications;

- control of targeted use of medicines by patients;
- advising patients on safety of the medicines' use;
- three sessions on re-infection prevention;
- motivational counseling on the specific features of taking the medications and complications resulting from non-compliance with the treatment regimen.

Development of adherence started even before the start of hepatitis C virus treatment. The physician and social worker held motivational counseling for patients. In order to monitor patients' visits to the physician and their receiving the medicines, the social worker used a variety of methods – reminders on the cell phone, telephone calls, drug intake diaries, etc. To reduce the risk of re-infection, each participant took part in three dedicated prevention sessions, where they discussed possible ways of HCV transmission and reinfection, as well as safe behavior models.

> *In the middle of my treatment [...], I was tested, and the virus no longer manifested itself. I was absolutely sure that I no longer needed to take the medication. If it had not been for the social worker... I'm still grateful to her! Once and forever, she correctly and calmly explained everything to me. And I heard her and realized that if I stop taking the medicine, I would do worse for myself. And I continued the treatment..*
>
> **(Patient, Kyiv)**

4.9 TREATMENT MONITORING

4.9.1 LABORATORY MONITORING OF TREATMENT

For the sake of clinical assessment of the patient's health status and to control his/her adherence to treatment, patients visited their physicians once a week. Planned laboratory tests in the course of treatment were performed according to ***Tables 5*** to ***7*** and depending on duration of treatment (12, 16, or 24 weeks).

4.9.2 CLINICAL MONITORING OF ADVERSE REACTIONS

During each visit to a physician, patients were assessed for adverse reactions, such as weakness, depression, irritability, sleep disorders, skin reactions, dyspnea, etc.

4.9.3 TREATMENT EFFECTIVENESS MONITORING

HCV viral load was determined with the PCR method before the start of the antiviral therapy and to monitor treatment effectiveness at the 4th and 12th weeks of treatment in case of a 12-week AVT course (or at weeks 16/24 after treatment completion), as well as 12 weeks after treatment completion to assess SVR12.

The total of 5,000 HCV RNA viral load tests were made free of charge for the Project's patients.

TABLE 5. *Laboratory monitoring of HCV infection treatment (duration 12 weeks)*

Test	Week # after the start of therapy						
	1	2	4	6	8	10	12
Total blood count (advanced)*		+	+		+		+
General urinalysis	+			+	+		+
Biochemical blood test (ALT, AST, GGT, ALP, thymol test, total protein, albumin, bilirubin, creatinine (calculating creatinine clearance to estimate GFR), urea, PTI)	+	+	+		+		+
TTG							+
HCV RNA (quantitative method)			+				+

** If the tendency for anemia is observed – weekly monitoring is performed*

TABLE 6. *Laboratory monitoring of HCV infection treatment (duration 16 weeks)*

Test	Week # after the start of therapy							
	1	2	4	6	8	10	12	16
Total blood count (advanced)*		+	+		+		+	+
General urinalysis	+			+			+	+
Biochemical blood test (ALT, AST, GGT, ALP, thymol test, total protein, albumin, bilirubin, creatinine (calculating creatinine clearance to estimate GFR), urea, PTI)	+	+	+		+		+	+
TTG							+	
HCV RNA (quantitative method)			+					+

** If the tendency for anemia is observed – weekly monitoring is performed*

TABLE 7. *Laboratory monitoring of HCV infection treatment (duration 24 weeks)*

Test	Week # after the start of therapy									
	1	2	4	6	8	10	12	16	20	24
Total blood count (advanced)*		+	+		+		+	+		+
General urinalysis	+			+			+			+
Biochemical blood test (ALT, AST, GGT, ALP, thymol test, total protein, albumin, bilirubin, creatinine (calculating creatinine clearance to estimate GFR), urea, PTI)	+	+	+		+		+	+	+	+
TTG							+			+
HCV RNA (quantitative method)			+							+

** If the tendency for anemia is observed – weekly monitoring is performed*

4.10 COMPLETION OF TREATMENT

Out of 1907 patients on HCV therapy 1400 were HCV/HIV co-infected, including those 1360 (97.1%) receiving ART. Out of 1360 patients on antiretroviral therapy 98 (7.2%) patients were receiving both ART and OST: 65 persons were on methadone (66.3%) and 33 (33.7%) on buprenorphine treatment. 67 patients receive only OST: 50 (74.6%) – methadone and 17 (25.4%) – buprenorphine.

4.10.1 PATIENTS' ADHERENCE TO TREATMENT

During 2015-2017, 1,907 treatment courses were administered to key population representatives within the Project, of which 468 included combination ledipasvir/soforbuvir direct-acting antiviral and 953 – non-interferon treatment regimens. 1,873 patients successfully completed a full treatment course.

The retention on treatment rate was 98.2%.

34 patients (1.8%) terminated treatment for various reasons, 6 of them then re-started their treatment within the Project.

Treatment interruption causes:

- 12 patients – due to severe adverse reactions;
- 8 – personal refusal to continue treatment;
- 6 – loss of contact/low adherence to treatment;
- 6 – because of the patient's death;
- one patient with the treatment regimen of ***SOF+RBV 24 weeks*** had detectable HCV VL after 12 weeks of treatment – the physician made the decision to terminate the treatment;
- one patient was referred to an oncology center due to detection of cervical cancer (later she was repeatedly enrolled for treatment).

Of the 1,873 patients who successfully completed a full course of treatment, 1,837 were screened for HCV RNA 12 weeks after completion of their AVT course to assess treatment effectiveness. Contact was lost with 36 patients after they had completed their course of treatment. .

Thank you for offering this chance (treatment for hepatitis C virus).
Because on the payable basis it would be all too expensive, impossible.
Thank you with all my heart!

(Patient, Poltava)

4.10.2 PATIENT TREATMENT EFFECTIVENESS

The overall effectiveness of hepatitis C virus treatment within the Project was 95%. Effectiveness data, broken down by sex, HIV status, liver fibrosis stage, PWID and genotype are presented in ***Figures 5, 6, 7, 8*** and ***9***.

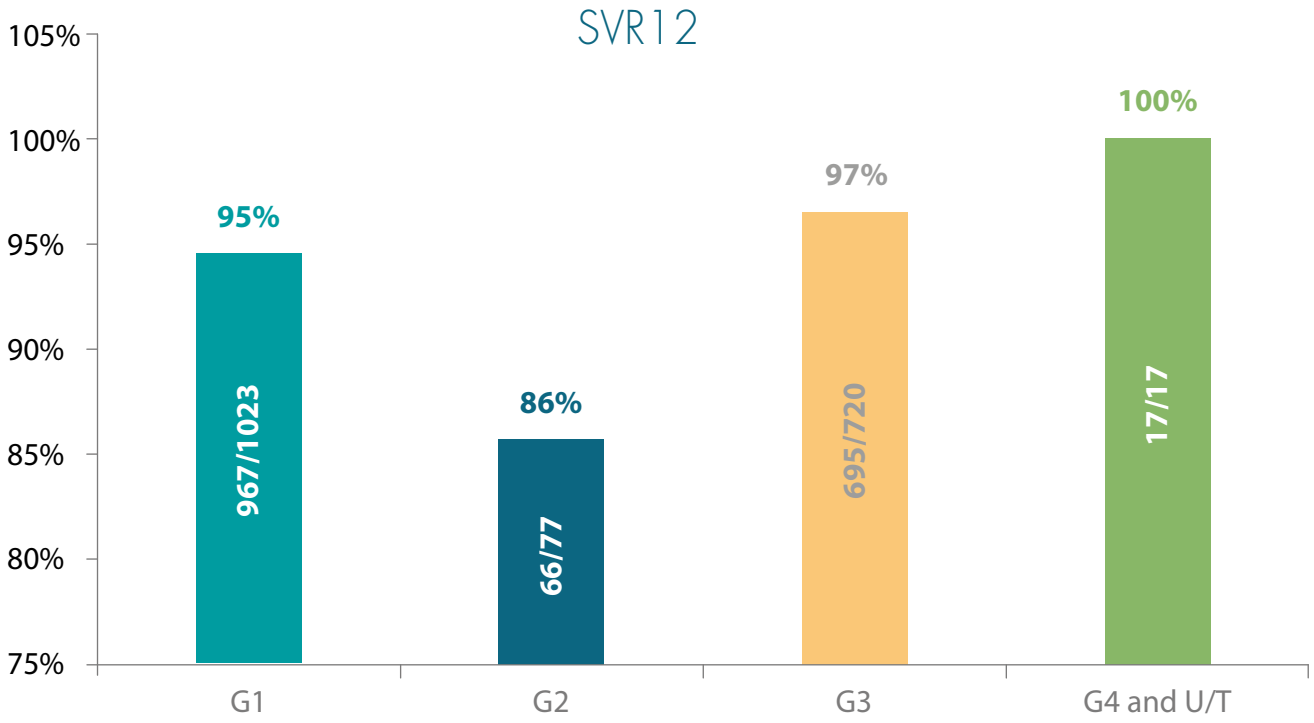


FIG. 5. Effectiveness of HCV AVT (achieving SVR12), broken down by genotype

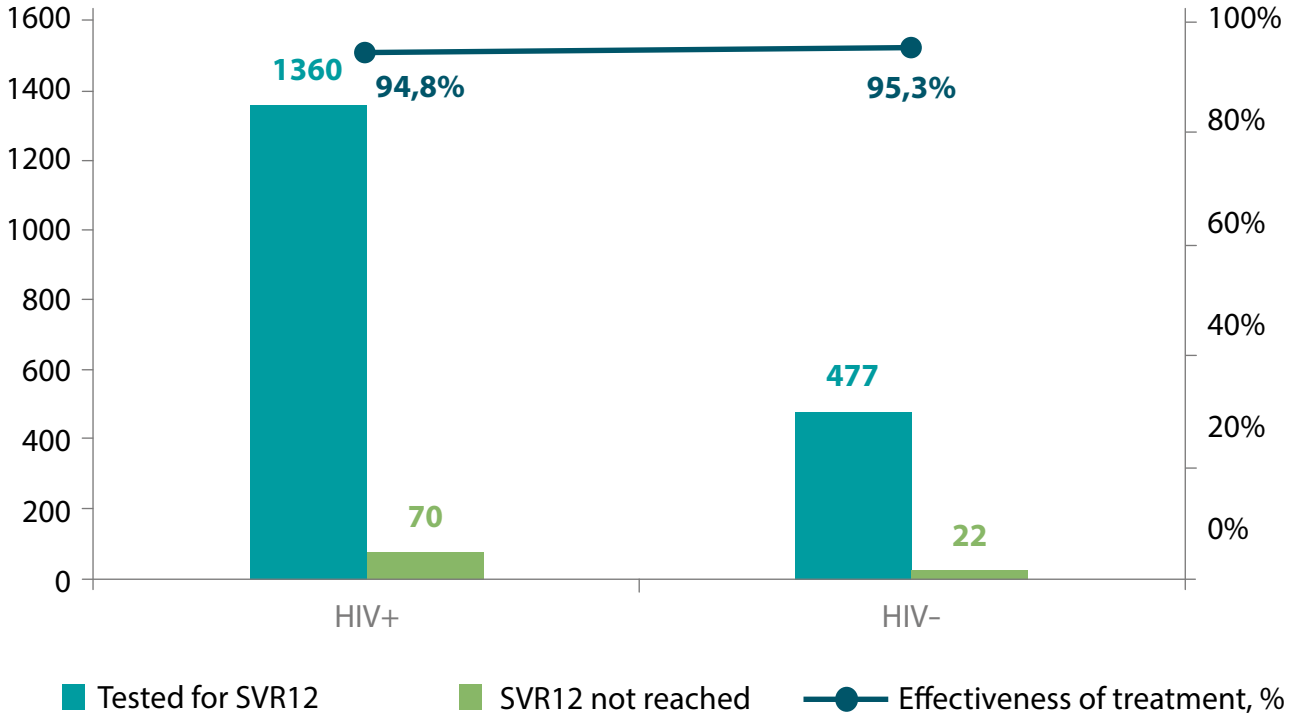


FIG. 6. Effectiveness of HCV AVT (achieving SVR12), broken down by HIV status

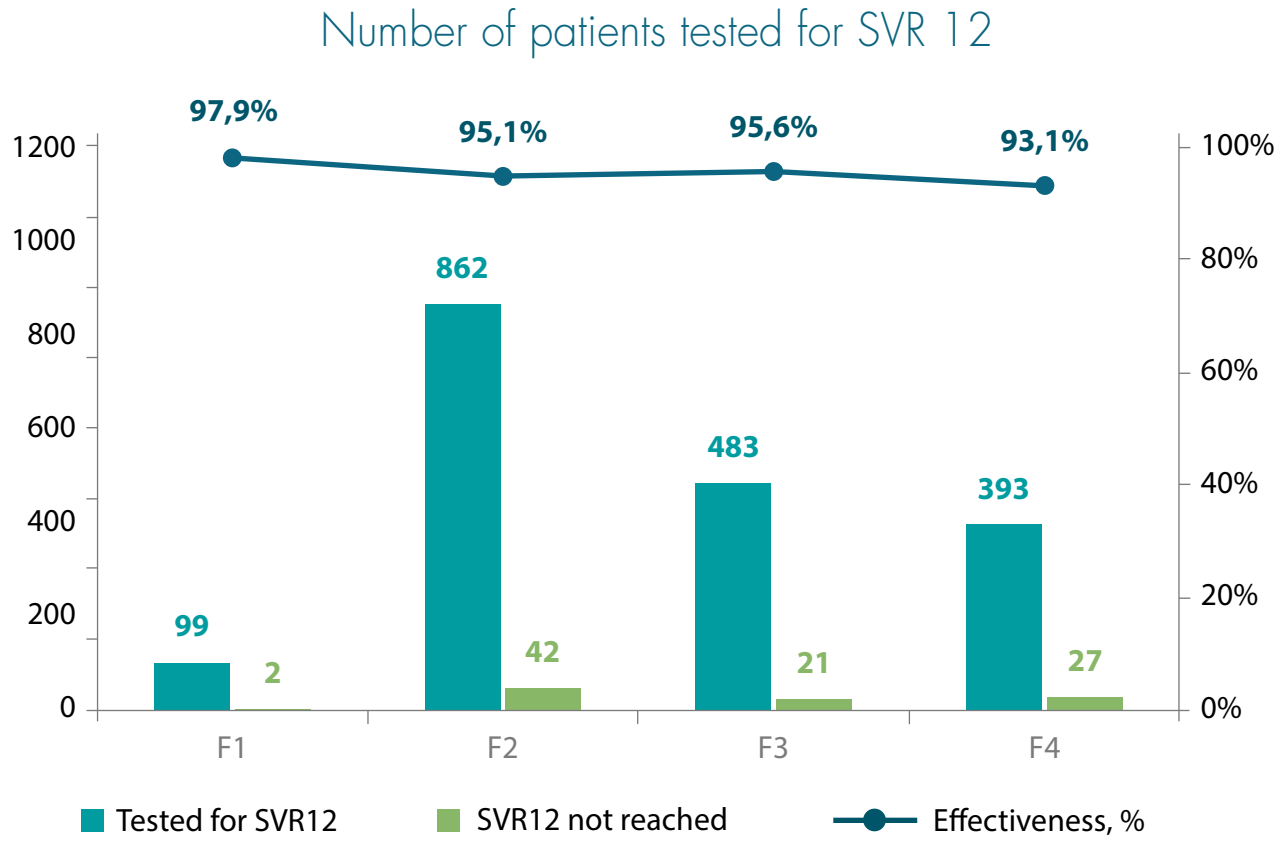


FIG. 7. Effectiveness of HCV AVT (achieving SVR12), broken down by liver fibrosis stage

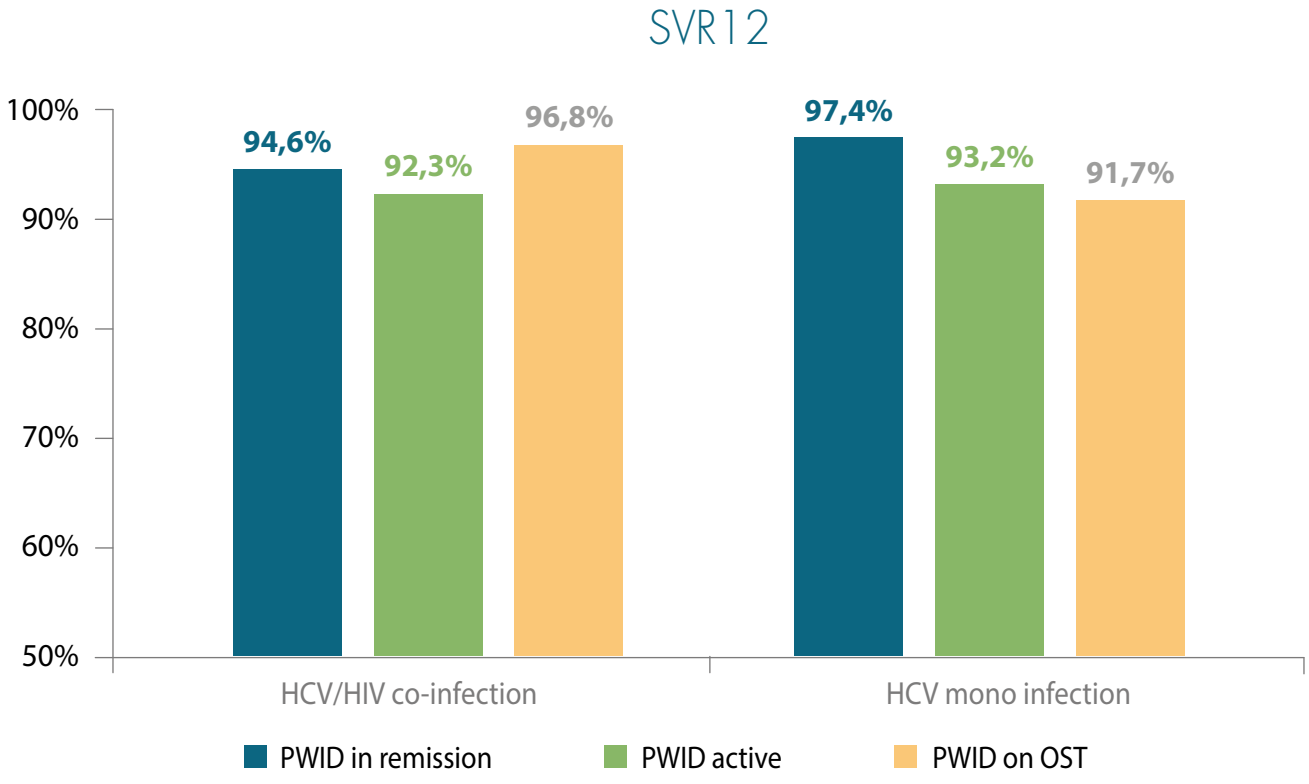


FIG. 8. Effectiveness of HCV AVT (achieving SVR12) among PWID (n=1479)

5. The operational research within the Project

5.1 THE GOAL AND OBJECTIVES OF THE RESEARCH

Effectiveness of the Hepatitis C Virus (HCV) Treatment Program for Vulnerable Populations in the Resource-Constrained Ukraine operational research was organized and conducted in the framework of the Project (hereinafter referred to as the Operational Research) aimed at assessing factors related to adherence to DAA HCV treatment, success of such treatment, as well as risks of HCVreinfection and liver fibrosis regression. It is expected that this research will form the basis for identifying and assessing the required changes to improve the service delivery model for HCV treatment among KPs.

The Operational Research included the following components:

1. A quantitative research, designed to determine the degree of patient adherence to treatment and the factors that affect this, to analyze cases of adverse event manifestations, as well as mitigation of risky behaviors and improving the HCV awareness level (hereinafter referred to as the ***research on adherence to HCV treatment and retention barriers***); and a qualitative research, which included analysis of individual and organizational barriers and obstacles that hinder patient engagement into treatment, as well as impede their retention in the treatment process (hereinafter – the ***qualitative research***).
2. The quantitative research of the risks and HCV recurrence factors after achievement of SVR12 (hereinafter – the ***research on the HCV reinfection risk)***.
3. The quantitative study on the risks and factors of liver fibrosis regression after achievement of SVR12 (hereinafter – the ***research on liver fibrosis regression***).

Objectives of the operational research:

- To determine HCV treatment effectiveness and assess success of treatment laboratory criteria for different categories of patients, depending on the HCV genotype, severity of liver damage, and occurrence of side effects.
- To assess the degree of adherence to treatment and its factors.

- To investigate cases of adverse event manifestations [11] (number, frequency, severity) and their association with early discontinuation of treatment.
- To determine whether risky behaviors are mitigated and the HCV awareness level improves in the course of participation in the treatment Project and case management.
- To analyze individual and systemic (institutional) barriers and obstacles that limit patient engagement in treatment, as well as their retention in the treatment Project. To determine the prevalence of HCV recurrence among Project patients at least 48 weeks after reaching SVR12 and assess factors associated with increased risks of HCV re-infection.
- To explore changes in severity of liver fibrosis among Project patients whose viral load is not detectable in at least 48 weeks after reaching SVR12 (regression and its severity), and to determine the factors that affect lack of improvement in the liver status (fibrosis regression).

5.2 RESEARCH GEOGRAPHY

The research was conducted in 18 regions[12] where the Project was implemented: Vinnytsya, Dnipropetrovsk, Donetsk, Zhytomyr, Zaporizhzhia, Ivano-Frankivsk, Kyiv, Kirovohrad, Lviv, Odesa, Poltava, Rivne, Sumy, Kharkiv, Kherson, Khmelnytsky, Cherkasy Oblasts, and the city of Kyiv. See the list of health care facilities and non-governmental organizations involved into the operational research in ***Table 8.***

11 Adverse events refer to any negative/adverse medical phenomena related or not related to administration of the drug. Adverse events include side reactions.

12 An exception is Mykolayiv Oblast, since at the time of patient selection for the research patients of Mykolayiv Oblast AIDS Prevention and Control Center were already undergoing treatment or had completed it and/or did not meet the inclusion criteria.

TABLE 8. *HCFs and NGOs involved into the Project Operational Research*

No.	Oblast, city	Health care facility	NGO/independent case manager	Research on adherence to HCV treatment and retention barriers	Qualitative research	Research on the risk of HCV re-infection/Research on liver fibrosis regression
1	Vinnytsia	ME Vinnytsia Regional AIDS Prevention and Control Center	Vinnytsia Oblast Branch of Charitable Organization "All-Ukrainian Network of People Living with HIV/AIDS"	+	+	+
2	Dnipropetrovsk	ME Dnipropetrovsk Regional AIDS Prevention and Treatment Center	"Doroha Zhyttya Dnipro"	+	-	+
3	Dnipropetrovsk	ME Krivy Rih Infection Disease Hospital No.1 of Krivy Rih City Council	Charitable Organization Charitable Foundation "Hromadske Zdorovya", Kryvy Rih	+	-	-
4	Donetsk	Mariupil AIDS Prevention and Control Center MH No. 4 named after I.K. Matsuka	NGO Mariupil Youth Union	+	-	-
5	Zhytomyr	Zhytomyr Regional AIDS Prevention and Treatment Center	Zhytomyr Oblast NGO "Perspectiva"	+	-	+
6	Zaporizhzhia	MS Zaporizhzhya Regional AIDS Prevention and Treatment Center	Charitable foundation "Spodivannya"	+	-	+
7	Ivano-Frankivsk	Ivano-Frankivsk Regional Center for HIV Prevention and AIDS Control (Ivano-Frankivsk Oblast Clinical Infectious Disease Hospital)	CO CF "Zahid Shans"	+	+	+
8	The city of Kyiv	Kyiv City Clinical Hospital No.: Kyiv City AIDS Prevention and Control Center	National Charitable Organization "Convictus Ukraine"	+	-	- [13]

13 *The facility was invited to participate in the 2nd component of the research, but the HCF failed to fulfill its obligations and its patients were not engaged into the research*

No.	Oblast, city	Health care facility	NGO/independent case manager	Research on adherence to HCV treatment and retention barriers	Qualitative research	Research on the risk of HCV re-infection/Research on liver fibrosis regression
9	The city of Kyiv	SI “Institute of Epidemiology and Infectious Diseases named after L.V. Gromashevsky, the National Academy of Medical Sciences of Ukraine”	Independent social worker	+	+	+
10	Kyiv	ME of KRC Kyiv Regional HIV/ AIDS Prevention and Control Center	National Charitable Organization "Convictus Ukraine"	+	-	+
11	The city of Kyiv	National Military Medical Clinical Center "The Main Military Clinical Hospital"	National Charitable Organization "Convictus Ukraine"	+	-	-
12	The city of Kyiv	Kyiv City Clinical Narcology Hospital "Sociotherapy"	National Charitable Organization "Convictus Ukraine"	+	-	-
13	Kirovohrad	ME Kirovohrad Regional AIDS Prevention and Control Center	Kirovohrad Oblast Branch of National Charitable Organization "All-Ukrainian Network of People Living with HIV/AIDS”	+	-	+
14	Lviv	ME Lviv Regional AIDS AIDS Prevention and Control Center	Charitable foundation SALYUS	+	-	+
15	Mykolaiv	Mykolaiv Regional AIDS AIDS Prevention and Control Center	Independent social worker	-	-	-
16	Odessa	Municipal Institution Odessa Regional AIDS Prevention and Control Center	Odesa Charitable Foundation for Rehabilitation and Social Adaptation of Homeless Citizens "Shlyah Dodomu"	+	+	+
17	Poltava	MI Poltava Regional HIV Prevention and AIDS Control Center	Charitable Association "Svitlo Nadii"	+	+	+

No.	Oblast, city	Health care facility	NGO/independent case manager	Research on adherence to HCV treatment and retention barriers	Qualitative research	Research on the risk of HCV re-infection/Research on liver fibrosis regression
18	Poltava	Poltava Regional Clinical Infectious Disease Hospital	Charitable Association "Svitlo Nadii"	+	-	+
19	Rivne	ME Regional AIDS AIDS Prevention and Control Center at Rivne Regional Council	Rivne Oblast Charitable Foundation "Nashe Maybutne"	+	-	+
20	Sumy	Oblast Municipal Institution Sumy Regional Infectious Disease Clinical Hospital named after Krasovytsky	NGO "Shans" Club	+	-	+
21	Kharkiv	MHCF Regional AIDS AIDS Prevention and Control Center	Charitable Organization 100 Percent of Life Network, Kharkiv	+	+	+
22	Kharkiv	LTD Kharkiv Medical Center “Alternatyva”	Independent social worker	+	-	-
23	Kherson	Kherson Regional AIDS Prevention and Control Center	Kherson Oblast Charitable Foundation "Mangust"	+	-	+
24	Khmelnytsky	Khmelnytsky Regional AIDS Prevention and Control Center	Khmelnytsky Association for Drug Abuse and AIDS Combating Advancement "Viktoria"	+	-	-
25	Cherkasy	Municipal Non-Commercial Enterprise Cherkasy City Infectious Disease Hospital, Cherkasy City Council	Charitable foundation "Insight"	+	-	+

5.3 RESEARCH DESIGN AND METHODS

The research on adherence to HCV treatment and retention barriers was based on the cohort prospective design and included three structured "face to face" interviews with Project participants: at the start of the treatment (baseline assessment), after treatment completion, and 12 weeks after treatment completion. Each interview could be held in the period within two weeks before and after the specified date. Consequently, the baseline assessment was performed in the range of +/- 14 days from: the date of the start of HCV treatment, after treatment completion, and 12 weeks after treatment completion. The cohort research also included collection of clinical history data prior before the start of HCV treatment, on treatment regimens, clinical test results throughout the treatment, and 12 weeks after its completion (SVR12 achievement assessment).

The qualitative research included in-depth interviews with MDT members, mainly physicians and social workers, as well as focus group interviews with Project patients.

The researches on the risk of HCV reinfection and liver fibrosis regression had the cross-sectional design and were conducted simultaneously in the form of one structured face-to-face interview with Project participants, which included questions about their behavior and HCV awareness after successful completion of treatment, as well as collection of the required clinical data (medical history before the start of treatment and before the tests, HCV RNA test, and liver fibrosis status).

5.4 CRITERIA FOR PROJECT PARTICIPANTS ENROLLMENT INTO THE RESEARCH

As the Operational Research started after completion of the first phase of the Project, only participants in the second and third stages of the Project that had not started their treatment or had started it recently (less than 14 days before) were enrolled into the ***research on HCV treatment adherence and retention barriers***. Enrollment into the research happened after receiving an informed consent for participation in the Project and in the research. Thus, all research participants also met the clinical and social criteria of the Project mentioned above (see ***Sections*** 2.5, 2.6).

The ***qualitative research*** involved individual participants of the ***HCV treatment adherence and treatment barriers*** research, as well as the MDT members who provided them with medical and social support. According to the protocol, the qualitative research envisaged coverage of all MDT members. In the process of data collection, the criteria for Project staff inclusion were modified. Considering the lesser role of a nurse in servicing Project patients, the qualitative research was only held among physicians and social workers.

Enrollment criteria for involving participants into the ***risk of HCV reinfection*** research were identified as: being a key population member at the start of treatment (PWID – active or in the state of remission, PWID partners, SW, MSM, ATO participants); completion of a full course of HCV treatment and attaining SVR12); at least 48 weeks have passed after attaining SVR12; provision of the informed consent to participate in the research, and collection of clinical data.

The ***research on liver fibrosis regression*** had the same inclusion criteria as the ***research on the risks and factors of HCV reinfection***. This research also included exclusion criteria: absence of expressed fibrosis before the start of treatment (F1, F2) and presence of HCV reinfection (at the moment of screening, the HCV RNA viral load was determined for inclusion into the research).

5.5 RESEARCH SAMPLE

Within quantitative components of the operational research (***research on adherence to HCV treatment and retention barriers, research on the risk of HCV reinfection, liver fibrosis regression research***), the sample design included selection of all the patient who were Project participants meeting inclusion criteria for the respective researches ("convenience sample"). No random sampling was made.

The actual sample of the ***HCV treatment adherence and retention barriers research*** was 900 persons – 97% of the planned sample population and 47% of the total number of Project participants. Of the 900 participants who were subject to the baseline assessment before the start of treatment, 93% and 92% participated in the interview after completion of the treatment and 12 weeks after treatment completion, respectively. The loss of respondents at each sampling were because of:

- patients' refusal to continue the treatment program/early termination of treatment;
- patients' refusal to participate in the research;
- patients' changing their place of residence;
- death of patients;
- hospitalization of patients (rehabilitation center/hospital);
- no communication with the participants (change of the patient's telephone number after treatment completion and absence of other ways of communication);
- communication difficulties between the physician, the interviewer, and the social worker.

456 people participated in the ***research on the risk of HCV reinfection***, which is 91% of the planned sample population and 24% of the total number of Project participants.

The ***research on liver fibrosis regression*** covered all the participants of the ***research on the risk of HCV reinfection*** who did not meet the exclusion criteria (no expressed fibrosis and presence of HCV reinfection), the total of 350 people. This was 70% of the planned sample population and 18% of the total number of Project participants.

The key reason of the unsuccessful recruiting of patients for the quantitative research was the difficulty in establishing collaboration among interviewers, health professionals, and social workers. But these misunderstandings were resolved at all the health care facilities as a result of holding additional meetings and after a clear distribution of duties among all team members.

The key reasons for the incomplete sample population:

- untimely notification by health professionals about the patient's invitation for the first meeting or a change in the time/date of the meeting with the respondent;
- patients' changing the time and/or place of the meeting, later – their refusal to participate in the research;
- the interviewer's being unable to arrive at a certain time to meet the respondent;

- patients' moving to other regions of Ukraine or abroad;
- patients' refusal to provide contact information and to participate in the research;
- high workload on the health professionals at the main job and the impossibility of greater involvement into the Project's implementation.

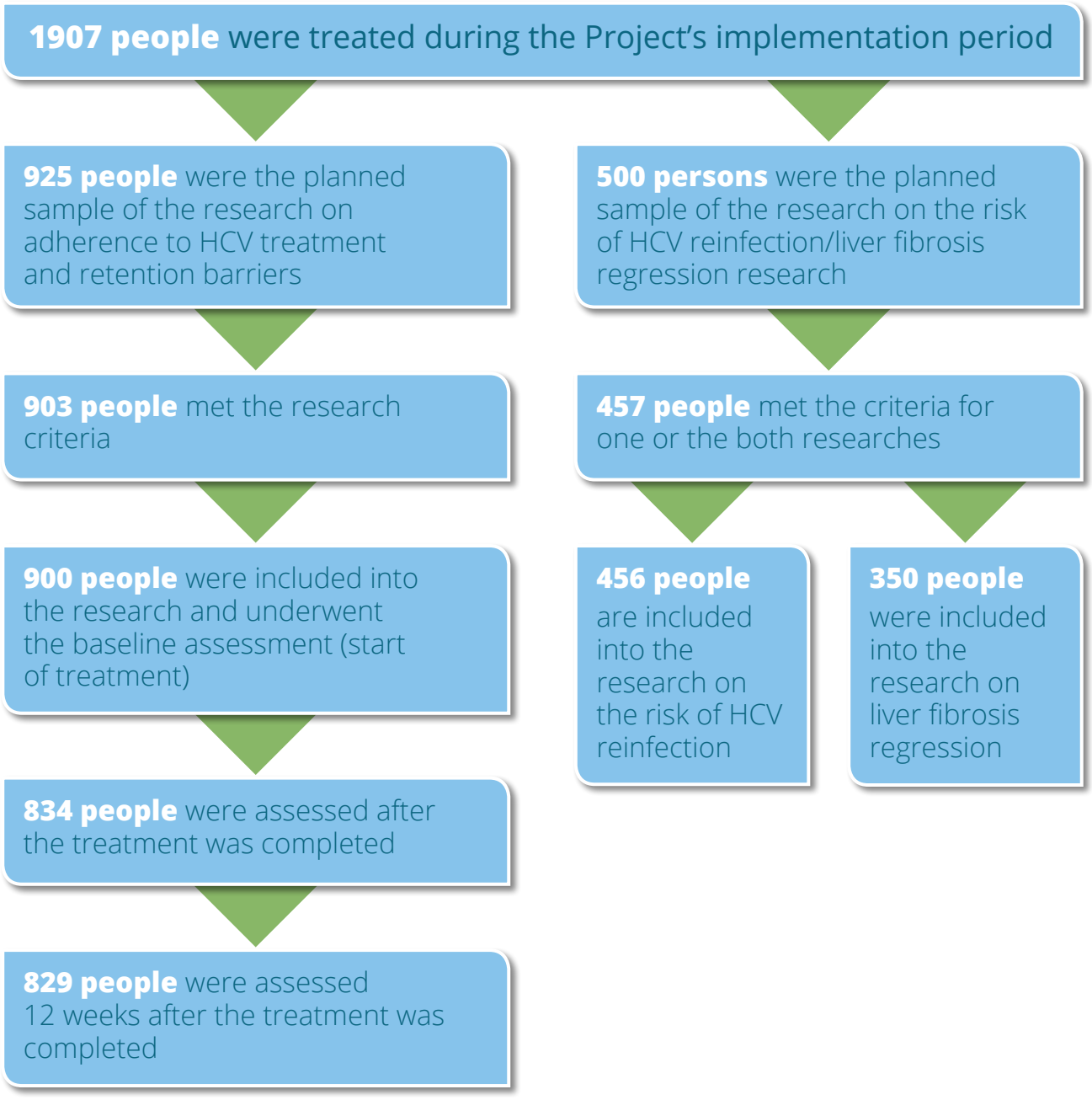


FIG. 9. The actual sample of the quantitative components of the operational research, persons

TABLE 9. *The actual sample of the quantitative components of the operational research by region and HCF, persons*

No.	Oblast, city	Health care facility	Research on adherence to HCV treatment and retention barriers (as on the baseline assessment date)	Research on the risk of HCV reinfection	Liver fibrosis regression research
1	Vinnytsia	ME Vinnytsia Regional AIDS Prevention and Control Center	99	50	42
2	Dnipropetrovsk	ME Dnipropetrovsk Regional AIDS Prevention and Treatment Center	35	26	23
3	Dnipropetrovsk	ME Krivy Rih Infection Disease Hospital No.1 of Krivy Rih City Council	28	-	-
4	Donetsk	Mariupil AIDS Prevention and Control Center MH No. 4 named after I.K. Matsuk	14	-	-
5	Zhytomyr	Zhytomyr Regional AIDS Prevention and Treatment Center	7	26	21
6	Zaporizhzhia	MS Zaporizhzhya Regional AIDS Prevention and Treatment Center	34	15	12
7	Ivano-Frankivsk	Ivano-Frankivsk Regional Center for HIV Prevention and AIDS Control (Ivano-Frankivsk Oblast Clinical Infectious Disease Hospital)	54	15	8
8	The city of Kyiv	Kyiv City Clinical Hospital No. 5: Kyiv City AIDS Prevention and Control Center	36	-	-
9	The city of Kyiv	SI “Institute of Epidemiology and Infectious Diseases named after L.V. Gromashevsky, the National Academy of Medical Sciences of Ukraine”	152	150	116
10	Kyiv	ME of KRC Kyiv Regional HIV/AIDS Prevention and Control Center	42	20	15
11	The city of Kyiv	National Military Medical Clinical Center "The Main Military Clinical Hospital"	31	-	-
12	The city of Kyiv	Kyiv City Clinical Narcology Hospital "Sociotherapy"	20	-	-
13	Kirovohrad	ME Kirovohrad Regional AIDS Prevention and Control Center	28	14	10

No.	Oblast, city	Health care facility	Research on adherence to HCV treatment and retention barriers (as on the baseline assessment date)	Research on the risk of HCV reinfection	Liver fibrosis regression research
14	Lviv	ME Lviv Regional AIDS AIDS Prevention and Control Center	33	20	14
15	Odessa	Municipal Institution Odessa Regional AIDS Prevention and Control Center	37	24	22
16	Poltava	MI Poltava Regional HIV Prevention and AIDS Control Center	31	20	11
17	Poltava	Poltava Regional Clinical Infectious Disease Hospital	36	20	14
18	Rivne	ME Regional AIDS AIDS Prevention and Control Center at Rivne Regional Council	37	9	8
19	Sumy	Oblast Municipal Institution Sumy Regional Infectious Disease Clinical Hospital named after Z.I. Krasovytsky	54	16	9
20	Kharkiv	MHCF Regional AIDS AIDS Prevention and Control Center	37	5	4
21	Kharkiv	LTD Kharkiv Medical Center “Alternatyva”	19	-	-
22	Kherson	Kherson Regional AIDS Prevention and Control Center	6	13	13
23	Khmelnytsky	Khmelnytsky Regional AIDS Prevention and Control Center	28	-	-
24	Cherkasy	Municipal Non-Commercial Enterprise Cherkasy City Infectious Disease Hospital, Cherkasy City Council	2	13	8

The qualitative research sample – 46 patients of the Project and 11 MDT members. In total, 5 focus group discussions and 11 in-depth interviews were conducted. Vinnytsya is the only city where in-depth interviews were conducted with all MDT members. Further on, due to the limited role of nurses in providing patient care, in-depth interviews were only conducted with the physician and the social worker.

TABLE 10. *Focus group interview sample characteristics (patients), by region*

City	Total number of participants	Number of women	Number of men	Average age*	Number of participants on a 12-week treatment regimen	Number of participants on a 24-week treatment regimen
Vinnytsya	10	3	7	32	2	8
Poltava	9	0	9	–	3	6
Kyiv	8	1	7	38	6	2
Ivano-Frankivsk	8	2	6	–	7	1
Odessa	11	2	9	45	10	1

** Patients in Poltava and Ivano-Frankivsk did not indicate their age.*

TABLE 11. *In-depth interview sample characteristics (MDT members), by region*

City	Total number of participants	Infectious disease physician	Nurse	Social worker
Vinnytsya	3	1	1	1
Poltava	2	1	–	1
Ivano-Frankivsk	2	1	–	1
Kharkiv	2	1	–	1
Odessa	2	1	–	1

5.6 DATA COLLECTION: THE PERIOD AND PROCEDURES

All in all, data collection for the operational research was held from May 2016 till July 2018

TABLE 12. *The period of data collection for the operational research*

Operational research component	Data collection period
Research on adherence to HCV treatment and retention barriers.	May 2016 – March 2018
Qualitative research	April – November 2017
Research on the risk of HCV reinfection	April – July 2018
Liver fibrosis regression research	April – July 2018

Procedures of the research on adherence to HCV treatment and retention in treatment barriers. MDT physicians selected project participants meeting the research criteria. If a patient met the research criteria, the physician identified him/her as a potential participant and invited him/her for a meeting with the social worker and an interviewer who, in turn, explained the goals, objectives, benefits and risks associated with the research, as well as the Project participation terms and the terms of exiting the Project. Thereafter, an informed consent to participate in the research (2 copies) was signed, and contact information was recorded for organization of further visits and for baseline assessment. Further interviews were conducted by interviewers in collaboration with MDT physicians. The average duration of each interview was 45 minutes, and tablets (an on-line questionnaire) were used to hold them.

Qualitative research procedures. Selection and engagement of patients of the qualitative research were carried out with the help of MDT members. To conduct the focus group discussions and in-depth interviews, a moderator was selected who had experience of participating in similar projects and had undergone special training. The average duration of one focus group/in-depth interview was one hour. All interviews within the qualitative research were accompanied by audio recording.

Procedures of the research on the risk of HCV re-infection and the research on liver fibrosis regression Selection of potential participants was based on the electronic patient registry, which did not contain personal data, but included unique codes. The list of the codes that met the inclusion criteria (pre-selection) was forwarded to the HCFs were patients received HCV treatment in the framework of the Project. Physicians identified the patients and, after the identification, they contacted them inviting them to participate in the researches.

If the patient gave oral consent to participate in the research, the first appointment was scheduled – it was to take place within 2 weeks of obtaining the patient's oral consent. During the meeting, the physician informed the patient about the nature of the two researches and invited the potential participant to sign the informed consent to participate. In case of giving the consent, the patient signed the document in 3 copies for the physician, interviewer, and patient.

The interview was conducted by a specially trained interviewer during the first meeting. The average duration of the interview was 30 minutes, tablets (on-line questionnaires) were used in the process. After the interview, the physician referred the patient for the required tests and appointed the date of the second meeting, during which the participant provided the physician with tests results, was advised on them, and received the compensation for his/her participation in the research.

Patients received financial incentives for participation in each of the components of the operational research.

Interviews with patients were conducted by interviewers of the Subsidiary Enterprise of the Institute of Sociology at the National Academy of Sciences of Ukraine "Center for Social Analysis named after Yuriy Sayenko".

5.7 RESEARCH FORMS

The informed consent to participate in the research. The operation research included two separate paper forms of informed consent to participate in the research on adherence to HCV treatment and retention barriers, including the qualitative component of the research, and to participate in the research on the risk of re-infection and the liver fibrosis regression research.

Questionnaires. The questionnaire ***for the research on adherence to HCV treatment and retention barriers*** included the following sections: socio-demographic data; quality of life; alcohol consumption pattern; drug use pattern, experience of drug-addiction treatment, ST experience; sexual behavior pattern; domestic HCV infection risks; HCV awareness; participation in harm reduction programs; information about HCV support and treatment results, in particular the frequency of attending the physician, the level of satisfaction with the services, adherence to treatment, barriers to treatment, etc. (only during the second interview, after the treatment is completed).

The ***research on the risk of HCV re-infection and liver fibrosis regression*** was based on a single questionnaire aimed at collecting retrospective data on possible barriers and factors affecting the re-infection risk and changes in fibrosis. The questionnaire included the following sections: socio-demographic data; alcohol and drug use patterns; risks of re-infection; ST experience; sexual behavior pattern; awareness about prevention of HCV infection, etc.

The both questionnaires were based on Qualtrics ***(http://www.qualtrics.com)***.

Medical data. The ***research on adherence to HCV treatment and retention barriers*** used the medical registry and reporting form for hepatitis C virus patient examination. The form was filled in by the physician in the electronic format (Excel table) for each patient participating in the research in parallel with reporting on the HCV infection treatment progress. The full form was completed 12 weeks after the end of treatment, when results of laboratory tests were obtained, including biochemical blood parameters and viral load data 12 weeks after the end of treatment. Findings of the primary examination, the patient history (presence of co-infection with HIV, HBV, tuberculosis, etc.), information about the prescribed treatment regimen, medical examination data during the period of drug intake and data on treatment side effects, information on changes in the prescribed treatment regimen, interruption of treatment, adherence to treatment assessment, laboratory test results were entered into the form.

Within the ***research on the risk of re-infection and liver fibrosis regression***, the physician supplemented the monthly reporting form above and the HCV patient registry used during the Project. Additional clinical and laboratory data required for the research were obtained from patient medical records (for example, laboratory test data) and from the objective status and life history obtained by the physician during the first patient appointments.

The data – questionnaire and medical ones – were combined with the unique patient code contained in each research form of quantitative components of the operational research. The SyrEx identification code was used – a combination of numbers and letters generated during the first visit within the Project based on information provided by the client, without any document check. The code generation algorithm is as follows:

- the first letter of the client's full name;
- the first letter of the full name of the mother;
- the first letter of the full name of the father;
- the two digits of the birth date (day);
- the last two digits of the year of birth;
- the first letter of the word corresponding to the client's sex (Ч (male)/Ж (female)/Т (transgender))

Focus group discussion guide. The key questions set in this form related to identification of systemic barriers and obstacles that limit patients' engagement into treatment, as well as their retention in treatment.

In-depth interview guide. Separate in-depth interview scenarios were developed for health professionals and social workers. The questions related to identification of systemic barriers and obstacles that, according to MDT members, limited patients' engagement, as well as their retention in treatment.

5.8 ETHICAL GROUNDS

The protocol and annexes to the operational research protocol were developed with the participation of national experts. Moreover, the protocol and the research toolkit were reviewed by the Ethics Committee of the SI Institute of Epidemiology and Infectious Diseases named after L.V. Gromashevsky, the National Academy of Medical Sciences of Ukraine. It was concluded that there was no violation of medical or ethical standards in conducting the research. The research was conducted in compliance with provisions of Helsinki Declaration and the local regulatory policy. Patients received complete information on the benefits and risks of the research and gave their written informed consent to participate in it.

5.9 BENEFITS OF PARTICIPATING IN THE RESEARCH

At the time of the start of the operational research, DAA-based hepatitis C virus treatment regimens (sofosbuvir) were already available globally and had proved effective in clinical trials. Their application proved to be more effective than the previous standards based on interferon regimens (interferon + ribavirin). Use of DAAs minimized the number of adverse reactions, reduced the duration of treatment. In Ukraine, key population representatives had significantly restricted access to hepatitis virus treatment, given the frequent contraindications for treatment with PegIFN+RBV C-based regimens – the only ones for which scarce governmental funding was allocated (interferon therapy courses). Thus, participation in the Project and the operational research was virtually the only chance for KP representatives to be treated of hepatitis C virus. When patients were involved into the Project, coercion was unacceptable. Refusal to participate in the operational research in no way affected participation in the hepatitis C virus treatment Project and access to other services on the basis of NGOs or HCFs (psychosocial support, ART, ST, prevention services).

5.10 OBSTACLES IN THE COURSE OF THE RESEARCH

In preparation for the operational research, its team identified some possible obstacles and took a number of steps to mitigate them or, if possible, to completely eliminate them. The list of such obstacles is presented in ***Table 13***.

TABLE 13. *Obstacles to implementation of the operational research and measures to eliminate them*

Obstacle	Description	Measures taken to eliminate it
Natural dropout of participants	Due to the possible refusal of participants from further participation in the research, as well as to the probability of their being put in jail or of death, the expected rate of natural participant dropout was estimated as <20%.	MDT members and interviewers made every effort to retain the patients – both in the Project and in the research. They were instructed/trained on activities to encourage patients to participate in the Project and the research.
Frequent replacement of case management specialists	NGO staff often change jobs due to low salaries and the "professional burnout" syndrome. Training of new project staff results in increased workload for trainers and budget constraints.	Operational briefings for new staff were held via Skype or by phone.
Interviewer replacement	The interviewer could fail to cope with the tasks assigned to him/her or refuse to participate in the research for personal reasons.	Operative search for and replacement of the interviewer. Operational briefings for new interviewers via Skype or by phone were also held.
Bilingualism	As it was intended to reach participants from different Oblasts in all parts of Ukraine, availability of forms and other research tools in only one language could be an obstacle.	Part of the forms and tools were developed in two languages: Ukrainian and Russian. Interviewers were also instructed to translate the Research Questionnaire and, in the event of such a situation, they could explain or translate unclear questions for the respondent.

5.11 RESEARCH DATA COLLECTION QUALITY MONITORING

Several measures were implemented to ensure reliability of the data:

1. ***Training the operational research team.*** In the framework of the preparatory phase of the research, trainings were organized for interviewers, recruiters, physicians, quality controllers, during which the participants got acquainted with the research protocol, its stages, questionnaire forms, medical forms and other documents, their duties, possible problems that may arise during the study, and how to overcome them. The emphasis was placed on the quality of filling out all of the required forms and on monitoring the compliance. A special briefing for focus group discussion and in-depth interview moderators was also held. Moreover, within the framework of the Project, training sessions for MDTs were held on Project documentation and reporting used in the framework of the research. The emphasis was on correct filling of all the forms.
2. ***Use of electronic research forms.*** Use of on-line questionnaires and medical data electronic forms for data collection significantly reduced frequency of technically incorrect data entry. Control of timely transfer of on-line questionnaire data to the research team was performed.

3. ***Data quality control during the data collection period.*** Quality controllers and research implementers executed monthly control of reliability of data entered into the forms. Data entry by physicians into the HCV patient's Clinical Examination Form, compliance of HCV patient's Clinical Examination Form data with medical record data, as well as timeliness of holding clinical examinations in compliance with the Project Guide during treatment and 12 weeks after the end of treatment were controlled.
4. ***Regular monitoring visits to HCFs*** engaged into the research were held.
5. ***Data quality control after completion of data collection.*** Work on data array formation included combination of questionnaire data and clinical information, verification of their logic and consistency, analysis of missing data and outliers.

5.12 DATA PROCESSING

Based on results of the operational research, the following databases with variable directories were prepared:

- the database of prospective HCV treatment adherence and retention barriers research, combined with clinical data on patient history, the HCV treatment process, and treatment outcomes (in SPSS and MS Excel formats);
- the database of the HCV re-infection and liver fibrosis regression research, combined with clinical data on the patient's history, HCV treatment process and outcomes, HCV recurrence tests, and the fibrosis status (in SPSS and MS Excel format).

Qualitative research data processing included preparation of interview transcripts based on audio records in the MS Word format.

5.13 DATA ANALYSIS

Quantitative data analysis included:

- one-dimensional analysis of the socio-demographic profile and clinical characteristics of participants in the various components of the operational research;
- one-dimensional and two-dimensional analysis of patients' attitudes to various aspects of treatment and analysis of side effects (in particular, by the key population and the facility type), based on ***HCV treatment adherence and retention barriers***;
- testing statistical hypotheses regarding changes in behavior, awareness, and the quality of life during treatment based on the ***HCV treatment adherence and retention barriers data***;
- estimation of the prevalence of re-infection risks after HCV treatment (one-dimensional analysis);
- estimation of the key results (see ***Table 14***) of the various components of the operational research and factor simulation with the help of binary and multiple regression analysis

TABLE 14. *Key resulting variables in the operational research*

Resulting variables	Operational research component	Definition	Indicators
Early termination of HCV treatment	Research on adherence to hepatitis C virus treatment and retention barriers	Completion of HCV treatment before the term determined by the treatment regimen (12, 16, or 24 weeks).	The proportion of patients who completed HCV treatment early for various reasons vs the total population of patients to whom treatment was prescribed
Sustained virologic response (SVR) 12 weeks after the end of treatment	Research on adherence to hepatitis C virus treatment and retention barriers	No HCV RNA in serum of the patient detected using sensitive detection methods	The proportion of patients in whom the HCV RNA level is not detected 12 weeks after the end of treatment vs the general population of patients who completed treatment and underwent the respective examination
Prevalence of re-infection	Research on the risk of HCV reinfection	HCV RNA in blood serum of the patient detected using sensitive detection methods one or more years after achieving SVR PCR results show a different type of HCV genotype than the one that was found at the start of treatment	The proportion of patients with a detectable HCV viral load (blood plasma HCV RNA) vs all patients examined The proportion of patients who have a different HCV genotype vs the one that was found at the start of treatment, out of all patients examined
Prevalence of liver fibrosis regression	Liver fibrosis regression research	Reduced liver fibrosis vs the severity determined before treatment, based on indirect cirrhosis markers – APRI or FIB-4 index.	The proportion of participants whose florid fibrosis (F3-F4 at the start of treatment) changed for indolent (F1-F2 within the research framework): - based on APRI - based on FIB-4

Cochrane Q test (categorical indicators) and Friedman Q test (quantitative indicators) were used for simple statistical testing of the difference in the indicators for the various stages of the prospective research on adherence to HCV treatment and retention barriers. In case of statistical difference testing by independent groups (sex, age group, risk group, etc.), Chi-square test was used for categorical indicators and Mann-Whitney U-test and ANOVA (for quantitative indicators). To interpret results of statistical tests, p-values were used – the probability of that the differences found in the sample research are random and absent from the general population; $p<0.05$ is considered a sign of statistically significant differences by factor.

Regression analysis of all the determined results was held using Generalized Multilevel Linear Models that took into account the embedded data structure: patients in the facilities. Regression analysis included construction of binary and multiple logistic regression factors for early termination of HCV treatment and presence of the stable virological response (SVR) 12 weeks after completion of treatment. When interpreting logistic regression results, the odds ratio (OR) and 95% confidence intervals (CI) were used. If $OR>1.00$, this was a positive ratio, the number of times the chances for the result in a particular group vs the reference category were higher (categorical factor), or how many times chances for the result increase if the factor value increases by one point on the scale (quantitative factor). If $OR<1.00$, this was a negative ratio, the odds of the result in a certain group are (1-OR)*100 percent less than in the reference category, or the odds of the result are reduced by (1-OR)*100 percent if the factor value increases by one point on the scale (quantitative factor). If the CI is 1.00, the factor is not related to the result.

Simulation of HCV reinfection and fibrosis regression factors was performed using of Cox regressions, which take into account the time before achievement of these results in addition to the remaining selected factors. When interpreting Cox regressions results, the risk ratio (RR) and their 95% confidence intervals (CI) were used. Similar to OR, if RR >1.00, this was a positive ratio, the number of times the risk for the result in a particular group vs the reference category were higher (categorical factor), or how many times the risk for the result increases if the factor value increases by one point on the scale (quantitative factor). RR<1.00, this was a negative ratio, the risk of the result in a certain group is (1-OR)*100 percent less than in the reference category, or the risk of the result is reduced by (1-OR)*100 percent if the factor value increases by one point on the scale (quantitative factor). If the CI is 1.00, the factor is not related to the result.

Determination of optimal regression models was carried out according to a number of statistical features, such as logarithmic likelihood, Akaike information criterion (AIC), Bayesian information criterion (BIC).

Quantitative analysis was performed in SPSS (one- and two-dimensional analysis) version 20 and R 3.4.4 (regression analysis).

In the framework of ***qualitative research data analysis***, thematic analysis of transcripts of focus group discussions with patients and in-depth interviews with Project staff was held with inductive coding of text segments related to the research issues – the barriers and favorable factors associated with engagement into the HCV treatment program and adherence formation, as well as other unplanned key topics that arose in the course of the research. The encoding and analysis were performed using the MAXQDA software.

Success story

OLEKSANDER (Kharkiv City)

"Several years ago I was diagnosed with hepatitis C. I was very concerned about this, because I did not know where to go and from whom to seek medical aid. Not that long ago, I found out that in our city there is the medical center, "Alternativa"... Before the start of treatment, I had all the tests done as ordered by the infectious disease doctor, treatment was prescribed to me, I started taking the drug within the strict time limits as indicated by my attending physician. Three months passed, and the result was a success. I was cured with the drug, Harvoni, which was provided by International Charitable Foundation "Alliance for Public Health". This innovative antiviral drug was really a good option for me, because it did not cause any adverse reactions, and most importantly, after a repeated test for HCV in my blood, the result was negative.

Thanks to Kharkiv "Alternativa" Medical Center and the Alliance, I now feel great!"

6. Key results of the Operational Research

Detailed research analysis and results are presented in ***Annex 1. Results of the Effectiveness of the Hepatitis C Virus (HCV) Treatment Program for Vulnerable Populations in the Resource-Constrained Ukraine operational research within Scaling Up Accessible and Effective Hepatitis C Virus (HCV) Treatment Through Community-Based Treatment Model for Most Vulnerable Populations in the Resource-Constrained Ukraine Project.***

6.1 THE SOCIO-DEMOGRAPHIC PROFILE OF THE PATIENTS

The vast majority of the patients who participated in the research were men (over 70%), their age was on average around 40 y.o. Approximately half of the research participants had secondary vocational or incomplete higher education. More than 50% were married or living with a regular sexual partner. The vast majority of participants in each of the researches (approximately 80%) had injection drug use experience in their lives.

6.2 KEY FINDINGS OF THE OPERATIONAL RESEARCH

Project participants have shown a high level of adherence to treatment of hepatitis C virus infection. Project results have supported high effectiveness of viral hepatitis C treatment using DAAs in key patient groups. There were only rare cases of HCV RNA detection 48 weeks after SVR12 achievement. In the vast majority of patients who had florid fibrosis at the start of treatment the liver status improved after HCV eradication.

Patients in all the key populations showed a high level of satisfaction with MDT work and with the quality of Project services due to friendly attitude, no stigma or discrimination, comfort, attention to the patient's individual needs and provision of quality care services.

Barriers for engagement and retention in DAA-based hepatitis C virus infection treatment mostly included social factors. ***The low level of welfare and significant costs of pre-treatment diagnostic tests are the key barriers at the stage of engagement for treatment***.

Myths about treatment mostly affected the participants in early stages of the Project, while afterwards, after dissemination of information about success of DAA-based treatment in the community of key populations, this factor weighted less.

Side effects of medicines and depression are the key barriers that affect patient retention. At the same time, research results indicate that use of DAAs (non-interferon treatment regimens), psychological and social support are a pre-requisite for successful patient retention in treatment.

High effectiveness of treatment / the low level of HCV RNA detection 12 weeks after treatment (achievement of SVR12 by the vast majority of participants) are both due to high efficiency of DAAs and high patient adherence to treatment.

Availability of social support is a critical component of HCV infection treatment among key populations. As results of the research prove, both patients and medical staff recognize social support as an extremely important tool for achieving success in treatment and high adherence (98% of patients completed a full course of treatment).

Active PWID are the most vulnerable group among those who took part in the Project. They were more in need of social and physical support to reach the health facility, but at the same time they were less satisfied with health professionals and showed a higher risk of treatment termination vs PWID in remission. Among active PWID, the highest incidence of HCV RNA detection 48 weeks after achieving SVR12 was registered, which is likely to be due to a higher incidence of risk behaviors in this key population and a higher risk of reinfection.

There is the need to expand the list of priority target groups for free for patient hepatitis C virus treatment, as well as to expand the inclusion criteria for the treatment program. Based on results of the qualitative research, there is a significant demand for viral hepatitis C treatment with DAAs among patients with low-grade fibrosis. Regarding expansion of target groups, it is important to engage regular partners of key population representatives infected with hepatitis C virus but not meeting certain criteria for inclusion into the treatment program.

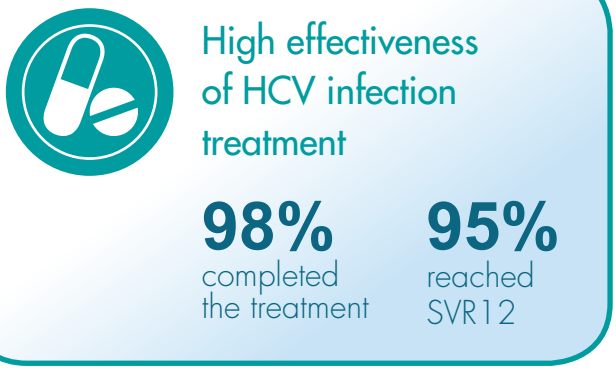
As to their general awareness about hepatitis C virus, patients mostly lacked information about HCV transmission risks. In patient counseling, there should be a greater focus on this information.

According to available research, ***SVR12 achievement significantly increases likelihood of improved liver status***. The Project participants are no exception, most patients had fibrosis regression – a change from florid fibrosis (F3-F4) to F1-F2 – after 48 or more weeks after achieving SVR12. However, the Project participants who had HIV infection, previous experience of HCV treatment without DAAs (pegIFN+RBV), and/or another HCV genotype but for the first and second ones had a higher risk of absence of fibrosis regression one year after achieving SVR12.

The relatively low incidence of detectable HCV RNA VL levels after achieving SVR12 and changes in patient behavior, in particular reduction of risky injections and sexual practices, both in the short and long term, prove effectiveness of reinfection prevention services. In general, the majority of the sporadic cases of HCV recurrence revealed during the research were observed among the participants who, after achieving SVR12, had high risks when injecting drugs, practiced sexual contacts in the state of alcohol or drug intoxication, or had surgical interventions due to complications of more intense injection drug use. The experience of participating in activities to prevent HCV reinfection in the framework of social support during treatment was one of statistically significant factors of reducing the risk of HCV reinfection, based on the research results.

7. Key Project outcomes

- Direct-acting antivirals were included into the hepatitis C virus treatment regimens in the Unified Clinical Protocol for Primary, Secondary (Specialized), and Tertiary (Highly Specialized) Medical Care "Hepatitis C Virus in Adults" in Ukraine;
- The cost of a course of treatment with direct-acting antivirals – sofosbuvir and sofosbuvir/ ledipasvir – had been significantly reduced, which was the ground for expanding access to modern effective DAA-based viral hepatitis C treatment in Ukraine and in the region.



- 1,907 patients from among representatives of key populations received access to hepatitis C virus treatment with direct-acting antivirals;
- Out of 1,907 patients on HCV therapy 1,400 were HCV/HIV co-infected, including those 1360 (97.1%) receiving ART. Out of 1,360 patients on antiretroviral therapy 98 (7.2%) patients were receiving both ART and OST;
- 80.3% of Project participants were PWIDs (1,531 out of 1,907 patients);
- 98% of Project patients completed the course of HCV infection treatment;
- 95% of patients who completed the treatment reached SVR12;
- 50% discount on the complex laboratory diagnostics was provided to all potential Project participants before enrollment; laboratory monitoring of treatment was made free of charge to all Project patients;
- Up to date model of hepatitis C virus treatment (DAAs-based) at the community level was developed and successfully implemented by the Alliance with engagement of non-governmental organizations;
- Each patient involved into the Project was offered the opportunity to receive social support;

- Operational research showed that
  - **a.** 3% of successfully treated patients (15 participants out of the 456 involved into the research) had detectable HCV RNA viral load 48 weeks after achieving SVR12;
  - **b.** 94% (based on the FIB4 index) of successfully treated patients (326 participants out of the 348 involved into the research) showed improved liver status 48 weeks after achieving SVR12; 87% – based on the APRI index (302 participants out of the 348 involved into the research);
  - **c.** the Project considerably raised general awareness about hepatitis C virus among patients from KG, as most of them lacked information about HCV transmission risks at the start of treatment;
  - **d.** three sessions on re-infection delivered to the Project patients by case managers provided low level of detectable HCV RNA viral load 48 weeks after achieving SVR12;
  - **e.** Project patients in all the key populations showed a high level of satisfaction with MDT work and with the quality of Project services;
  - **f.** implemented in the Project model for highly efficient treatment of hepatitis C virus with DAAs in combination with social support at the community level in the resource-constrained situation can be considered a best practice of service provision for key population representatives.

Annex 1.

RESULTS OF THE OPERATIONAL RESEARCH "EFFECTIVENESS OF THE HEPATITIS C VIRUS (HCV) TREATMENT PROGRAM FOR VULNERABLE POPULATIONS IN THE RESOURCE-CONSTRAINED UKRAINE"

PERFORMED WITHIN THE PROJECT "SCALING UP ACCESSIBLE AND EFFECTIVE HEPATITIS C VIRUS (HCV) TREATMENT THROUGH COMMUNITY-BASED TREATMENT MODEL FOR MOST VULNERABLE POPULATIONS IN THE RESOURCE-CONSTRAINED UKRAINE"

The Operational Research included the following components:

1. A quantitative research, designed to determine the degree of patient adherence to treatment and the factors that affect this process, to analyze cases of adverse event manifestations, as well as mitigation of risky behaviors and improving the HCV awareness level (hereinafter referred to as the ***research on adherence to HCV treatment and retention barriers***); and a qualitative research, designed to analyze individual and organizational barriers and obstacles that hinder patient engagement into treatment, as well as their retention in treatment (hereinafter – the ***qualitative research***).
2. The quantitative research of the risks and HCV reinfection factors after achievement of SVR12 (hereinafter – the ***research on the HCV reinfection risk***).
3. The quantitative study on the risks and factors of liver fibrosis regression after achievement of SVR12 (hereinafter – the ***research on liver fibrosis regression***).

THE PARTICIPANT PROFILE AT THE START OF THE RESEARCH

THE SOCIO-DEMOGRAPHIC PROFILE OF THE PATIENTS

In all the three components of the research, most patients were men (over 70%), their average age was about 40 y.o. (See ***Table 1***). The education level distribution is virtually the same in all the three components of the operational research: half of the participants had secondary vocational or incomplete higher education (***52% in the research on HCV treatment adherence and retention barriers, and 46% in the re-infection and fibrosis regression risk research***). Moreover, in all the three components most of the participants (more than 50%) were married or living with a regular sexual partner.

TABLE 1. The socio-demographic profile of the Project's patients participating in the research, q-ty and %		Research on adherence to HCV treatment and retention barriers (N=900)		Research on the risk of HCV reinfection (N=456)		Liver fibrosis regression research (N=350)	
		N	%	N	%	N	%
Average age (standard deviation)		40 (8)		43 (7)		43 (7)	
Sex	Male	643	71%	335	74%	265	76%
	Female	257	29%	121	27%	85	24%
Employment	Study	8	1%	1	0%	1	0%
	Work	495	55%	320	70%	241	69%
	Study and work	12	1%	5	1%	4	1%
	Do not study and do not work	385	43%	130	29%	104	30%
Education	Basic elementary education (not completed 9 years at school)	11	1%	0	0%	0	0%
	Basic incomplete secondary education (completed 9 years at school)	44	5%	14	3%	13	4%
	Completed secondary education (11 9 years at school)	148	16%	84	18%	67	19%
	Vocational school	230	26%	100	22%	68	19%
	College	160	18%	80	18%	69	20%
	Incomplete higher education	68	8%	28	6%	23	7%
	Completed higher education (Bachelor's or Master's Degree)	239	27%	149	33%	109	31%
	Other	0	0%	1	0%	1	0%
Marital status	Married and live with the spouse	461	51%	271	59%	215	61%
	Married, but live with another regular sexual partner	8	1%	2	0%	2	1%
	Married, but do not live with the spouse or with another sexual partner	21	2%	6	1%	4	1%
	Single, but live with a regular sexual partner	101	11%	49	11%	35	10%
	Single and do not live with a regular sexual partner	309	34%	123	27%	92	26%
	Other	0	0%	5	1%	2	1%
Individual monthly income level	Under UAH 1,000	136	15%	18	4%	13	4%
	UAH 1,001-2,000	195	22%	70	15%	57	16%
	UAH 2,001-3,000	160	18%	38	8%	29	8%
	UAH 3,001-5,000	203	23%	88	19%	62	18%
	More than UAH 5,000	113	13%	196	43%	156	45%
	Refused to answer	93	10%	46	10%	33	9%
Experience of injecting drugs in life	Yes	720	80%	350	77%	268	77%
	No	178	20%	105	23%	81	23%
	Difficult to answer	2	0%	1	0%	1	0%
Imprisonment experience in life*	Yes	13	1%				
	No	887	99%				

** This question was only included in the research on adherence to HCV treatment and retention barriers.*

The proportion of people who do not study and not work (43%) was higher in the research on adherence to HCV infection treatment and retention barriers; in the research on the risk of re-infection and fibrosis regression, that was less than a third (29% and 30%, respectively). Due to differences in the employment status, participants in the first (***HCV infection treatment adherence and retention barriers***) and the repeated research (***re-infection risks and fibrosis regression***) differ significantly in terms of their welfare; in the studies of the risks of re-infection and fibrosis regression, the proportion of patients with a sufficiently high income (with the individual monthly income of over UAH 5,000) is three times higher.

The majority of participants in all research components (approximately 80%) had injection drug use experience in their lives.

THE CLINICAL PROFILE OF THE PATIENTS

In the first component (***HCV infection treatment adherence and retention in treatment barriers***) and in the following components (***the risk of HCV re-infection and liver fibrosis regression***), patients differed in the key population that was determined as of the moment of their enrollment into the Project (see ***Table 2***). Activists and ATO veterans (currently – the Joint Forces Operation) were not included into the research on the risks of HCV reinfection and liver fibrosis regression. These patients were only enrolled into the Project at the third enrollment stage, and therefore they did not meet all the inclusion criteria – at least 48 weeks from the time when the patients reached SVR12 had not yet passed. In the repeated research, the proportion of active PWID was twice smaller, whereas there was a bigger proportion of PWID in the state of prolonged remission (more than 12 months). As for the other key populations, such as PWID partners, SWs, and MSM, their distribution in all the three components of the research is virtually the same: 7% and 9% of PWID partners in the ***research on adherence to HCV infection treatment and the retention barriers*** and in that on the ***risks of reinfection and of fibrosis regression***, respectively; 4% of SWs in all the research; 3% and 4% of MSM in the research on adherence to HCV infection treatment and retention barriers and on the risks of reinfection and of fibrosis regression, respectively.

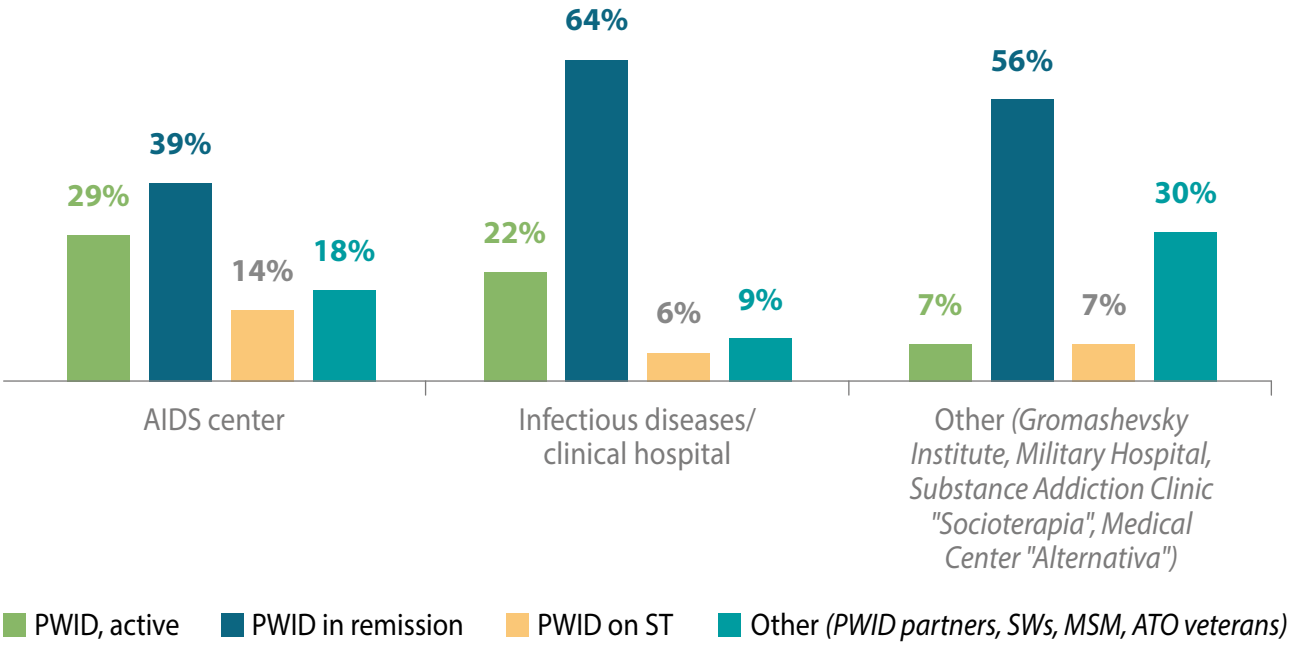


FIGURE 1. *Key population distribution by the facility type in the research on adherence to HCV treatment and retention barriers (N=900), %*

Active PWID patients mostly received treatment at AIDS centers (29% of research participants) and infectious disease clinics (22%) (see ***Figure 1***). PWID in remission are the key group of patients, therefore, in all the specialized facilities, including infectious disease clinics, their proportion was the highest vs. other facilities (64% vs. 56% at specialized facilities, and 39% at AIDS centers). PWID partners, SWs, MSM, and JFO veterans more often became Project participants at specialized facilities, such as the Institute of Epidemiology and Infectious Diseases named after L.V. Gromashevsky, the National Military Medical Clinical Center "Main Military Clinical Hospital", the Substance-Addiction Treatment Hospital "Socioterapia," and "Alternativa" Medical Center (30% of participants at this facility type).

TABLE 2. Research participants' medical history before the start of treatment, q-ty and %		Research on HCV infection treatment adherence (N=900)		Research on the risk of HCV reinfection (N=456)		Liver fibrosis regression research (N=350)	
		N	%	N	%	N	%
The key population based on the physician's definition	Activists	2	0.2%	0	0	0	0
	PWID, active	181	20%	37	8%	30	9%
	PWID in remission for more than 12 months	306	34%	242	53%	191	55%
	PWID in remission for 6 to 12 months	84	9%	39	9%	24	7%
	PWID in remission for up to 6 months	73	8%	30	7%	27	8%
	PWID on ST	93	10%	30	7%	18	5%
	PWIDs' partners	60	7%	39	9%	30	9%
	SWs	32	4%	19	4%	15	4%
	ATO (JFO) veterans	39	4%	0	0%	0	0%
	MSM	30	3%	20	4%	15	4%
HIV-positive status	Yes	593	66%	356	78%	275	79%
	No	307	34%	100	22%	75	21%
Median CD4 levels, cells/ml, according to the latest test (IQR) (for HIV-positive patients)		489 (338)		499 (311)		501 (305)	
Receive ART (for HIV-positive patients)	Yes	579	98%	350	77%	271	99%
	No	14	2%	106	23%	4	1%
ART regimen (for patients receiving ART)	TDF/FTC+EFV	208	36%	114	33%	83	31%
	TDF/FTC+LPV/r	137	24%	116	33%	96	35%
	AZT+3TC+LPV/r	45	8%	7	2%	7	3%
	TDF+3TC+LPV/r	43	7%	51	15%	37	14%
	ABC+3TC+LPV/r	36	6%	18	5%	7	3%
	AZT+3TC+EFV	22	4%	1	0%	1	0%
	Other	88	15%	43	12%	40	15%
Presence of HBV	Yes	79	9%	34	7%	20	6%
	No	821	91%	422	93%	330	94%

TABLE 2. Research participants' medical history before the start of treatment, q-ty and %		Research on HCV infection treatment adherence (N=900)		Research on the risk of HCV reinfection (N=456)		Liver fibrosis regression research (N=350)	
		N	%	N	%	N	%
History of TB	Yes	185	21%	100	22%	79	23%
	No	715	79%	356	78%	271	77%
Receive ST	Methadone	67	7%	16	4%	11	3%
	Buprenorphine	26	3%	14	3%	7	2%
	Do not receive	807	90%	426	93%	332	95%
Median HCV RNA level, IU/ml (IQR)		839000 (2760000)		855500 (3120000)		835000 (3308829)	
HCV genotype	Genotype 1	551	61%	200	44%	153	44%
	Mixed genotype 1b/4	1	0.1%	0	0%	0	0%
	Genotype 2	29	3.2%	26	6%	21	6%
	Genotype 3	315	35%	223	49%	170	49%
	Genotype 4	2	0.2%	3	1%	3	0.5%
	Not detected	2	0.2%	4	1%	3	0.5%
Liver fibrosis grade	F1	14	2%	6	1%	0	0%
	F2	469	52%	87	19%	0	0%
	F3	245	27%	192	42%	185	53%
	F4	172	19%	171	38%	165	47%
History of HCV infection treatment with PEG+RIB	Yes	88	10%	56	12%	43	12%
	No	812	90%	400	88%	307	88%

Taking into account the fact that at the beginning of the Project implementation the priority group was HIV/HCV co-infection patients, and patient enrollment into the Project was mainly held based on AIDS centers, most participants in the three parts of the research have the positive HIV status (66% in the research on adherence to HCV infection treatment and retention barriers, and 78% and 79% in HCV reinfection and liver fibrosis regression research, respectively). The percentage of HIV-positive ART-treated patients in the ***study on HCV treatment adherence and retention barriers and the one on liver fibrosis regression*** was 98% and 99%, respectively, in the research on HCV reinfection risks – 77%.

In all the three components of the research, the proportion of patients with the history of HBV infection is almost the same. The proportion of patients with HBV infection in the ***research on adherence to HCV infection treatment and retention in treatment barriers*** is 9%; in the ***research on the risk of HCV reinfection*** – 7%, in the ***research on liver fibrosis regression*** – 6%. The same applies to the TB history as reported by 21% of the patients who participated in the ***research on adherence to HCV infection treatment and retention barriers*** and 23% of liver fibrosis regression research participants. There is a slightly different figure in the ***research on the risk of HCV reinfection*** (7% of patients with the history of TB). PWID on ST in the ***research on adherence to HCV infection treatment and retention barriers*** were mostly administered methadone (67 out of 93 persons). In the research ***on the risk of reinfection*** and ***fibrosis regression***, approximately the same proportions

of patients on ST received methadone and buprenorphine: 16 out of 30 patients in the research on risks of HCV reinfection on ST received methadone; in liver fibrosis regression – 11 of 28 patients on ST received methadone.

Results of the analysis show differences in the clinical profile of patients depending on the HCV genotype and the grade of fibrosis before the start of treatment. In the ***research on HCV infection treatment adherence and retention in treatment barriers***, the proportion of patients with genotype one (61% vs. 44% in the research on HCV reinfection and fibrosis regression risks) and 1 or 2 grade fibrosis was higher (54% in the research on HCV infection treatment adherence and retention in treatment barriers; 20% in the research on the risk of HCV reinfection, and 0% in the liver fibrosis regression research). These differences are due to design specifics of the research on HCV reinfection and liver fibrosis regression.

The differences in HCV treatment regimens in the three parts of the research are due to differences in HCV genotypes and the grade of fibrosis in Project patients. Given the large sample ***of the HCV treatment adherence and retention barriers research*** (900 participants vs. 456 participants in the ***risk on HCV reinfection risks*** and 350 participants in the ***liver fibrosis regression research***), a wider range of HCV treatment regimens are presented (see ***Figure 2***). The DAA combination of sofosbuvir and ledipasvir in one tablet (LDV/SOF) only became available for treatment in the third phase of the Project. The patients receiving this drug were not included into the research on the risks of HCV reinfection and liver fibrosis regression due to their non-compliance with the inclusion criterion – at least 48 weeks after achievement of SVR12. In all the three components of the research, patients were predominantly administered a 12-week course of treatment for hepatitis C virus.

In the research on the ***risks of HCV reinfection and liver fibrosis regression***, additional patient history data were collected at the time of conducting this research to study the possible impact factors. Judging by the results obtained, more than a third of patients had pre-obesity, and one in ten had obesity. Among the total number of participants in the ***research on the risk of HCV reinfection and fibrosis regression***, 3% had diabetes, 5% suffered cardiovascular diseases. In the ***research on the risk of HCV reinfection***, 4% of participants had a chronic kidney disease, in the ***fibrosis regression research***, these were 5%. One participant (0.2%) in the ***research on the risk of HCV reinfection*** had blood transfusion after completion of treatment, while in the ***research on liver fibrosis regression*** no such cases were recorded. Prevalence of surgical interventions was higher (7%) in the both parts of the research.

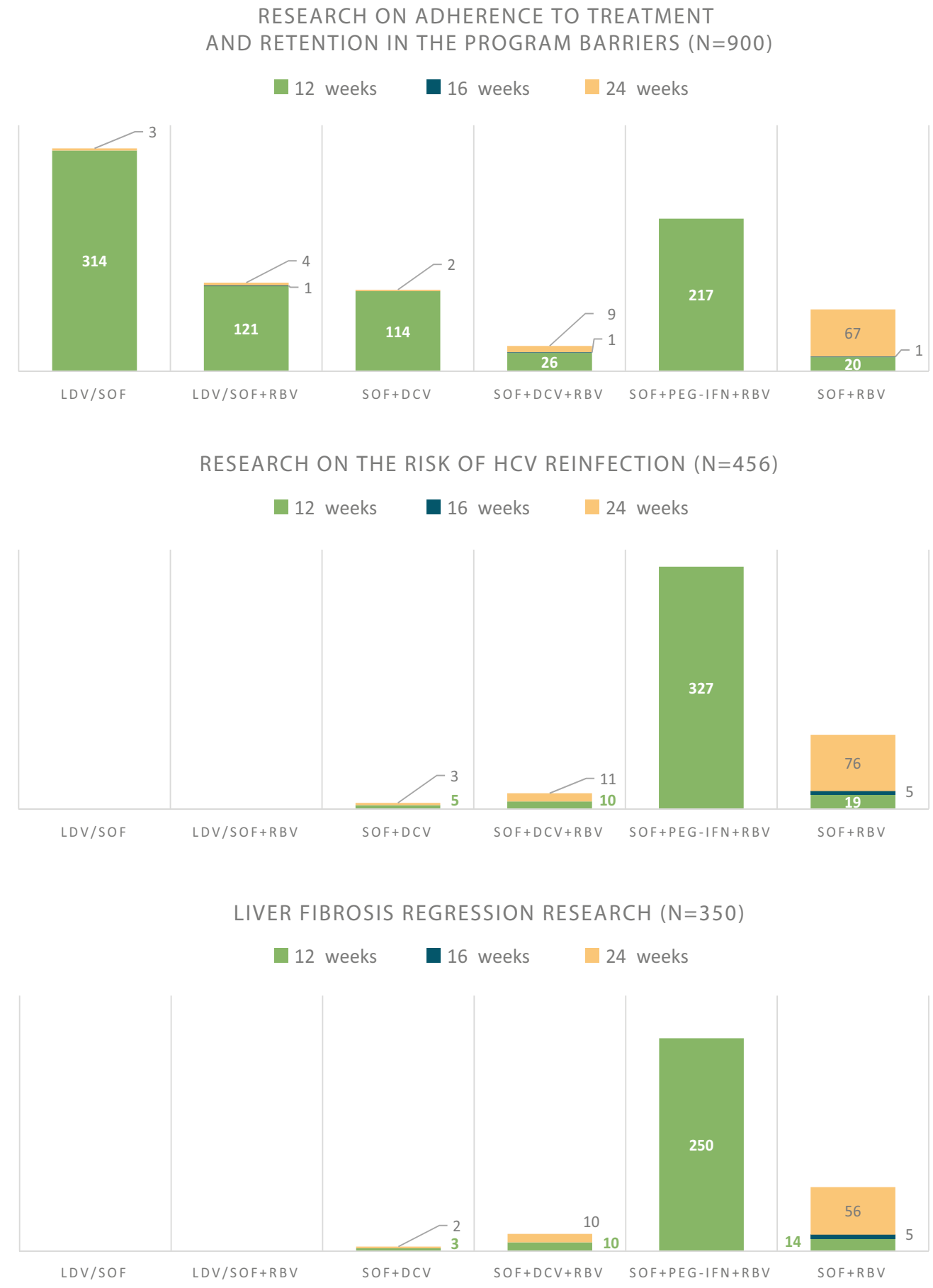


FIGURE 2. *Operational research participant distribution by HCV infection treatment regimens, persons*

TABLE 3. Additional clinical characteristics of participants at the time of the research on the risks of reinfection and fibrosis regression, frequency and %		Research on the risk of HCV reinfection (N=456)		Liver fibrosis regression research (N=350)	
		%	N	%	
Body mass index	Insufficient weight (≤18.4)	9	2%	6	2%
	Normal weight (18.5-24.9)	239	52%	178	51%
	Pre-obesity (25.0-29.9)	159	35%	128	37%
	Obesity grade 1 (30.0-34.9)	38	8%	30	9%
	Obesity grade 2 (35.0-39.9)	4	1%	3	1%
	Obesity grade 3 (≥40.0)	2	0.4%	2	0.6%
	No data available	5	1%	3	1%
HBV	Yes	24	5%	15	4%
	No	432	95%	335	96%
Diabetes mellitus	Yes	12	3%	11	3%
	No	444	97%	339	97%
History of TB	Yes	98	21%	79	23%
	No	358	79%	271	77%
Active TB (for those with TB history)	Yes	6	6%	4	5%
	No	92	94%	75	95%
Receive TB treatment (for those with TB history)	Yes	9	9%	6	8%
	No	89	91%	73	92%
HIV infection	Yes	355	78%	274	78%
	No	101	22%	76	22%
Receive ART (for HIV-positive patients)	Yes	353	99%	272	99%
	No	2	1%	2	1%
Cardiovascular diseases	Yes	24	5%	18	5%
	No	432	95%	332	95%
Chronic kidney disease	Yes	19	4%	16	5%
	No	437	96%	334	95%
Blood transfusion	Yes	1	0.2%	0	0%
	No	455	99.8%	350	100%
Surgical interventions	Yes	34	7%	25	7%
	No	422	93%	325	93%

BARRIERS AND OBSTACLES LIMITING PATIENTS' ENGAGEMENT FOR TREATMENT

BARRIERS FOR ENGAGEMENT AND RETENTION IN DAA-BASED HEPATITIS C VIRUS TREATMENT MOSTLY INCLUDED SOCIAL FACTORS. THE LOW LEVEL OF WELFARE AND SIGNIFICANT COSTS OF PRE-TREATMENT DIAGNOSTIC TESTS ARE THE KEY BARRIERS AT THE STAGE OF ENGAGEMENT FOR TREATMENT.

Taking into account the clinical and social criteria for participation in the Project and the limited number of treatment courses, physicians and social workers had difficulties counseling the patients who were motivated for treatment but did not meet inclusion criteria. In some regions, patients were referred to national treatment programs, but these did not fully meet the current need for treatment of hepatitis C virus.

"Some get very upset, even to tears, they call us – how come I was not admitted? And there were those who become rude and behave in a very ugly way. [...] They complain, to the point of "you promised it to me." I have heard a lot of negative stuff over the past two weeks about that "we have been waiting for a whole year," "we were asked to wait last June, why are we not in treatment"?

(Social worker, Poltava)

"I was indignant about one issue. Suppose that lying under the fence is already past for me, I have abandoned drugs, 15 years have passed, I have a wife and two children, but we do not get into this program. And we do not get into it because we have been in remission for 15 years, because we are not drug addicts and not prostitutes. This is the disadvantage. One takes part in all of these movements – and you are admitted. But the more you get rid of your problems, the less they care about you.".

(Patient, Odessa)

In addition to the limitations associated with patients' not meeting inclusion criteria and the insufficient number of treatment courses, the following two key barriers to patient involvement can be identified: financial constraints and the prevailing myths regarding (no) success of treatment. Financial barriers predominantly arise in the context were one needs to pay for medical tests before starting treatment. During treatment, in case of adverse reactions, patients had to undergo additional tests, which were not funded by the Project. Different regions of the country had varying accessibility levels of free tests and, accordingly, varying costs before and during treatment; median costs for patients vary from UAH 200 to 8,000 (see ***Table 4***).

TABLE 4. Costs of tests within HCV infection treatment, based on results of the adherence to HCV treatment and retention barriers research		Break down of answers to the question: **"Did you pay for tests before or during the HCV treatment?"** (for the participants who took part in the second interview and answered the question, N = 832)*				**Costs of tests**, UAH (for the participants who paid)*			
		Paid		Did not pay					
		N	%	N	%	Median	IQR	Minimum	Maximum
Key population	PWID, active	46	28%	118	72%	1560	3000	80	10000
	PWID in remission	202	47%	229	53%	2500	3150	50	20000
	PWID on ST	22	27%	61	74%	1900	2160	200	11000
	Other (PWID partners, SWs, MSM, ATO veterans)	68	44%	86	56%	2000	3000	200	10000
Facility type	AIDS center	78	18%	361	82%	625	1797	50	8000
	Infectious diseases/clinical hospital	97	52%	90	48%	1500	2400	80	20000
	Other (Gromashevsky Institute, Military Hospital, Substance Addiction Clinic "Socioterapia", Medical Center "Alternativa")	163	79%	43	21%	3000	3000	200	20000
Oblast	Vinnytsia	1	1%	89	99%	-	-	3000	3000
	Dnipropetrovsk	19	31%	43	69%	2000	2520	135	4600
	Zhytomyr	0	0%	7	100%	-	-	-	-
	Zaporizhzhia	2	8%	24	92%	8000	0	8000	8000
	Ivano-Frankivsk	34	69%	15	31%	700	1020	50	3000
	Kyiv	219	85%	39	15%	3000	3400	80	20000
	Kirovohrad	1	4%	27	96%	-	-	700	700
	Lviv	5	17%	25	83%	200	300	120	4000
	Odessa	1	3%	30	97%	-	-	2500	2500
	Poltava	30	45%	37	55%	425	1800	80	20000
	Rivne	4	13%	27	87%	600	2350	300	5000
	Sumy	21	40%	32	60%	2000	1700	100	10000
	Kharkiv	0	0%	53	100%	-	-	-	-
	Kherson	0	0%	5	100%	-	-	-	-
	Khmelnytsky	1	4%	27	96%	-	-	500	500
	Donetsk	0	0%	14	100%	-	-	-	-
Total		338	41%	494	59%	2000	**3160**	**50**	20000

* *834 out of 900 participants were interviewed after HCV treatment, 2 of them did not answer these questions.*

Statistically significant differences by the key population, type of facility, and oblast ($p<0.001$).

Although the treatment was free, individual participants spent up to UAH 20,000 for tests before and/or during treatment. Patients who were not involved into the Project at the first stage of the enrollment process, despite meeting the inclusion criteria, and were granted access to treatment at subsequent stages expressed their dissatisfaction with the requirement to undergo all the tests again (in particular, the expensive Fibroscan). At the same time, in 5 Oblasts (Zhytomyr, Kharkiv, Kherson, Cherkasy, and Donetsk Oblasts), none of the patients indicated that they had incurred additional costs for tests before or during the treatment.

A qualitative analysis of in-depth interviews with MDT members did not record cases where the financial challenge caused the patients to refuse HCV infection treatment. Social workers helped raise funds for patient tests before the start of treatment via financial assistance programs. Physicians tried to order most of the tests from the facilities where they were provided free of charge. Patients at AIDS centers paid much less for tests before and during treatment than infectious disease hospital patients (18% vs. 52% at infectious disease hospitals) due to the different infrastructure and different degrees of laboratory testing availability at different HCFs.

Myths about treatment of hepatitis C virus are usually associated with the fear of severe adverse reactions and perception of the Program as a kind of a "clinical trial." Such myths were mostly disseminated by patients of previous hepatitis C treatment programs, non-DAA-based ones. Lots of inaccurate and/or false information was received by patients via the Internet. Myths about treatment mostly affected the participants in early stages of the Project, while afterwards, after dissemination of information about success of DAA-based treatment in the community of key populations, this factor weighted less. Participants also mentioned other obstacles: doubts about and fears of losing their permanent job, the risk of losing full-fledged communication with friends, etc. Some patients had low motivation for treatment because they did not feel being sick.

"The rumors were that it was an experiment [...], that the tablet was not the real one, on the Internet it was yellow. I had to persuade one client not to break or chew the tablets, not to look what's inside. And then he says: "But I looked up on the Internet." [...] Then [...] his test results were good, he calmed down.

(Social worker, Kharkiv)

"I had doubts, I did not feel that I had it. [...] Because I did not feel pain. […].

(Patient, Odessa)

At the start of treatment, patients encountered certain organizational issues. In some of the regions where the Project was implemented on the basis of AIDS centers, patients with the HCV mono-infection (negative HIV status) could not access treatment at the AIDS center due to restrictions set out in the HCF's constituent documents.

"Treatment based on the AIDS Center is very good. There are good doctors, good nursing staff, quality services. But the fact that clients without the co-infection could not freely join the project – that was a challenge. Possibly, it is necessary to set up two or three points of treatment, then all those who wish will be able to come."

(Social worker, Odessa)

All other restrictions were mostly not critical for patients to refuse treatment. The strong desire to be treated motivated them to look for ways out, the participants claimed that they did not need extra arguments to participate in the Project. The fact of free of charge treatment with direct-action antivirals with high effectiveness and low incidence of adverse reactions vs. use of interferon treatment regimens, as well as the vast positive feedback – all these served as strong motivation for patients to participate in the Project.

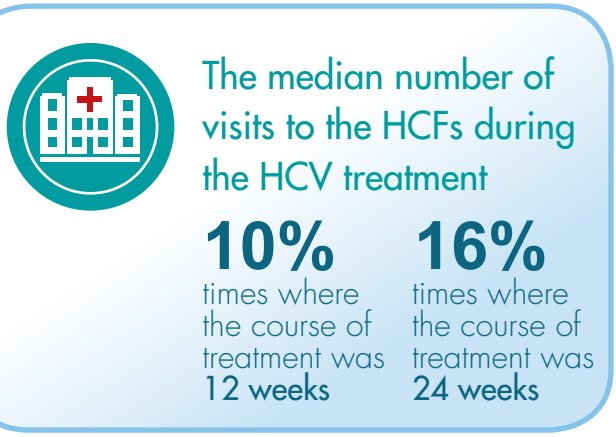
"We need to keep in mind how much of money we spent on drugs[...]. So it is better to pay the money for health, than to pay for ruining one's their health."

(Patient, Vinnytsia)

THE TREATMENT PROCESS BASED ON FEEDBACK FROM PATIENTS AND SERVICE PROVIDERS

THE NUMBER OF VISITS TO THE HCFs

The procedure of dispensing drugs to patients was in line with the treatment protocol: during the first month of treatment, all patients, as a rule, received the drugs once a week, less frequently – once every 2 weeks. Given the high level of adherence to treatment further on, the medications were dispensed once every 2 weeks, very rarely – once a month.



On average, one patient who has a 12-week course of treatment visited the HCF 10 times, and 16 times with a 24-week course. The number of visits varied by region (see ***Figure 3***). In Zhytomyr Oblast, 75% of patients with a 12-week course of treatment mentioned that they had visited the health care facility more than 25 times (twice a week or more frequently). Drug dispensing for 2 or more weeks was more commonly practiced in Poltava, Vinnytsia, Rivne, Kirovohrad, and Kyiv Oblasts.

If patients were not able to receive the medicines (for example, in the case of hospitalization), they were delivered by social workers. There were also sporadic cases where the drugs were given to patients' relatives.

"The fact is that during the treatment I broke my leg and could not come. I called Volodymyr [social worker] and told him that my mother would come. He approved that, they gave the medicine to my mom."

(Patient, Odessa)

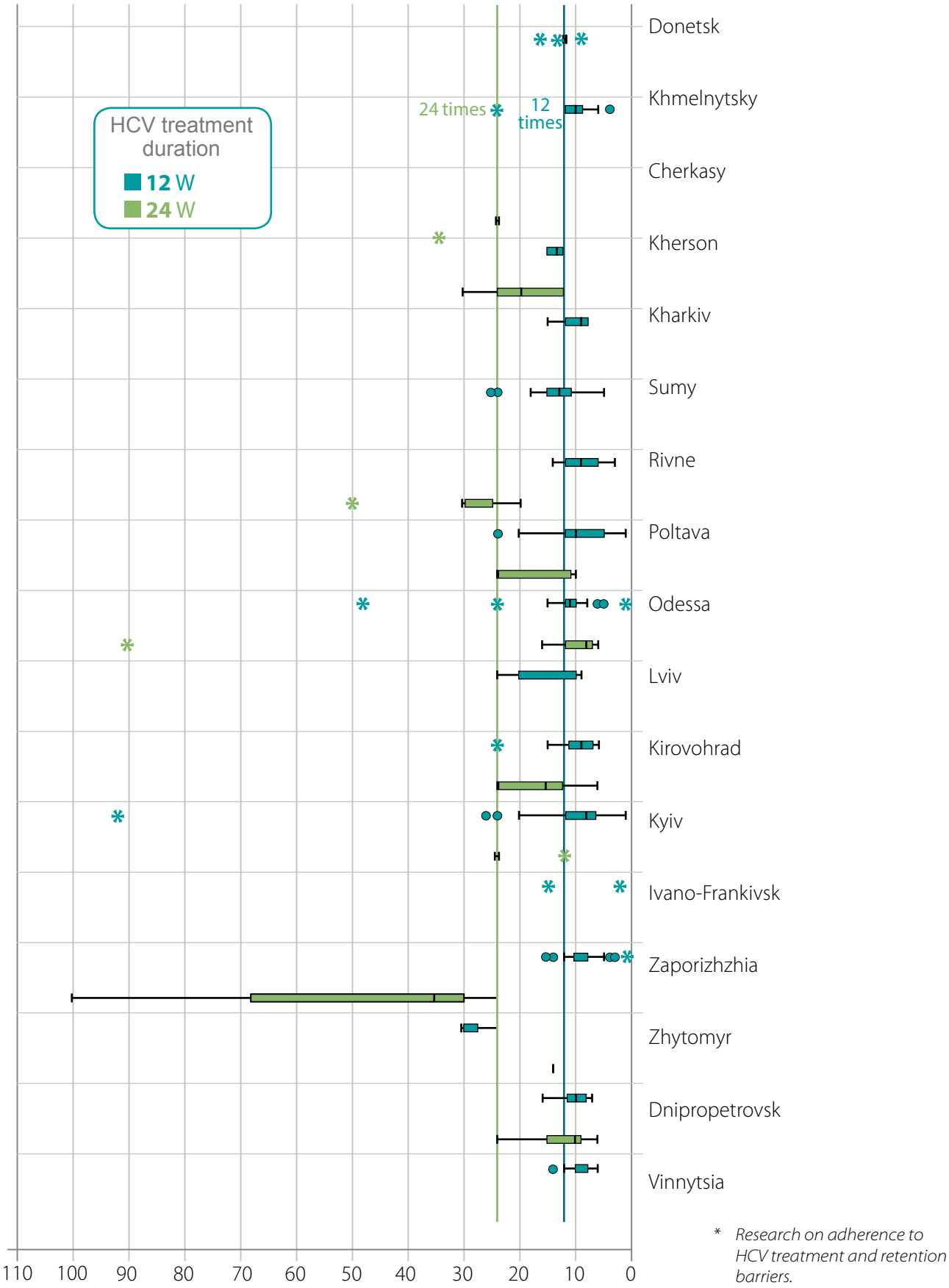
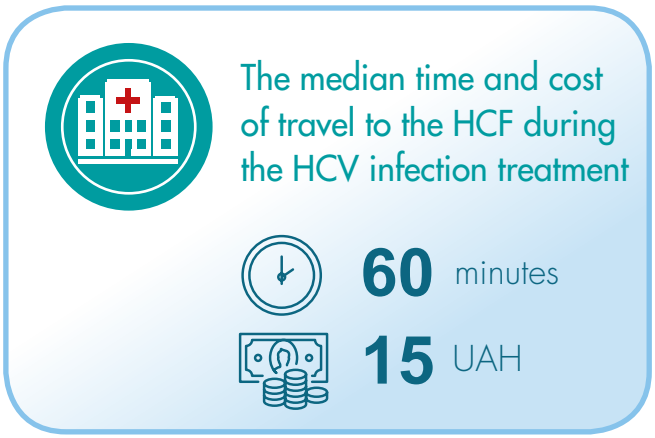


***FIGURE 3.** Break down of the number of visits to the facility where the HCV infection treatment was held, by region, times* *(based on the participants' information, during the entire period of treatment; among those interviewed after treatment completion, N=834)*

ACCESSIBILITY AND CONVENIENCE OF SERVICES

In almost all the regions where the HCV treatment adherence and treatment barriers research was held, a significant proportion of patients were people who did not live in the Oblast center where the health care facility was located (from 9% in Sumy Oblast to 46% in Kirovohrad Oblast, in the total sample – 25%). This resulted in a wide range of amounts of time and money spent by patients to visit the HCFs by regions (see ***Figure 4***).



On average, the patient spent an hour on a one-way travel to the HCF where hepatitis C was treated. The median cost of such a trip by public transport was UAH 15. Kyiv and Kyiv Oblast is one of the regions where not only local patients, but also residents of other Oblasts were treated. A quarter of patients (25%) who were treated for HCV infection in Kyiv spent more than three hours and approximately UAH 140 on a one-way trip to the doctor.

Taking into account the considerable time spent by patients traveling, the experts engaged into the Project tried to minimize the time spent by patients in the HCFs. An effective practice was delimitation of time for drug dispensing within the Project and within other programs (e.g., ART). In the regions where this practice was not introduced, patients and MDT members often registered the problem of long waiting time for the medication.

"Sometimes patients have to wait long for their medication. People would come here from Kosiv, they had to wait for two hours, they complained. It also has a negative impact, because the person feels bad."

(Infectious disease doctor, Ivano-Frankivsk)

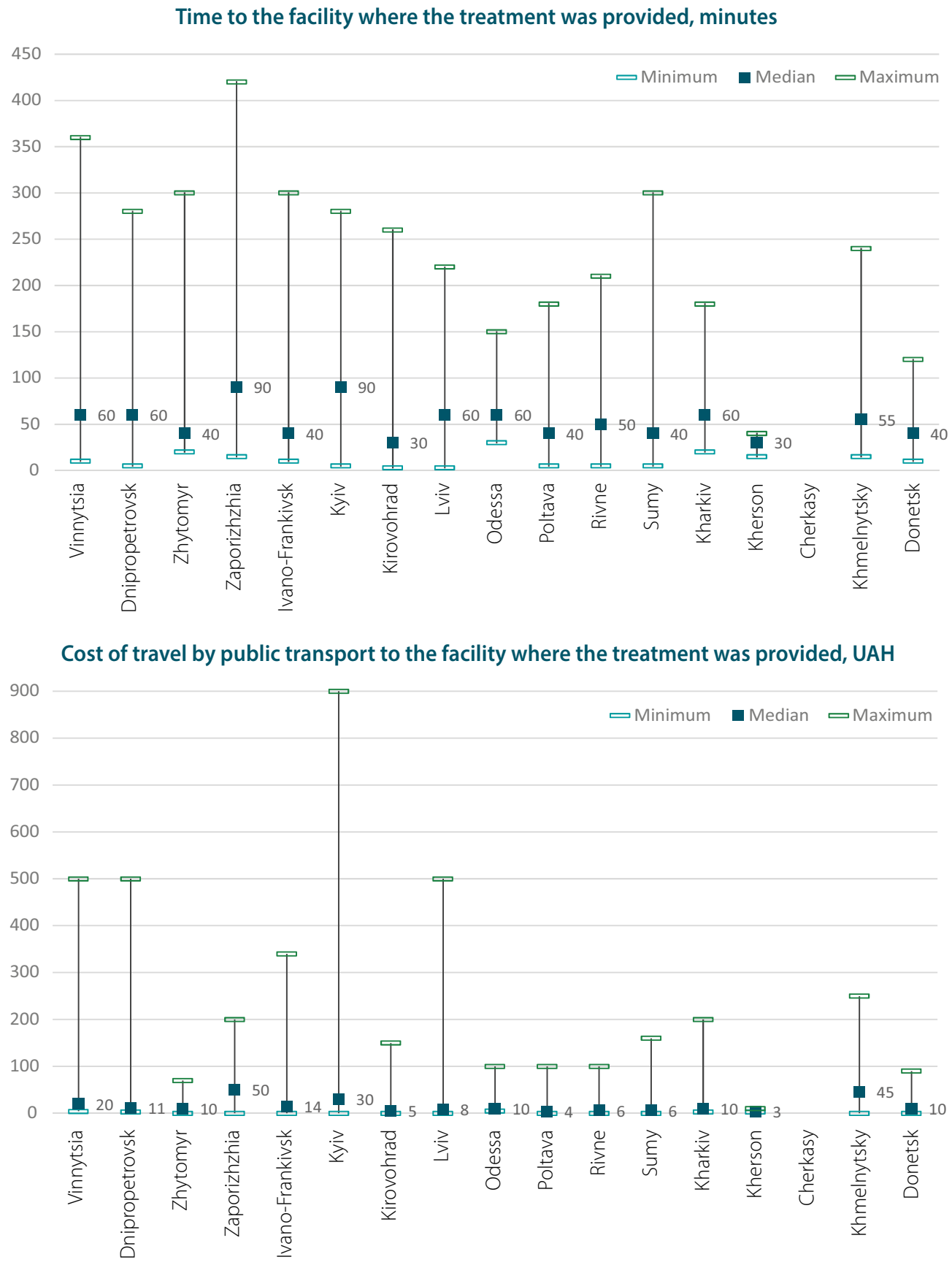
"We used to come at a certain time, from 8 till 10 am, we were immediately seen, without waiting in a queue. We just passed on into the doctor's office. And the rest of the people in the queue had to sit and wait while they were dealing with hepatitis. [...] It's good that the social workers took us in when there were some troubles, supported each other. One on the ground floor, another – on the first floor. So that we did not mix with the crowd of those who came for ARV therapy."

(Patient, Odessa)

Appointing dedicated days for the Project's patients contributed not only to minimization of waiting lines, but also promoted communication among patients at different stages of treatment. Exchange of experience and feedback on the positive effects of treatment motivated participants for greater adherence to taking the medications, despite side effects or other barriers.

"It really helped a lot when people who had undergone this kind of treatment could talk about that it really worked. When someone saw a case of successful treatment, he was no longer so apprehensive about that the treatment would not work."

(Social worker, Odessa)



** Research on adherence to HCV treatment and retention barriers.*

***FIGURE 4.** Time and cost of a one-way trip by public transport to the facility where hepatitis C was treated, by Oblast* *(based on the participants' information; among those interviewed after treatment completion, N=834)*

The procedure of dispensing the medications included administration of one tablet right there, at the HCF. Periodic laboratory control of the treatment process was also performed in line with the Project guidelines. Patients say that they sometimes faced some discomfort when visiting the HCFs, in particular no water for taking a tablet or no containers for urine tests.

"I remember that it was very uncomfortable. There was no way to obtain a container for urine, no pharmacy next door, nothing. I had to travel four stops from there to just buy a container. I.e. while blood could still be taken in the hospital, for urine... There are no containers, and that's it, you've got a problem."

(Patient, Odessa)

"They made us take the tablets right in the office. But the water rarely available. Well, even a glass of water for the client was not provided. And what if one forgets to bring water? One just puts it on the tongue and swallows with saliva."

(Patient, Odessa)

The original packaging of the medicines did not match the dispensing procedure (7 tablets per week or 14 tablets for two weeks). In the regions, they developed different approaches to packaging of drugs to be dispensed. Some specially bought plastic bags with a zipper for packaging the drugs, while others already had such packages available. Sometimes patients were asked to bring their own containers (tablet boxes, zipped bags, etc.).

"Each time we were instructed to take a container for the pills, and I forgot every time. As a re-sult, they bought such bags that can be zipped and sealed on top. And they gave us the pills, it was very nice, they did not say that this was your problem, pour that into your pocket and go away."

(Patient, Odessa)

The Project's patients received a special calendar with the dates of the required laboratory tests throughout the course of treatment. In some regions, the staff supplemented this calendar with other information: contact details of MDT members, recommendations for taking medication and diet, etc. According to patients' feedback, they virtually never used this calendar. Patients pointed out that they often had memory problems, perhaps it was a side effect of treatment, and it was difficult for them to independently follow the schedule of laboratory treatment monitoring. In this context, telephone reminders by social workers worked better.

"I had a problem, I kept forgetting when I was supposed to undergo the tests. They always called and reminded me that I needed to have those tests. I said – ok, clear, I'm going. The calendar did not help. Nastia [social worker] is the best calendar.

(Patient, Poltava)

SOCIAL SUPPORT AND PREVENTION OF REINFECTION

Social support included several components: identification of clients' problems and the plan to address them, formation of adherence to treatment, counseling and physical support, prevention of HCV reinfection. In the process of communicating with social workers, patients discussed current affairs and difficulties, side effects of drugs, received reminders of visits, required tests, moral and psychological support in the event of complications. Social support could include delivery of the medications or assistance in organizing laboratory tests where patients could not do that on their own.

«"I can say that the role of the social worker in this program was very important for me. [...] We clearly realized the general goals, what we needed to control the patients. If I had a question, she [the social worker] always helped me solve it – summon patients, control their having their tests, etc."

(Infectious disease doctor, Poltava)

"Vova [the social worker] calls and reminds me: "Do you remember that you need to hand over your tests on the 21st? Come, be sure to take the paper." It was very helpful.

(Patient, Odessa)

All in all, 87% of patients received social support during the HCV infection treatment (see ***Table 5***). Social support was more frequently received by older patients (over 35 years – 89% in this group), active PWID (93%), and patients treated outside of AIDS centers (95% at infectious disease hospitals, 96% at other HCFs).

Social support in the treatment of HCV infection

96% of attended patients received services for prevention of HCV reinfection

87% took advantage of the social support service

In some cases, patients communicated with social workers, involved in other programs, not with those who were part of the MDTs; these were the patients who received case management services from HIV servicing NGOs before participating in the Project. Some of the patients in the key populations themselves had the experience of being social workers or were currently working at HIV servicing NGOs, and the importance of social support for them was less relevant.

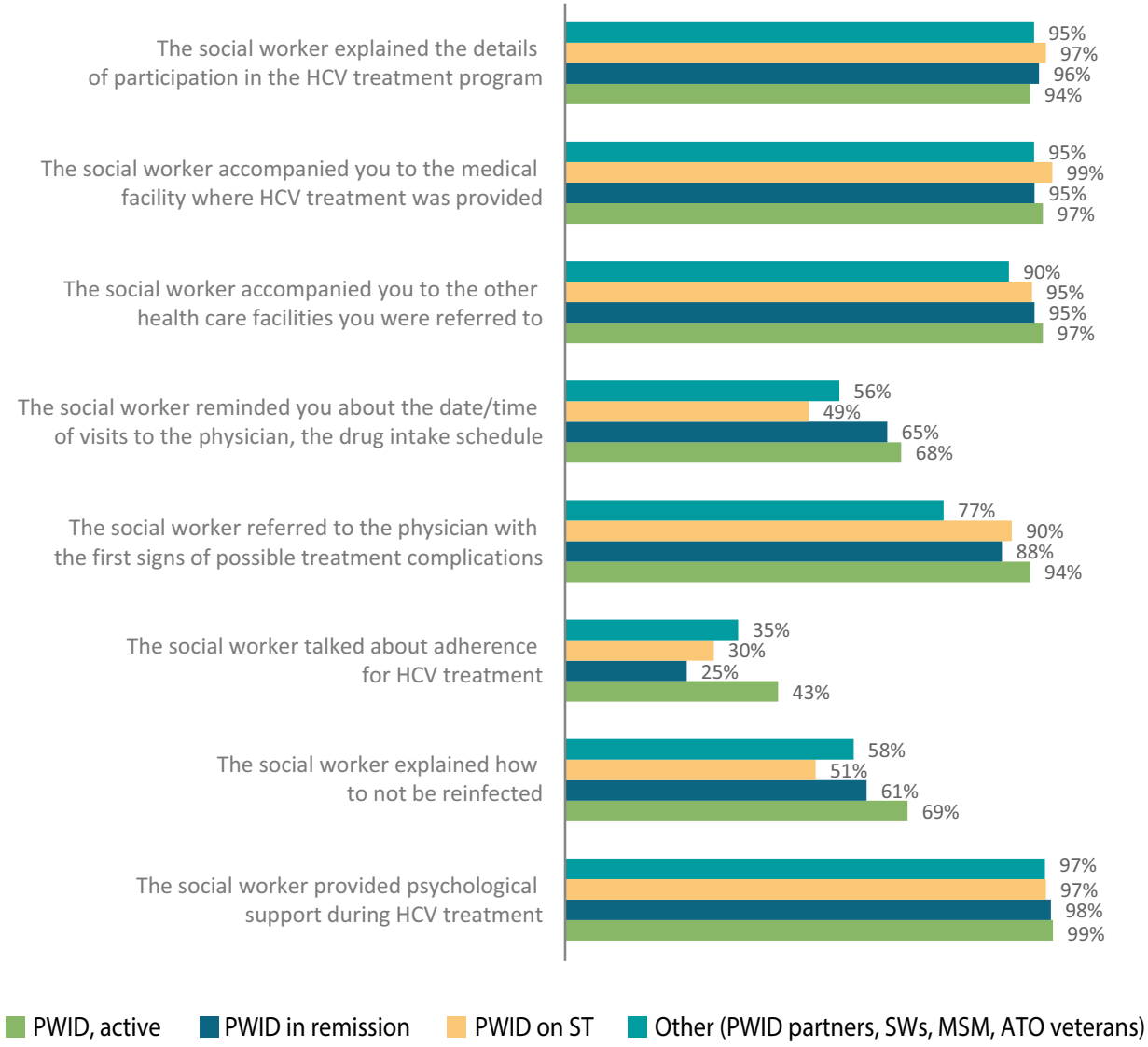
The most popular social support services were consultations regarding aspects of participation in the Project (98%), prevention of reinfection (96%), psychological support (95%), counseling on adherence to treatment (94%), reminders of dates and time of tests and monitoring of medication intake (88%).

Almost a third of patients who received social support services (31%) were accompanied by a social worker – an MDT member – to other health care facilities to undergo tests following the physician's referral. Active PWID were more likely to receive the services of physical accompanying to the facilities where HCV infection treatment took place, as well as to other HCVs in the case of referral for tests (69% – services of physical accompanying to the HCF where the treatment was received, 43% – to other HCFs) (see ***Figure 5***).

TABLE 5. Break down of answers to the question: **"Did you receive the social support service (case management) during the HCV infection treatment?"** (for those who were interviewed after treatment completion and who answered the question, N=831)		**Received**		**Did not receive**	
		N	%	N	%
Sex (p=0.076)	Male	507	86%	83	14%
	Female	218	91%	23	10%
Age (p=0.019)	≤35 y.o.	194	83%	40	17%
	>36 y.o.	531	89%	66	11%
Employment (p=0.568)	Work and/or study	418	88%	58	12%
	Do not study and do not work	307	87%	48	14%
Education (p=0.267)	Completed secondary or lower	155	84%	29	16%
	Secondary vocational or incomplete higher	371	87%	54	13%
	Higher (Bachelor, Master)	199	90%	23	10%
Family status (p=0.282)	Married or an unregistered couple (live with a regular partner)	483	88%	65	12%
	Not married and have no regular partner	242	86%	41	15%
Individual month-ly income (p=0.981)	≤UAH 3,000	386	87%	60	14%
	> UAH 3,000	256	87%	40	14%
	Refused to answer	83	93%	6	7%
Key population (p=0.024)	PWID, active	153	93%	11	7%
	PWID in remission	362	84%	68	16%
	PWID on ST	73	88%	10	12%
	Other (PWID partners, SWs, MSM, ATO veterans)	137	89%	17	11%
Type of facility (p<0.001)	AIDS center	351	80%	88	20%
	Infectious diseases/clinical hospital	176	95%	10	5%
	Other (Gromashevsky Institute, Mili-tary Hospital, Substance Addiction Clinic "Socioterapia", Medical Center "Alternativa")	198	96%	8	4%
Total		**725**	**87%**	**106**	**13%**

* *Research on adherence to HCV treatment and retention barriers. 834 out of 900 participants were interviewed after HCV treatment, 3 of them did not answer this question.*

p = p-value, probability value or asymptotic value; p<0.05 indicates statistically significant factor differences



* *Research on adherence to HCV treatment and retention barriers. 834 out of 900 participants were interviewed after HCV treatment, 3 of them did not answer this question.*

***FIGURE 5.** The proportion of participants who received certain services by the social worker during treatment, by key population, % (for those who were interviewed after treatment completion and who answered the question, N=831)*

Social workers had three sessions with patients on prevention of hepatitis C reinfection, awareness raising, and formation of motivation for safe behavior. Usually, the meetings were individual and lasted for about an hour. According to MDTs' feedback, patients were not always willing to attend such sessions, given that most of them had long been aware of their status and believed that they had a sufficient level of awareness about hepatitis C. At the same time, according to the questionnaire results, patients did not use this information sufficiently.

"Three sessions. At the start of treatment, in the middle, and at the end. A person could share his/her worries. [...] We could do group work if it was a family couple. Or when a relative wanted to be present – we had a client who [...] came for such sessions with his mother. [...] At the second session out of the three, there was the task to prepare some artwork about hepatitis C. Someone wrote a poem, some – just an oral essay, somebody made a collage."

(Social worker, Odessa)

"You need to swap places, so that they told you, asked some questions. [...] And then it turns out that we do not know this, and we do not know that. And many of them became so aware."

(Social worker, Poltava)

According to MDT members' observations, one of inadvisable practices was a wide range of social support objectives. Social workers, together with patients, determined their needs, goals, and the action plan not only for the immediate participation in the Project, but also for other aspects: relationships with people around, employment, etc. Setting long-term objectives was ineffective, as social support was limited to a relatively short period of time (the 3 or 6 months of treatment, depending on the AVT regimen). Accordingly, no work to track progress for such objectives was held.

Availability of social support is a critical component of HCV infection treatment among key populations. As results of the research prove, both patients and medical staff recognize social support as an extremely important tool for achieving success in treatment and high adherence (98% of patients completed a full course of treatment).

Active PWID are the most vulnerable group among those who took part in the Project. They were more in need of social and physical support to reach the health facility, but at the same time they were less satisfied with health professionals and showed a higher risk of treatment termination vs PWID in remission. Among active PWID, the highest incidence of HCV RNA detection 48 weeks after achieving SVR12 was registered, which is likely to be due to a higher incidence of risk behaviors in this key population and a higher risk of reinfection.

PHYSICAL ACCOMPANYING

The majority of participants (64%) independently visited the health care facility (see ***Table 6***). More than a third of patients (37%) received the service of physical accompanying to the facility from time to time, mostly those were active PWID (49%) and patients who did not have formal employment (43% among those who did not study and did not work).

Patients of AIDS centers (48%) most often received the physical accompanying service vs. other HCFs (31% out of patients of infectious diseases hospitals, 18% among patients of specialized institutions).

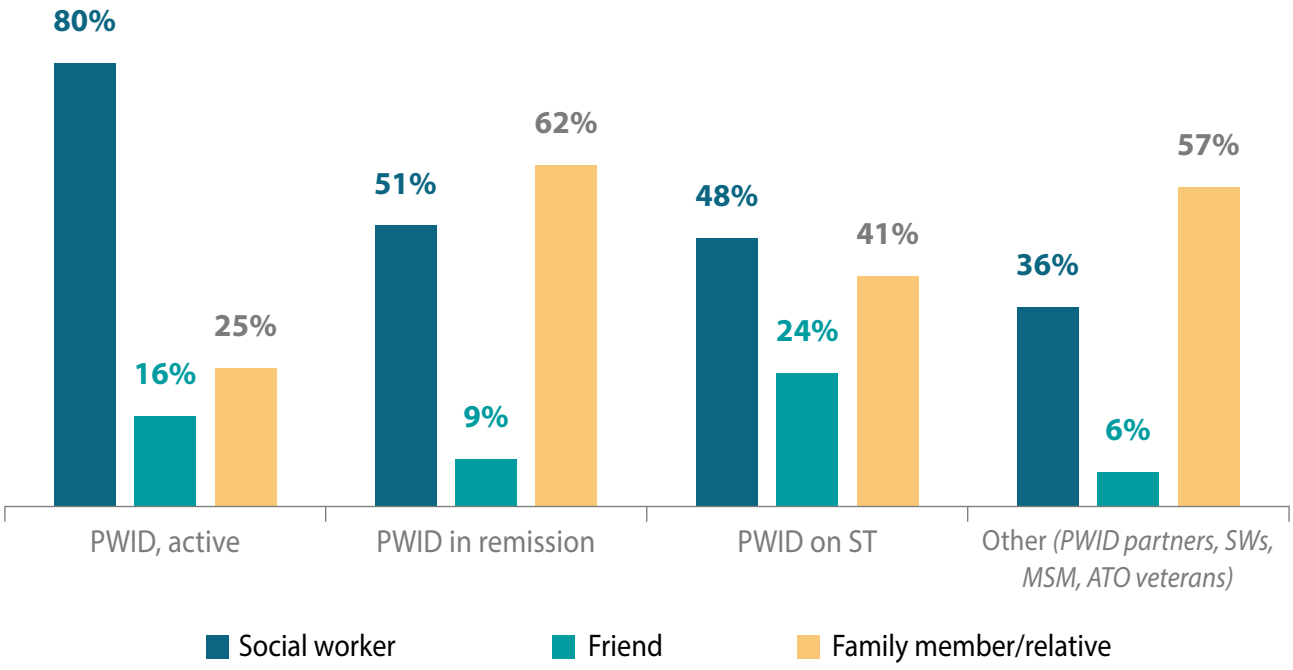
TABLE 6. Break down of answers to the question **"Did someone accompany you when you visited the AIDS Center/infectious disease hospital?"** (for those who were interviewed after treatment completion and who answered the question, N=832)		**Accompanied**		**Did not accompany**	
		N	%	N	%
Sex (p=0.156)	Male	207	35%	384	65%
	Female	97	40%	144	60%
Age (p=0.890)	≤35 y.o.	85	36%	150	64%
	> 36 y.o.	219	37%	378	63%
Employment (p=0.001)	Work and/or study	151	32%	326	68%
	Do not study and do not work	153	43%	202	57%
Key population (p=0.003)	PWID, active	80	49%	84	51%
	PWID in remission	148	34%	283	66%
	PWID on ST	29	35%	54	65%
	Other (PWID partners, SWs, MSM, ATO veterans)	47	31%	107	70%

TABLE 6. Break down of answers to the question **"Did someone accompany you when you visited the AIDS Center/infectious disease hospital?"** (for those who were interviewed after treatment completion and who answered the question, N=832)		**Accompanied**		**Did not accompany**	
		N	%	N	%
Type of facility (p<0.001)	AIDS center	211	48%	228	52%
	Infectious diseases/clinical hospital	57	31%	130	70%
	Other (Gromashevsky Institute, Military Hospital, Substance Addiction Clinic "Socioterapia", Medical Center "Alternativa")	36	18%	170	83%
Total		**304**	**37%**	**528**	**64%**

* *Research on adherence to HCV treatment and retention barriers. 834 out of 900 participants were interviewed after HCV treatment, 2 of them did not answer this question.*

p = p-value, probability value or asymptotic value; p<0.05 indicates statistically significant factor differences..

In the total number of patients who received the service of physical accompanying to a health care facility, this was most often the case for active PWID (80%) and PWID on ST (48%) (see Figure 6). PWID in remission (62%) and representatives of other key populations (57%) most often visited their physicians accompanied by relatives, family members, or friends.



* *Research on adherence to HCV treatment and retention barriers.*

***FIGURE 6.** The proportion of patients who visited the facility where the treatment was held accompanied by the social worker, friends or relatives, by key population, % (for those who visited the facilities with accompaniment, N=304)*

SATISFACTION LEVEL

Patients in all the key populations showed a high level of satisfaction with MDT work and with the quality of Project services due to friendly attitude, no stigma or discrimination, comfort, attention to the patient's individual needs and provision of quality care services.

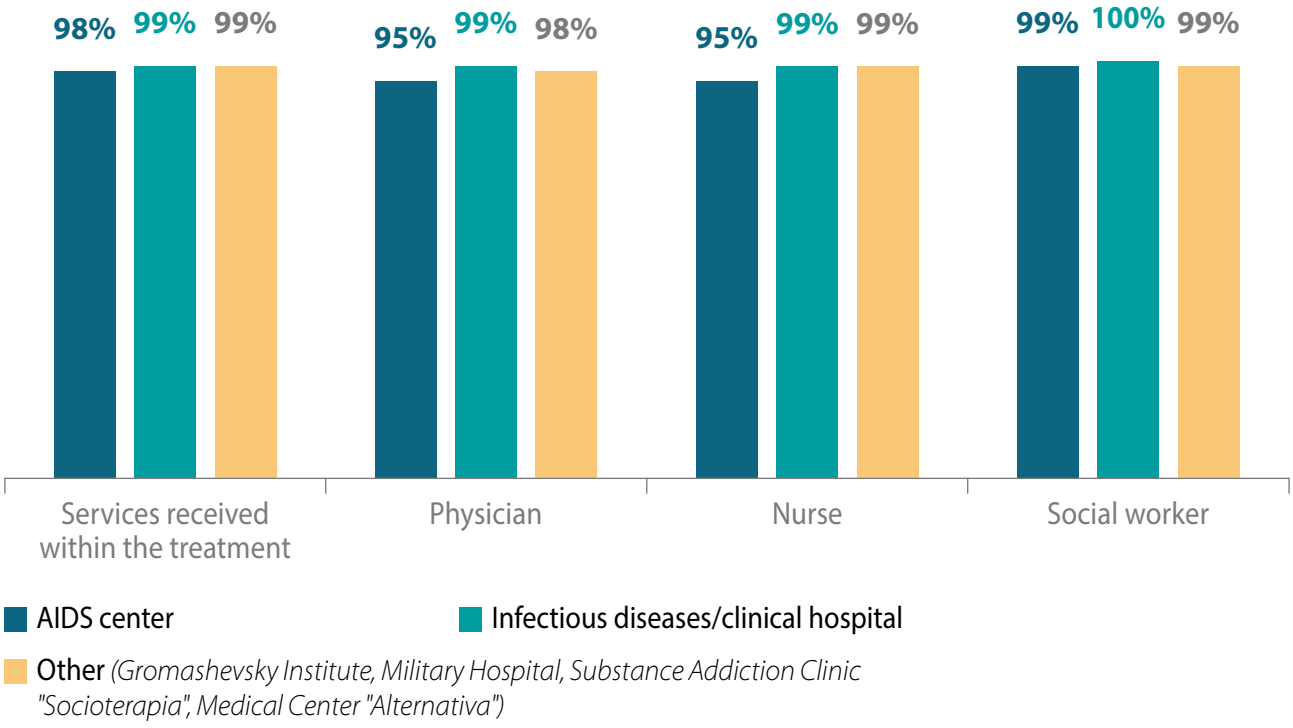
According to the research results, patients' satisfaction level with the Project was very high. 99% of the patients indicated that they were completely or rather satisfied with the services received in the framework of HCV infection treatment.

A high satisfaction level among the Project's patients

97% were completely or rather satisfied with the **physician and the nurse**

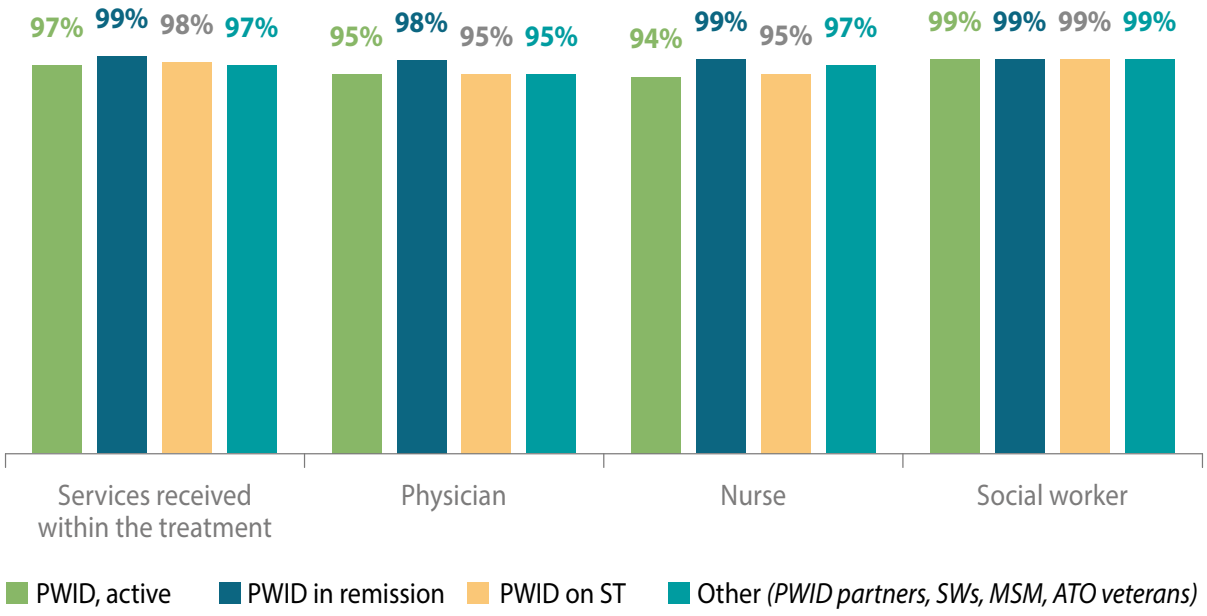
99% were completely or rather satisfied with the **social worker**

The level of patient satisfaction with the services received was equally high for all patient categories and HCFs, however, there were some differences in the degree of satisfaction with work of the medical staff. Among AIDS centers' patients, 5% were dissatisfied with the physician and the nurse, while at other facilities those were 1% ($p<0.05$) (see ***Figure 7***). Dissatisfaction was most often expressed by active PWID (see ***Figure 8***).



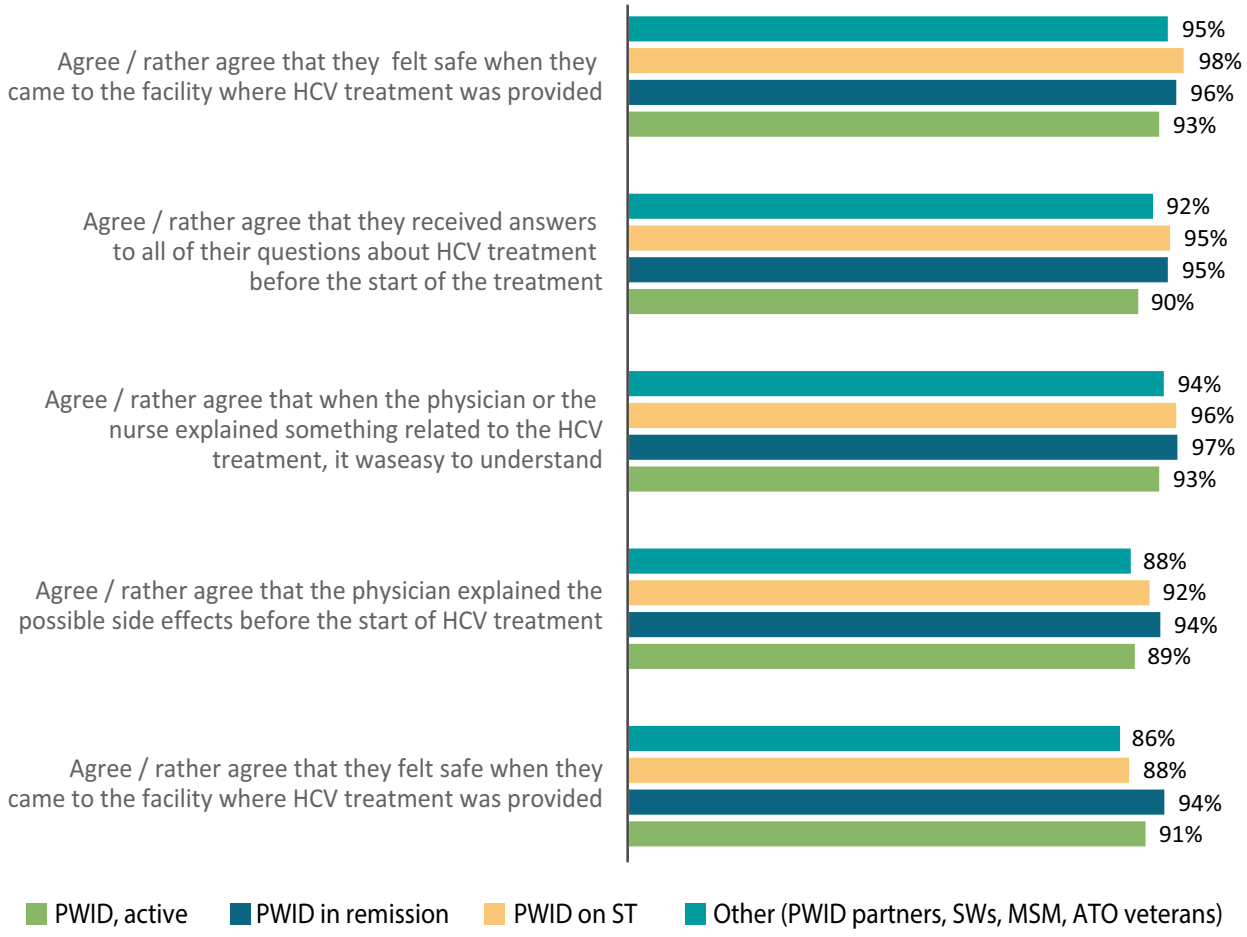
* *Research on adherence to HCV treatment and retention barriers.*

FIGURE 7. *The proportion of participants fully or rather satisfied with the services received and with the staff, by facility type, %* *(among those interviewed after treatment completion, N=834)*



* *Research on adherence to HCV treatment and retention barriers.*

FIGURE 8. *The proportion of participants fully or rather satisfied with the services received and with the staff, by the key population, %* *(among those interviewed after treatment completion, N=834)*



* *Research on adherence to HCV treatment and retention barriers.*

FIGURE 9. *C. Perception of the quality of services within HCV infection treatment based on different aspects among the patients, by key population, %* *(among those interviewed after treatment completion, N=834)*

Almost all Project patients emphasized friendly attitude of the staff and high quality of the services received. More than 90% of patients in all key populations felt safe at the treatment facilities and received clear answers to all of their questions about HCV infection treatment (see ***Figure 9***).

ADVERSE REACTIONS DURING TREATMENT

Data about incidence of adverse reactions received from the HCFs and from patients differed significantly. 85% of respondents interviewed reported having adverse reactions during treatment, while according to HCF specialists' estimations only 11% of the patients actually had them (2% were serious and 10% – not serious) (see ***Table 7***).

According to data obtained from the HCF, serious adverse reactions were most commonly observed for those who had a long-term treatment course – in 6% of patients with a 16-week or 24-week course of treatment vs. 2% of patients with a 12-week course (p=0.014). Non-serious adverse reactions were mostly observed for young people under 35 y.o. (13%), PWID on ST (16%), and non-PWID (14%).

The highest proportion of adverse reactions was observed among patients receiving the 12-week course of treatment with SOF+pegIFN+RBV: 6% – serious and 23% – non-serious (see Table 8). Instead, patients who received the 12-week course of hepatitis C virus treatment with SOF/LDV or SOF+DCV regimens had the least number of adverse reactions (0.3% – serious and 1% – non-serious).

Results of the research on adherence to ***HCV infection treatment and retention barriers*** indicate that the following side effects were most commonly observed: fatigue (79%), irritability and aggression (67%), and headaches (63%) (see ***Figure 10***). Half of the patients (51%) who experienced side effects had problems with sleep, nausea, loss of appetite or diarrhea, as well as muscle and joint pain. Serious adverse reactions were predominantly observed in patients to whom combination treatment regimens including not only DAAs were prescribed. Patients receiving ART did not report any problems of combining ARVs with antivirals for hepatitis C virus therapy. Individual ST patients indicated the need to increase the usual dose of methadone during the HCV infection treatment.

«"They administer the injection, for 2 or 3 days one has fever. Then the fever is gone and you start having... well, those who took drugs will understand. Like some tina come up. Yes, you start going schizo, no way to put it otherwise. [...] Fever, depression. [...] You duck out for a day, and then again.

(Patient, Kyiv)

"For the first two months I was flying, I worked, everything was fine. In the third month, ST seemed to be not enough, they increased the dose a little, by just 5 mg."

(Patient, Odessa)

TABLE 7.
Prevalence of adverse reactions associated with the HCV infection treatment based on various data sources

		Based on participants' questionnaires (for those who were interviewed after treatment completion and who answered the question, N=834)*					According to data provided by HCFs (for participants in the research on adherence to HCV treatment and retention barriers, N=900)														
							Serious side effects					Non-serious side effects					Serious and/or non-serious side effects				
		Had		Did not have		p	Had		Did not have		p	Had		Did not have		p	Had		Did not have		p
		N	%	N	%		N	%	N	%		N	%	N	%		N	%	N	%	
Sex	Male	499	84%	94	16%	0.273	13	2%	630	98%	0.768	68	11%	575	89%	0.363	76	12%	567	88%	0.467
	Female	210	87%	31	13%		6	2%	251	98%		22	9%	235	91%		26	10%	231	90%	
Age	≤35 y.o.	203	86%	32	14%	0.487	7	3%	250	97%	0.419	34	13%	223	87%	**0.041**	40	16%	217	84%	**0.011**
	>36 y.o.	506	85%	93	16%		12	2%	631	98%		56	9%	587	91%		62	10%	581	90%	
Marital status	Married or an unregistered couple (live with a regular partner)	463	84%	87	16%	0.350	11	2%	580	98%	0.471	57	10%	534	90%	0.623	66	11%	525	89%	0.828
	Not married and have no regular partner	246	87%	38	13%		8	3%	301	97%		33	11%	276	89%		36	12%	273	88%	
Employment	Work and/or study	403	84%	75	16%	0.510	8	2%	507	98%	0.178	46	9%	469	91%	0.217	52	10%	463	90%	0.176
	Do not study and do not work	306	86%	50	14%		11	3%	374	97%		44	11%	341	89%		50	13%	335	87%	
Individual monthly income	≤UAH 3,000	396	89%	51	11%	**0.002**	13	3%	478	97%	0.604	46	9%	445	91%	0.269	54	11%	437	89%	0.290
	> UAH 3,000	239	81%	58	20%		3	1%	313	99%		34	11%	282	89%		36	11%	280	89%	
	Refused to answer	74	82%	16	18%		3	3%	90	97%		10	11%	83	89%		12	13%	81	87%	
Key population	PWID, active	131	80%	33	20%	0.236	4	2%	177	98%	0.382	17	9%	164	91%	**0.033**	19	11%	162	90%	**0.032**
	PWID in remission	373	86%	60	14%		7	2%	456	99%		36	8%	427	92%		42	9%	421	91%	
	PWID on ST	72	87%	11	13%		4	4%	89	96%		15	16%	78	84%		17	18%	76	82%	
	Other (PWID partners, SWs, MSM, ATO veterans)	133	86%	21	14%		4	3%	159	98%		22	14%	141	87%		24	15%	139	85%	
Duration of HCV treatment	12 weeks	648	85%	116	15%	0.602	14	2%	798	98%	**0.014**	76	9%	736	91%	0.052	84	10%	728	90%	**0.004**
	16 or 24 weeks	61	87%	9	13%		5	6%	83	94%		14	16%	74	84%		18	21%	70	80%	
Total		**709**	**85%**	**125**	**15%**	-	**19**	**2%**	**881**	**98%**	-	**90**	**10%**	**810**	**90%**	-	**102**	**11%**	**798**	**89%**	-

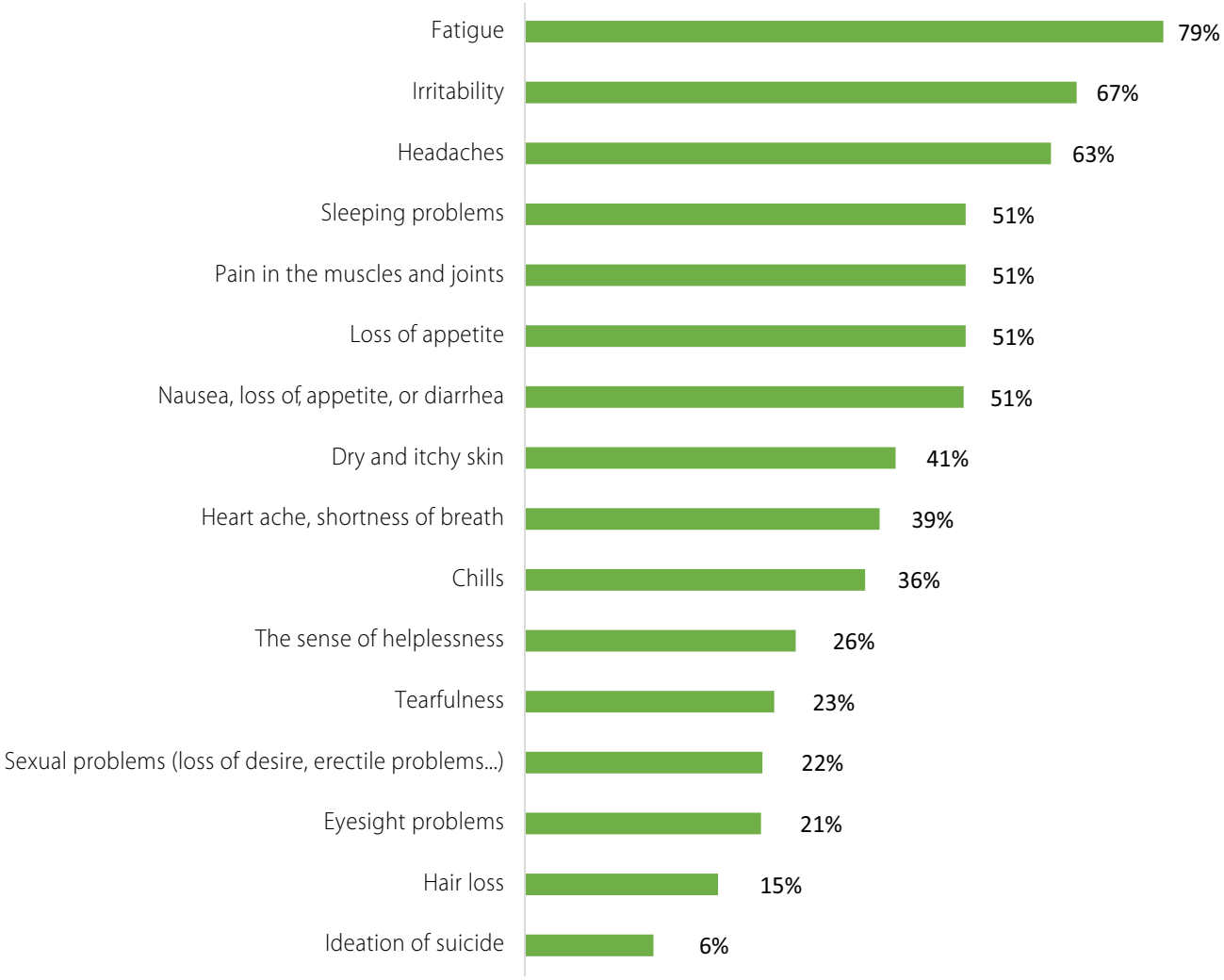
* *Research on adherence to HCV treatment and retention in treatment barriers*

p = p-value, probability value or asymptotic value; p<0.05 indicates statistically significant factor differences.

TABLE 8.
Prevalence of adverse reactions depending on the HCV infection treatment regimen based on various data sources

	Based on participants' questionnaires (for those who were interviewed after treatment completion and who answered the question, N=834)*				**According to data provided by HCFs** (for participants in the research on adherence to HCV infection treatment and retention barriers, N=900)											
					Serious side effects				Non-serious side effects				Serious and/or non-serious side effects			
	Had		Did not have		Had		Did not have		Had		Did not have		Had		Did not have	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
SOF/LDV 12 W	229	77%	68	23%	1	0.3%	313	99.7%	7	2%	307	98%	8	3%	306	97%
SOF/LDV 24 W	2	100%	0	0%	0	0%	3	100%	0	0%	3	100%	0	0%	3	100%
SOF/LDV+RBV 12 W	108	93%	8	7%	1	0.8%	120	99.2%	13	11%	108	89%	14	12%	107	88%
SOF/LDV+RBV 16 W	0	0%	0	0%	0	0%	1	100%	0	0%	1	100%	0	0%	1	100%
SOF/LDV+RBV 24 W	3	100%	0	0%	0	0%	4	100%	0	0%	4	100%	0	0%	4	100%
SOF+DCV 12 W	80	73%	30	27%	0	0%	114	100%	1	1%	113	99%	1	1%	113	99%
SOF+DCV 24 W	2	100%	0	0%	0	0%	2	100%	0	0%	2	100%	0	0%	2	100%
SOF+DCV+RBV 12 W	21	84%	4	16%	0	0%	26	100%	4	15%	22	85%	4	15%	22	85%
SOF+DCV+RBV 16 W	0	0%	1	100%	0	0%	1	100%	0	0%	1	100%	0	0%	1	100%
SOF+DCV+RBV 24 W	9	100%	0	0%	2	22%	7	78%	1	11%	8	89%	3	33%	6	67%
SOF+Peg-IFN+RBV 12 W	194	99%	3	2%	12	5.5%	205	94.5%	49	23%	168	77%	55	25%	162	75%
SOF+RBV 12 W	16	84%	3	16%	0	0%	20	100%	2	10%	18	90%	2	10%	18	90%
SOF+RBV 16 W	1	100%	0	0%	0	0%	1	100%	1	100%	0	0%	1	100%	0	0%
SOF+RBV 24 W	44	85%	8	15%	3	4.5%	64	95.5%	12	18%	55	82%	14	21%	53	79%

** Research on adherence to HCV treatment and retention in treatment barriers*



** Research on adherence to HCV treatment and retention in treatment barriers.*

***FIGURE 10.** Prevalence of various types of adverse reactions: proportions of the participants who had these adverse reactions, % (for those who reported side effects, N=709)*

In general, 25% of patients reporting side effects spent out-of-pocket money on medicines to treat them (see ***Table 9***). The median costs for treatment of adverse reactions amounted to UAH 500 for the entire period of the HCV infection treatment. However, the cost range was very wide: from UAH 10 to UAH 40,000.

TABLE 9.
COSTS OF TREATMENT OF SIDE EFFECTS,
based on results of the adherence to HCV treatment and retention barriers research

		Payed for the treatment of adverse reactions during the treatment (for those who reported side effects, N=709)*				**Costs of treatment of adverse reactions**, UAH (for the participants who paid)**			
		Paid		Did not pay					
		N	%	N	%	Median	MKB	Minimum	Maximum
Key population	PWID, active	29	22%	102	78%	800	2800	20	10000
	PWID in remission	91	24%	282	76%	475	1320	20	9000
	PWID on ST	15	21%	57	79%	500	1800	170	40000
	Other (PWID partners, SWs, MSM, JFO veterans)	40	30%	93	70%	590	1800	10	30000
Facility type	AIDS center	91	24%	284	76%	400	1800	10	40000
	Infectious diseases/clinical hospital	40	25%	121	75%	400	900	20	5000
	Other (Gromashevsky Institute, Military Hospital, Substance Addiction Clinic "Socioterapia", Medical Center "Alternativa")	44	25%	129	75%	1000	1600	10	10000
Oblast	Vinnytsia	35	42%	48	58%	500	1800	70	30000
	Dnipropetrovsk	16	36%	28	64%	220	390	40	2800
	Zhytomyr	4	57%	3	43%	4000	4500	2000	9000
	Zaporizhzhia	6	38%	10	63%	275	200	200	2300
	Ivano-Frankivsk	8	19%	35	81%	250	440	10	1000
	Kyiv	69	31%	153	69%	1000	1700	10	10000
	Kirovohrad	3	12%	23	89%	1000	1200	300	1500
	Lviv	5	19%	22	82%	2000	5600	200	6500
	Odessa	4	15%	23	85%	2250	20100	300	40000
	Poltava	6	10%	55	90%	700	1700	20	3000
	Rivne	5	17%	24	83%	200	30	30	200
	Sumy	12	23%	41	77%	55	610	20	2000
	Kharkiv	0	0%	42	100%	-	-	-	-
	Kherson	0	0%	4	100%	-	-	-	-
	Khmelnytsky	2	9%	20	91%	445	290	300	590
	Donetsk	0	0%	3	100%	-	-	-	-
Total		**175**	**25%**	**534**	**75%**	**500**	**1800**	**10**	**40000**

** The differences by population and facility type are not statistically significant (p=0.090 and p=0.956, respectively), statistically significant differences are observed by Oblasts (p<0.001).*

*** The differences by population and facility type are not statistically significant (p=0.783 and p=0.074, respectively), statistically significant differences are observed by Oblasts (p=0.009).*

CHANGES IN RISK BEHAVIORS, HCV AWARENESS LEVEL, AND THE QUALITY OF LIFE OF THE PROJECT'S PATIENTS DURING THE TREATMENT COURSE

As to their general awareness about hepatitis C virus, patients mostly lacked information about HCV transmission risks. In patient counseling, there should be a greater focus on this information.

The relatively low incidence of detectable HCV RNA VL levels after achieving SVR12 and changes in patient behavior, in particular reduction of risky injections and sexual practices, both in the short and long term, prove effectiveness of reinfection prevention services. In general, the majority of the sporadic cases of HCV recurrence revealed during the research were observed among the participants who, after achieving SVR12, had high risks when injecting drugs, practiced sexual contacts in the state of alcohol or drug intoxication, or had surgical interventions due to complications of more intense injection drug use. The experience of participating in activities to prevent HCV reinfection in the framework of social support during treatment was one of statistically significant factors of reducing the risk of HCV reinfection, based on the research results.

At the start of treatment, 53% of patients had insufficient information about possible ways of transmission and prevention of hepatitis C virus. After treatment completion and three educational sessions on preventing HCV reinfection, this figure went down to 41% ($p<0.001$) (see Figure 11). During the final interview, which was held 12 weeks after treatment completion, 62% of the respondents correctly answered all the 10 questions about HCV.

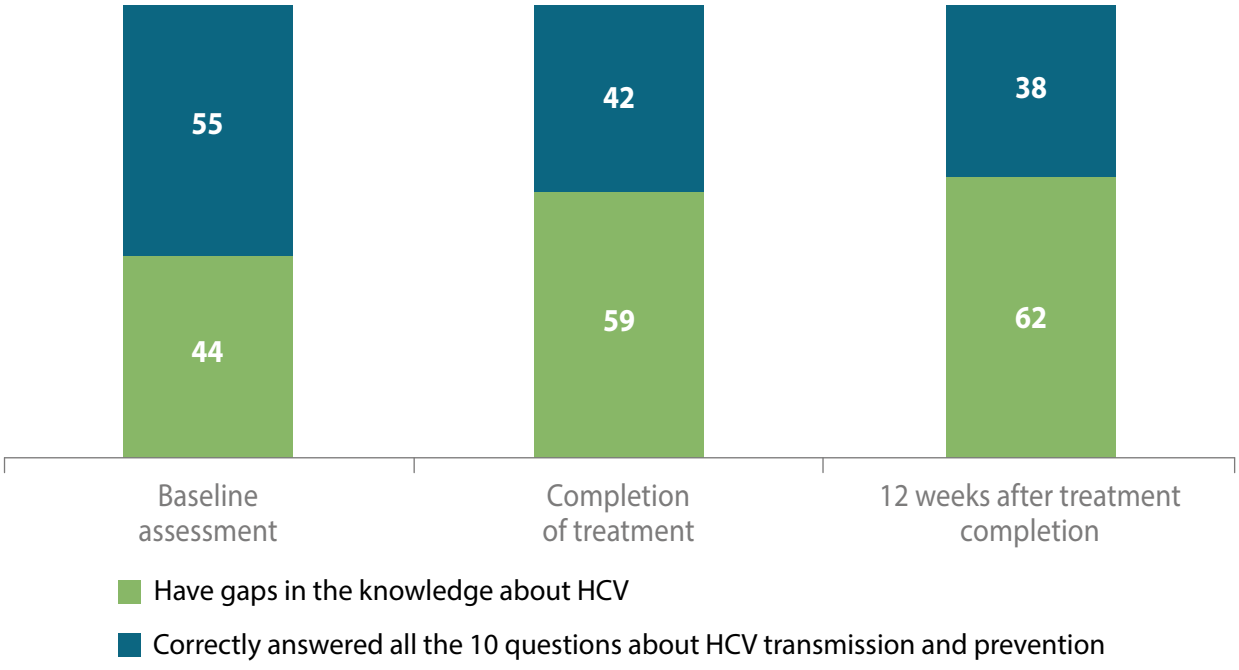


FIGURE 11. *HCV awareness level among project participants*, %*
(for those who took part in all the three interviews, N=795)

** Research on adherence to HCV infection treatment and retention barriers.*

$p<0.001$, statistically significant differences by the assessment period.

Based on results of the qualitative research, patients mostly noted that they had previously understood the possible risks of hepatitis C transmission via non-sterile syringes or sex without a condom, but before the start of treatment they had not thought about the risks of transmission through personal hygiene products (razors, manicure instruments, etc.).

Based on quantitative research data, at the time of the baseline assessment (see ***Table 10***), almost one in every five participants had gaps in their knowledge about HCV transmission when kissing and during childbirth. In addition to these aspects, one in every ten participants of the first interview was able to say if the following statements were correct: "If one becomes infected with hepatitis C, it may lead to the situation where the liver stops working" and "One can get infected with hepatitis C if having unprotected sex with a person having hepatitis C." After completion of the treatment and undergoing the three sessions on prevention of reinfection, most of incorrect answers were those to the questions about HCV transmission by kissing (15%) and during childbirth (12%).

Based on results of the questionnaire, changes in the awareness level were accompanied by changes in high-risk behaviors. While at the start of treatment 15% of patients had signs of alcohol addiction, after the treatment this figure decreased to 7%, and 12 weeks after treatment completion – to 5% ($p<0.001$) (see ***Table 11***). The proportion of active PWID decreased: from 23% at the start of the treatment to 11% after treatment completion, and 8% 12 weeks after treatment completion ($p<0.001$).

Prevalence of injection risks among active PWID, in particular use of non-sterile needles, shared drug preparation devices, or injections in the state of alcohol intoxication, decreased from 55% (the baseline before treatment) to 42% (after treatment completion), however, such differences were not statistically significant, given the small number of active PWID ($p=0.056$). Sexual behavior became safer – during participation in the Project, the proportion of patients who had anal or vaginal sex without a condom in the past 3 months with partners from high-risk groups decreased two times (from 19 to 8%, $p<0.001$).

Prevalence of risks associated with shared use of personal objects and of manicure and tattoo salon services damaging the skin and mucous membranes decreased from 11% (baseline) to 4% (treatment completion) ($p<0.001$).

TABLE 10.
HCV awareness level among project participants: answers to individual statements, frequency and % (for those who took part in all the three interviews, N=795)*

	Baseline assessment						Completion of treatment						12 weeks after treatment completion						p
	Yes		No		Don't know / No answer		Yes		No		Don't know / No answer		Yes		No		Don't know / No answer		
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	
If one gets infected with hepatitis C, it may lead to the situation where the liver stops working	687	86%	83	10%	25	3%	733	92%	48	6%	14	2%	748	94%	38	5%	9	1%	**<0.001**
Someone who looks and feels good may have hepatitis C.	752	95%	17	2%	26	3%	772	97%	19	2%	4	1%	760	96%	22	3%	13	2%	**0.022**
One may become infected with hepatitis C, if there was blood transfusion from an infected donor	783	98%	6	1%	6	1%	789	99%	3	0%	3	0%	774	97%	13	2%	8	1%	**0.015**
One may get infected with hepatitis C, if one shakes hands with a person with hepatitis C.	25	3%	760	96%	10	1%	22	3%	765	96%	8	1%	19	2%	758	95%	18	2%	0.656
One may become infected with hepatitis C, if one kisses someone with hepatitis C.	83	10%	648	82%	64	8%	71	9%	674	85%	50	6%	61	8%	687	86%	47	6%	0.133
One may get infected with hepatitis C, if one has sex without a condom with someone having hepatitis C.	695	87%	60	8%	40	5%	715	90%	56	7%	24	3%	732	92%	42	5%	21	3%	**0.001**
Hepatitis C may be transmitted from a mother who has hepatitis C to the baby during childbirth	637	80%	36	5%	122	15%	698	88%	26	3%	71	9%	699	88%	18	2%	78	10%	**<0.001**
One may become infected with hepatitis C, if pricked with a needle or a sharp on which there was blood with hepatitis C	775	97%	4	1%	16	2%	771	97%	13	2%	11	1%	756	95%	23	3%	16	2%	**0.011**
One may become infected with hepatitis C, if one works with someone with hepatitis C.	47	6%	728	92%	20	3%	45	6%	739	93%	11	1%	63	8%	717	90%	15	2%	0.096
One may become infected with hepatitis C, if one injects drugs and uses non-sterile instruments.	782	98%	9	1%	4	1%	786	99%	6	1%	3	0%	770	97%	5	1%	20	3%	**0.018**

** Research on adherence to HCV infection treatment and retention barriers.*

p = p-value, probability value or asymptotic value; p<0.05 indicates statistically significant factor differences.

TABLE 11. Changes in behaviors of patients during participation in the project, frequency and % (for those who took part in all the three interviews, N=795)			**Baseline assessment**		**After treatment completion**		**12 weeks after treatment completion**		p
			N	%	N	%	N	%	
Alcohol addiction	AUDIT≤7 points – no risk of alcohol addiction		675	85	740	93	757	95	**<0.001**
	AUDIT 8-15 points – a simple counseling session is needed on reducing alcohol consumption		75	9	39	5	31	4	
	AUDIT 16-19 points – counseling and follow-up required		25	3	7	1	5	1	
	AUDIT≥20 points – referral to a specialist for diagnosis and treatment is required		20	3	9	1	2	0	
	Total		795	100	795	100	795	100	
Injection drug use in the last 3 months – active PWID		Yes	145	23	65	11	53	8	**<0.001**
		No	650	82	730	92	742	93	
		Total	795	100	795	100	795	100	
Presence of risky injection practices in the last 3 months: use of non-sterile needles, shared equipment for preparation of drugs, or injections in the state of alcohol intoxication *(for active PWID)*		Yes	80	55	27	42	24	45	0.056
		No	65	45	38	58	29	55	
		Total	145	100	65	100	53	100	
Have had sexual contacts in the past 3 months		Yes	591	74	569	72	584	73	0.083
		No	204	26	226	28	211	27	
		Total	795	100	795	100	795	100	
Anal or vaginal sex without a condom in the past 3 months with partners from high-risk groups: casual or commercial partners, PWID partners, partners with HIV *(for those who had sex during this period)*		Yes	112	19	48	8	44	8	**<0.001**
		No	479	81	521	92	540	92	
		Total	591	100	569	100	584	100	
Sexual contacts in the state of alcohol intoxication in the past 3 months *(for those who had sexual contacts during this period)*		Yes	75	13	23	4	24	4	**<0.001**
		No	516	87	546	96	560	96	
		Total	591	100	569	100	584	100	
Other risks in the past month: contact with someone else's blood, tattoo, piercing with non-sterile instruments, use of other people's personal hygiene items		Yes	88	11	28	4	27	3	**<0.001**
		No	707	89	767	96	768	97	
		Total	**795**	**100**	**795**	**100**	**795**	**100**	

** Research on adherence to HCV infection treatment and retention barriers.*

p = p-value, probability value or asymptotic value; p<0.05 indicates statistically significant factor differences.

Patients indicated that they understood the value of the treatment received and had doubts about that they would have another chance to be treated of hepatitis C virus.

"If I go to a regular hospital to pass some test – to the city hospital – and not to Synevo or something [...], I necessarily buy gloves, give those to them, and ask them to put them on. Because they do not change them! And now it worries me. Now I'm so afraid to get infected, and I understand that there will be no such second chance for treatment"

(Patient, Poltava)

Patients emphasized that their quality of life improved, they were in a more optimistic mood, and had better relationships with their close ones. There was an improvement in both the physical and psychic health components (See ***Table 12***, ***Figure 12***). At start of treatment, the proportion of patients with depression symptoms was 33%, and 12 weeks after treatment completion this figure fell to 18% (p<0.001).

TABLE 12. Changes in patients' health during the Project, frequency and % (for those who took part in all the three interviews, N=795)	**Baseline assessment**		**After treatment completion**		**12 weeks after treatment completion**		p
	Average	St. deviation	Average	St. deviation	Average	St. deviation	
Physical health component, T-Score by questionnaire SF12v2 *	43.7	9.2	46.3	9.0	48.3	8.4	**<0.001**
Psychic health component, T-Score by questionnaire SF12v2*)	44.2	10.7	45.6	11.5	49.4	10.3	**<0.001**

* *Research on adherence to HCV treatment and retention barriers.*
T-Score>50 – better than the average for the population.
SF12v2 [14] – Short Form Health Survey (a short version of the health status questionnaire consisting of 12 questions).
p = p-value, probability value or asymptotic value; p<0.05 indicates statistically significant factor differences.

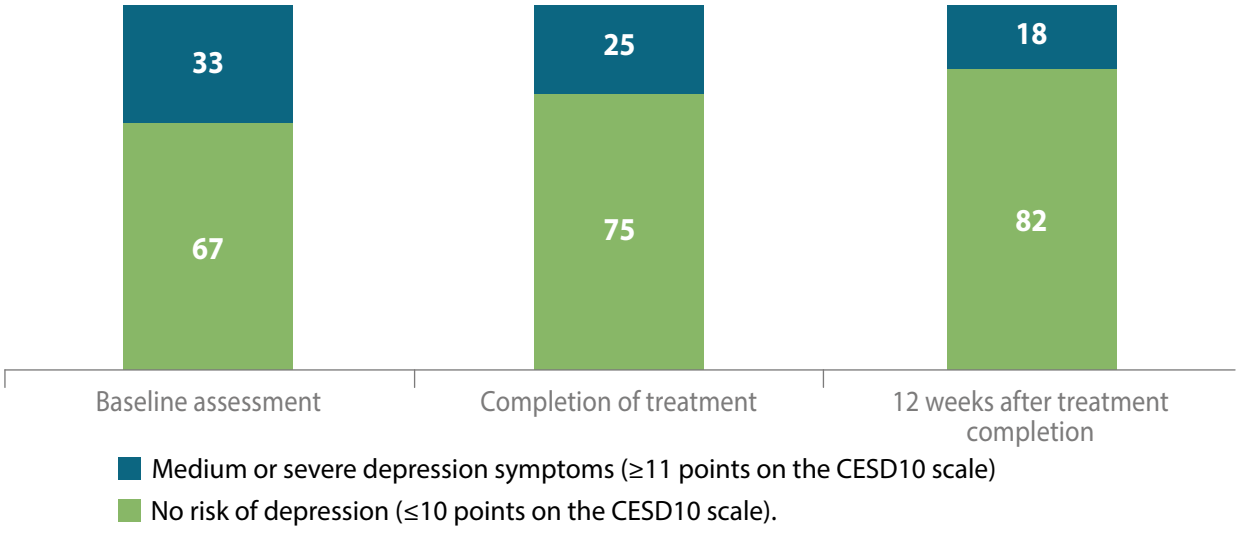


FIGURE 12. *PThe depression rate among project patients at the different stages*, %*
(for those who took part in all the three interviews, N=795)

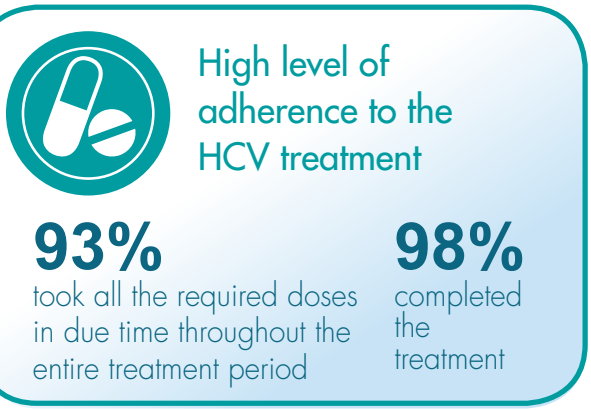
* *Research on adherence to HCV infection treatment and retention barriers.*
CESD10 [15] – Center for Epidemiological Studies Depression Scale Revised (a short version of the questionnaire for depression scoring of the Center for Epidemiological Studies consisting of 10 questions).
p<0.001, statistically significant differences by the assessment period.

14 *Ware J Jr, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey:construction of scales and preliminary tests of reliability and validity. Med Care. 1996 Mar; 34(3): 220-33*

15 *http://cesd-r.com, Andresen, E. M., Malmgren, J. A., Carter, W. B., & Patrick, D. L. (1994). Screening for depression in well older adults: Evaluation of a short form of the CES-D. American journal of preventive medicine, 10(2), 77-84.*

ADHERENCE TO TREATMENT

High effectiveness of treatment/the low level of HCV RNA detection 12 weeks after treatment (achievement of SVR12 by the vast majority of participants) are both due to high efficiency of DAAs and high patient adherence to treatment. Research results indicate that use of DAAs (non-interferon treatment regimens), psychological and social support are a pre-requisite for successful patient retention in treatment.



According to social workers, they often phoned patients daily to control their intake of the medications at the beginning of treatment (during the first weeks) to develop the habit and adherence. According to results of the survey, only 7% of patients, due to various life circumstances, shifted the time of taking their medications for several hours, but in most cases they timely addressed their physicians/social workers to adjust their dose (see ***Table 13***). Missing drug intake was most commonly reported among PWID on ST (16% in this group) and among patients with a 16- or 24-week treatment course (16%).

"I called them, my every morning began with a call. "Good morning, take your pill! Come to receive your pill!" In some cases, I worked as a reminder for about 2 weeks, and everything went on smoothly. The person would get used to the rhythm, and everything was fine."

(Social worker, Kharkiv)

TABLE 13. Break down of answers to the question: "Did it ever happen that you missed taking your medications while undergoing the HCV infection treatment?", frequency and % (for those who took part in the interview after treatment completion and answered the question, N=832)		**Yes**		**No**	
		N	%	N	%
Sex (p=0.786)	Male	41	7%	550	93%
	Female	18	8%	223	92%
Age (p=0.109)	≤35 y.o.	22	9%	213	91%
	>36 y.o.	37	6%	560	94%
Family status (p=0.012)	Married or an unregistered couple (live with a regular partner)	30	6%	518	94%
	Not married and have no regular partner	29	10%	255	90%
Employment (p=0.112)	Work and/or study	28	6%	449	94%
	Do not study and do not work	31	9%	324	91%
Individual monthly income (p=0.690)	≤UAH 3,000	32	7%	414	93%
	> UAH 3,000	19	6%	277	94%
	Refused to answer	8	9%	82	91%
Key population (p=0.014)	PWID, active	10	6%	154	94%
	PWID in remission	28	7%	403	93%
	PWID on ST	13	16%	70	84%
	Other (PWID partners, SWs, MSM, ATO veterans)	8	5%	146	95%
Type of facility (p=0.008)	AIDS center	32	7%	407	93%
	Infectious diseases/clinical hospital	5	3%	182	97%
	Other (Gromashevsky Institute, Military Hospital, Substance Addiction Clinic "Socioterapia", Medical Center "Alternativa")	22	11%	184	89%
Duration of HCV infection treatment (p=0.003)	12 weeks	48	6%	714	94%
	16 or 24 weeks	11	16%	59	84%
Total		**59**	**7%**	**773**	**93%**

* *Research on adherence to HCV infection treatment and retention barriers. 834 out of 900 participants were interviewed after HCV invection treatment, 2 of them did not answer this question.*
p = p-value, probability value or asymptotic value; p<0.05 indicates statistically significant factor differences.

The patients who missed taking their medications explained this predominantly with their forgetfulness (33 out of the 59 patients who reported missing drug intake) (See ***Figure 13***). Almost a quarter (13 out of 59) of patients among those who missed taking their medications did it because they did not have the required drugs at hand. Adverse reactions were rarely mentioned as the reason for missing drug intake

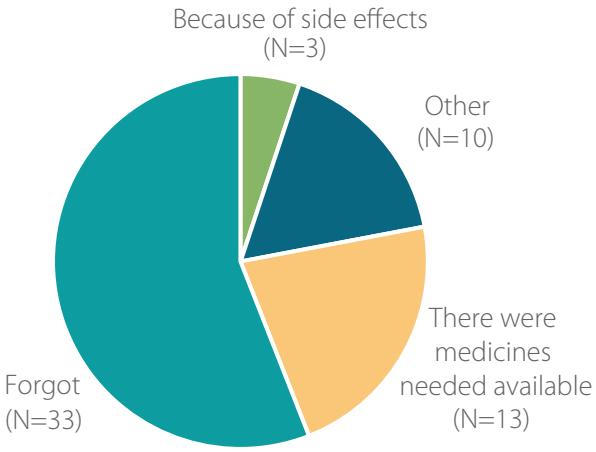


FIGURE 13. *Break down of answers to the question: "why did you miss taking your medications last?", %*
(for those who missed taking medications, N=59)

I had a kind of paranoia. It always seemed to me that I had forgotten to take them [medicines], or that I had already taken them.

(Patient, Kyiv)

Only 15 out of the 900 patients (1.7%) terminated their course of HCV infection treatment early, mainly due to occurrence of adverse reactions (see ***Figure 14***). Five patients had died before the treatment was completed for a variety of reasons.

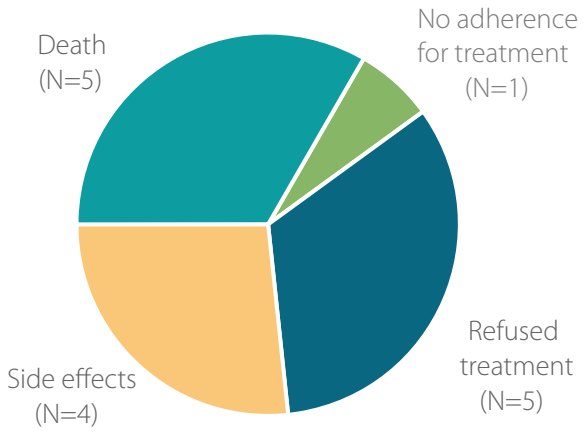


FIGURE 14. *Break down of causes for termination of HCV infection treatment by clinical data, %* *(for those who terminated their treatment, N=15)*

Patients treated with the pegylated interferon regimen (SOF+pegIFN+RBV) showed a six times higher risk of discontinuing the treatment early (HR=6.11; 95% CI: 1.23-30.31) (See ***Table 14***). As noted above, this hepatitis C virus treatment regimen was characterized by the highest prevalence of adverse reactions vs. the other regimens used within the Project. In general, presence of serious or non-serious adverse reactions was a key factor to the risk of HCV infection treatment termination (serious side effects: HR=11.79; 95% CI: 2.57-54.15; non-serious side effects: HR=3.97; 95% CI: 1.13-13.93). Besides, patients with symptoms of depression showed a higher risk of early hepatitis C virus treatment termination (HR=1.14; 95% CI: 1.05-1.25).

"There was time when I wanted to give up, but the social workers convinced me... Noise in my head, I thought I would die there."

(Patient, Vinnytsia)

"I had that after the first injection, [...] I was shaking, could not warm up, no blankets helped. Then there was a bit of nausea, from time to time my temperature went up to 38, and weakness [...] But nothing as incredible as people say, that they terminate their therapy – that was not the case. [...] ."

(Patient, Ivano-Frankivsk)

TABLE 14. **Factors for early termination of HCV infection treatment, multilevel COX regression** (for participants in the research on adherence to HCV infection treatment and retention barriers, N=900)		Early termination of HCV treatment		Completion of treatment		OR (95% CI)	Adjusted OR* (95% CI)
		N	%	N	%		
Sex	Male	12	2%	631	98%	2.12 (0.47-9.56)	1.79 (0.35-9.06)
	Female	2	1%	255	99%	ref.	ref.
Age	≤35 y.o.	3	1%	254	99%	0.57 (0.16-2.09)	0.59 (0.15-2.29)
	>36 y.o.	11	2%	632	98%	ref.	ref.
Employment	Work and/or study	6	1%	509	99%	0.67 (0.22-1.94)	-
	Do not study and do not work	8	2%	377	98%	ref.	-
Individual monthly income	≤UAH 3,000	10	2%	481	98%	1.89 (0.51-6.96)	-
	> UAH 3,000	3	1%	313	99%	ref.	-
Education	Completed secondary or lower	9	4%	194	96%	4.43 (0.94-20.91)	-
	Secondary vocational or incomplete higher	3	1%	455	99%	0.72 (0.12-4.33)	-
	Higher (Bachelor, Master)	2	1%	237	99%	ref.	-
Marital status	Married or an unregistered couple (live with a regular partner)	6	1%	585	99%	0.40 (0.14-1.18)	-
	Not married and have no regular partner	8	3%	301	97%	ref.	-
Key population	PWID, active	5	3%	176	97%	ref.	ref.
	PWID in remission	3	1%	460	99%	**0.22 (0.05-0.96)**	0.32 (0.07-1.56)
	PWID on ST	4	4%	89	96%	0.96 (0.23-3.94)	1.06 (0.25-4.59)
	Other (PWID partners, SWs, MSM, ATO (JFO) veterans)	2	1%	161	99%	0.37 (0.07-2.02)	0.49 (0.08-3.09)
The median level of alcohol addiction before treatment based on AUDIT (IQR)		0 (2)		1 (4)		1.03 (0.96-1.11)	-
Presence of high-risk injection practices in the last 3 months before the treatment: use of non-sterile needles, shared equipment for preparation of drugs, or injections in the state of alcohol intoxication (for the participants who injected drugs during this period)	Yes	3	3%	-	97%	1.98 (0.44-8.86)	
	No	4	2%	-	98%	ref.	
Presence of sex-related risks in the last 3 months before the treatment: sex without a condom or in the state of alcohol/drug intoxication (for the participants who had sexual contacts during this period)	Yes	3	2%	-	98%	1.04 (0.26-4.09)	
	No	7	2%	-	99%	ref.	
Other risks in the last month before the treatment: contact with someone else's blood, tattoo, piercing with non-sterile instruments, use of other people's personal hygiene items	Yes	2	2%	-	98%	1.32 (0.29-6.05)	
	No	12	2%	-	99%	ref.	

TABLE 14.
Factors for early termination of HCV infection treatment, multilevel COX regression (for participants in the research on adherence to HCV infection treatment and retention barriers, N=900)

			Early termination of HCV treatment		Completion of treatment		OR (95% CI)	Adjusted OR* (95% CI)
			N	%	N	%		
The median level of physical health, T-Score based on SF12v2 questionnaire before the treatment (IQR)			35.8 (21.2)		44.7 (12.6)		**0.93 (0.88-0.98)**	-
The median level of psychic health, T-Score based on SF12v2 questionnaire before the treatment (IQR)			39 (20.3)		44.5 (15.5)		**0.95 (0.90-0.997)**	-
The median depression level based on CESD10 before treatment (IQR)			13 (10)		7 (9.0)		**1.14 (1.05-1.25)**	**1.12 (1.03-1.23)**
Awareness level about HCV before treatment	Correctly answered all the 10 questions about HCV		6	2%	397	98%	1.23 (0.41-3.73)	-
	Had gaps in the knowledge		8	2%	489	98%	ref.	-
The median time of travel to the hospital where the treatment was provided, in minutes (IQR)			60 (40)		60 (83)		1.00 (0.98-1.01)	
The median cost of travel to the hospital where the treatment was provided, in UAH (IQR)			30 (68)		15 (55)		1.01 (0.98-1.05)	
Received social support (case management) during the treatment		Yes	6	1%	719	99%	0.78 (0.09-7.19)	-
		No	1	1%	105	99%	ref.	-
Duration of HCV treatment	12 weeks		11	1%	801	99%	3.51 (0.38-32.16)	-
	16 or 24 weeks		3	3%	85	97%	ref.	-
Treatment regimen	SOF+Peg-IFN+RBV		8	4%	209	96%	**6.11 (1.23-30.31)**	-
	SOF+RBV		3	3%	85	97%	0.80 (0.08-8.36)	-
	SOF+DCV or SOF+DCV+RBV		0	0%	152	100%	HP	-
	SOF/LDV+RBV		1	1%	125	99%	1.15 (0.10-13.00)	-
	SOF/LDV		2	1%	315	99%	ref.	-
Serious adverse reactions during the treatment (according to data provided by the HCF)	Present		3	16%	16	84%	**11.79 (2.57-54.15)**	**7.68 (1.40-42.20)**
	Absent		11	1%	870	99%	ref.	ref.
Non-serious adverse reactions during the treatment (according to data provided by the HCF)	Present		5	6%	85	94%	**3.97 (1.13-13.93)**	2.45 (0.64-9.31)
	Absent		9	1%	801	99%	ref.	ref.
History of HIV	Yes		10	2%	583	98%	1.39 (0.41-4.67)	-
	No		4	1%	303	99%	ref.	-
History of HBV	Yes		4	5%	75	95%	3.31 (0.88-12.43)	-
	No		10	1%	811	99%	ref.	-

TABLE 14. **Factors for early termination of HCV infection treatment, multilevel COX regression** (for participants in the research on adherence to HCV infection treatment and retention barriers, N=900)		Early termination of HCV treatment		Completion of treatment		OR (95% CI)	Adjusted OR* (95% CI)
		N	%	N	%		
History of TB	Yes	3	2%	182	98%	1.15 (0.31-4.29)	-
	No	11	2%	704	99%	ref.	-
The result of the HCV RNA VL test before treatment, IU/ml		735000 (2310000)		840000 (2760000)		1.00 (0.99-1.00)	
HCV genotype before treatment	Genotype 1	6	1%	545	99%	ref.	-
	Genotype 3	8	3%	307	98%	1.14 (0.45-4.42)	-
	Another genotype / not detected	0	0%	34	100%	NP	-
The grade of fibrosis before treatment	F3-F4	8	2%	409	98%	2.10 (0.71-6.24)	-
	F1-F2	6	1%	477	99%	ref.	-
History of pegIFN+RBV treatment	Yes	2	2%	86	98%	1.65 (0.36-7.56)	-
	No	12	2%	800	99%	ref.	-

HR = hazard ratio.

CI = confidence interval.

IQR = inter-quartile range, the difference between the 75 and 25 percentiles.

ref. = reference category.

NP = no possibility to calculate the hazard ratio because of the zero values (no event in a certain category).

*Interpretation: HR>1.00, this was a positive ratio, the number of times the chances for the result in a particular group vs the reference category were higher (categorical factor), or how many times chances for the result increase if the factor value increases by one point on the scale (quantitative factor). HR<1.00, this was a negative ratio, the odds of the result in a certain group is (1-HR)*100 percent less than in the reference category, or the odds of the result is reduced by (1-HR)*100 percent if the factor value increases by one point on the scale (quantitative factor). If the HR is 1.00, the factor is not related to the result.*

* *Adjusted regression analysis is limited to statistically significant factors only, as well as key socio-demographic characteristics (age and sex) that may have the co-founding effect. Certain statistically significant factors are not included into the adjusted analysis due to the multicollinearity issue*

Patients with a better physical and mental status showed lower risks of discontinuing the treatment early (HR=0.93; 95% CI: 0.88-0.98 for the SF12v2 physical health index; HR=0.95; 95% CI: 0.90-0.997 for the SF12v2 mental health index). There are no statistically significant differences in the risk of early termination of HCV infection treatment by demographic characteristics or behavioral factors.

Among key populations, there was a lower risk of treatment termination among PWID in remission (by 78% vs. active PWID (HR=0.22; 95% CI: 0.05-0.96)).

In the adjusted regression analysis by age, sex, and key population, serious side effects (adjusted HR=7.68, 95% CI: 1.40-42.20) and depression (adjusted HR=1.12, 95% CI: 1.03-1.23) remained statistically significant risk factors for early treatment termination.

TREATMENT EFFECTIVENESS

Success of the treatment was determined as achievement of sustainable virological response 12 weeks after treatment completion (SVR12). Among the general number of patients who completed their full course of treatment, were tested for HCV RNA 12 weeks after treatment completion, and received the result of it, 95% had undetected HCV RNA viral load.

Among the four most commonly used treatment regimens (12-week SOF/LDV, SOF/LDV+RBV, SOF+DCV, and SOF+Peg-IFN+RBV), the highest proportion of patients who did not achieve SVR12 had the 12-week SOF+pegIFN+RBV course (8%) (see ***Table 15***).

High level of HCV treatment efficacy

95%

of patients reached sustainable virological response 12 weeks after the treatment was completed

TABLE 15. **SVR12 achievement depending on the treatment regimen**, frequency and % (for participants of the research on adherence to HCV treatment and retention barriers who completed the full course of treatment, were tested for HCV RNA 12 weeks after treatment completion, and received their result, N=857)	Yes		No	
	N	%	N	%
SOF/LDV 12 W	293	98%	7	2%
SOF/LDV 24 W	3	100%	0	0%
SOF/LDV+RBV 12 W	114	95%	6	5%
SOF/LDV+RBV 16 W	1	100%	0	0%
SOF/LDV+RBV 24 W	4	100%	0	0%
SOF+DCV 12 W	104	95%	5	5%
SOF+DCV 24 W	1	50%	1	50%
SOF+DCV+RBV 12 W	26	100%	0	0%
SOF+DCV+RBV 16 W	1	100%	0	0%
SOF+DCV+RBV 24 W	9	100%	0	0%
SOF+Peg-IFN+RBV 12 W	186	92%	16	8%
SOF+RBV 12 W	15	75%	5	25%
SOF+RBV 16 W	1	100%	0	0%
SOF+RBV 24 W	55	93%	4	7%
Total	**813**	**95%**	**44**	**5%**

Patients' having HCV genotypes 2 and 4 (not the first and not the third ones) had 71% worse chances (OR=0.29; 95% CI: 0.10-0.80) (See ***Table 16***). Another factor in absence of the sustainable virological response were the risks associated with sharing of personal use items, manicure and tattoo salon services, which involved damage of skin and mucous membranes. The Project's patients who reported having contacts with someone else's blood, tattoo, piercing with non-sterile instruments, and/or using someone else's personal items 12 weeks after treatment completion had the 73% lower chance of achieving the sustainable virologic response (OR=0.27; 95% CI: 0.09-0.81). However, no statistically significant associations were detected between the probability of achieving SVR12 and other risky practices, including injection or sexual risks. Men were less likely to achieve SVR12 vs. women (OR=0.37; 95% CI: 0.15-0.88). Regarding the different treatment regimens, SOF+pegIFN+RBV and SOF+RBV were associated with lower treatment success rates (OR=0.27; 95% CI: 0.11-0.68 and OR=0.19; 95% CI: 0.07-0.52, respective of the regimen).

In the adjusted regression analysis, sex differences were not statistically significant (adjusted OR = 0.47; 95% CI: 0.18-1.16). Instead, there were age differences: younger patients under 35 years of age had better chances of achieving SVR12 vs. older ones (adjusted OR = 3.32; 95% CI: 1.13-9.76). Other key factors that lowered the chances of successful treatment were the risks associated with shared use of personal items and services for manicure and tattoo salons with damage to skin and mucous membranes (adjusted OR = 0.20; 95% CI: 0.06-0.67) and use of interferon-based treatment regimens (SOF+pegIFN+RBV: adjusted OR = 0.18; 95% CI: 0.06-0.56) or ribavirin (SOF+RBV: adjusted OR = 0.14; 95% CI: 0.03-0.67).

TABLE 16.
Factors of SVR12 achievement: HCV RNA not detectable 12 weeks after treatment completion, multilevel logistic regressions
(for participants of the research on adherence to HCV infection treatment and retention barriers who completed the full course of treatment, were tested for HCV RNA 12 weeks after treatment completion, and received their result, N=857)

		Achieved		Did not achieve		OR (95% CI)	Adjusted OR* (95% CI)
		N	%	N	%		
Sex	Male	569	94%	38	6%	**0.37 (0.15-0.88)**	0.47 (0.18-1.16)
	Female	244	98%	6	2%	ref.	ref.
Age	≤35 y.o.	234	96%	9	4%	1.57 (0.74-3.32)	**3.32 (1.13-9.76)**
	>36 y.o.	579	94%	35	6%	ref.	ref.
Employment	Work and/or study	466	95%	22	5%	1.34 (0.73-2.46)	-
	Do not study and do not work	347	94%	22	6%	ref.	-
Individual monthly income	≤UAH 3,000	444	95%	22	5%	1.00 (0.49-2.02)	-
	> UAH 3,000	290	95%	14	5%	ref.	-
Education	Completed secondary or lower	175	94%	12	6%	0.66 (0.28-1.56)	-
	Secondary vocational or incomplete higher	417	95%	22	5%	0.86 (0.40-1.84)	-
	Higher (Bachelor, Master)	221	96%	10	4%	ref.	-
Marital status	Married or an unregistered couple (live with a regular partner)	544	95%	26	5%	1.40 (0.75-2.60)	-
	Not married and have no regular partner	269	94%	18	6%	ref.	-
The key population by clinical data	PWID, active	160	93%	12	7%	ref.	-
	PWID in remission	430	96%	19	4%	1.76 (0.80-3.88)	-
	PWID on ST	78	93%	6	7%	0.99 (0.35-2.81)	-
	Other (PWID partners, SWs, MSM, ATO (JFO) veterans)	145	95%	7	5%	1.60 (0.60-4.28)	-
The median level of alcohol addiction based on AUDIT (IQR)	Baseline assessment	1 (4)		1 (5)		0.99 (0.94-1.04)	-
	Assessment after treatment completion	0 (3)		0 (4)		1.02 (0.93-1.12)	-
	Assessment 12 weeks after the treatment was completed	0 (3)		0 (2)		1.06 (0.92-1.21)	-

TABLE 16.
Factors of SVR12 achievement: HCV RNA not detectable 12 weeks after treatment completion, multilevel logistic regressions
(for participants of the research on adherence to HCV infection treatment and retention barriers who completed the full course of treatment, were tested for HCV RNA 12 weeks after treatment completion, and received their result, N=857)

			Achieved		Did not achieve		OR (95% CI)	Adjusted OR* (95% CI)
			N	%	N	%		
Presence of risky injection practices in the last 3 months: use of non-sterile needles, shared equipment for preparation of drugs, or injections in the state of alcohol intoxication	Baseline assessment	Yes	84	98%	2	2%	2.66 (0.57-12.34)	-
		No	227	94%	14	6%	ref.	-
	Assessment after treatment completion	Yes	26	96%	1	4%	1.78 (0.21-15.08)	-
		No	220	94%	13	6%	ref.	-
	Assessment 12 weeks after the treatment was completed	Yes	23	96%	1	4%	1.26 (0.15-10.33)	-
		No	182	95%	10	5%	ref.	-
Presence of sexual risks in the past 3 months (sex without a condom or in the state of alcohol/drug intoxication)	Baseline assessment	Yes	166	95%	8	5%	0.94 (0.40-2.17)	-
		No	443	96%	20	4%	ref.	-
	Assessment after treatment completion	Yes	64	94%	4	6%	0.73 (0.24-2.19)	-
		No	481	96%	22	4%	ref.	-
	Assessment 12 weeks after the treatment was completed	Yes	61	95%	3	5%	0.77 (0.22-2.67)	-
		No	504	96%	19	4%	ref.	-
Other risks in the last month before the treatment: contact with someone else's blood, tattoo, piercing with non-sterile instruments, use of other people's personal hygiene items	Baseline assessment	Yes	86	96%	4	4%	1.18 (0.41-3.39)	-
		No	727	95%	40	5%	ref.	-
	Assessment after treatment completion	Yes	24	89%	3	11%	**0.39 (0.13-1.51)**	-
		No	734	95%	40	5%	ref.	-
	Assessment 12 weeks after the treatment was completed	Yes	24	86%	4	14%	**0.27 (0.09-0.81)**	-
		No	741	96%	33	4%	ref.	-
The median level of physical health, T-Score based on SF12v2 questionnaire (IQR)	Baseline assessment		44.6 (12.5)		44.9 (15.5)		1.00 (0.97-1.04)	-
	Assessment after treatment completion		47.4 (12.3)		47.8 (10.7)		1.01 (0.98-1.05)	-
	Assessment 12 weeks after the treatment was completed		50.6 (12.4)		48.6 (14.2)		1.03 (0.99-1.07)	-
The median level of psychic health, T-Score based on SF12v2 questionnaire (IQR)	Baseline assessment		44.5 (15.3)		47.6 (16.6)		0.99 (0.97-1.02)	-
	Assessment after treatment completion		47.0 (16.7)		49.0 (20.1)		0.99 (0.96-1.02)	-
	Assessment 12 weeks after the treatment was completed		51.4 (14.5)		53.0 (12.9)		1.01 (0.98-1.04)	-

TABLE 16.
Factors of SVR12 achievement: HCV RNA not detectable 12 weeks after treatment completion, multilevel logistic regressions
(for participants of the research on adherence to HCV infection treatment and retention barriers who completed the full course of treatment, were tested for HCV RNA 12 weeks after treatment completion, and received their result, N=857)

			Achieved		Did not achieve		OR (95% CI)	Adjusted OR* (95% CI)
			N	%	N	%		
The median depression level based on CESD10 (IQR)	Baseline assessment		7 (9)		7 (10)		0.96 (0.92-1.01)	-
	Assessment after treatment completion		6 (8)		6 (8)		1.00 (0.95-1.05)	-
	Assessment 12 weeks after the treatment was completed		4 (8)		4 (9)		0.97 (0.92-1.02)	-
Awareness level about HCV	Baseline assessment	Correct answers to all the 10 questions	369	95%	21	5%	0.91 (0.50-1.67)	-
		Mistakes in the answers	444	95%	23	5%	ref.	-
	Assessment after treatment completion	Correct answers to all the 10 questions	441	94%	30	6%	0.60 (0.30-1.18)	-
		Mistakes in the answers	317	96%	13	4%	ref.	-
	Assessment 12 weeks after the treatment was completed	Correct answers to all the 10 questions	478	95%	24	5%	0.91 (0.45-1.81)	-
		Mistakes in the answers	286	96%	13	4%	ref.	-
The median time of travel to the hospital where the treatment was provided, in minutes (IQR)			60 (85)		75 (60)		1.00 (1.00-1.00)	
The median cost of travel to the hospital where the treatment was provided, in UAH (IQR)			14 (55)		20 (65)		1.00 (0.98-1.01)	-
Received social support (case management) during the treatment		Yes	654	94%	42	6%	0.15 (0.02-1.13)	-
		No	101	99%	1	1%	ref.	-
Duration of HCV infection treatment		12 weeks	738	95%	39	5%	1.26 (0.48-3.30)	-
		16 or 24 weeks	75	94%	5	6%	ref.	-
HCV infection treatment regimen		SOF+Peg-IFN+RBV	186	92%	16	8%	0.27 (0.11-0.68)	**0.18 (0.06-0.56)**
		SOF+RBV	71	89%	9	11%	0.19 (0.07-0.52)	**0.14 (0.03-0.67)**
		SOF+DCV+RBV or SOF+DCV	141	96%	6	4%	0.56 (0.18-1.68)	0.32 (0.08-1.25)
		SOF/LDV+RBV	119	95%	6	5%	0.47 (0.15-1.42)	0.35 (0.10-1.20)
		SOF/LDV	296	98%	7	2%	ref.	ref.
Serious adverse reactions during the treatment (according to data provided by the HCF)		Present	15	94%	1	6%	0.81 (0.10-6.26)	-
		Absent	798	95%	43	5%	ref.	-

TABLE 16.
Factors of SVR12 achievement: HCV RNA not detectable 12 weeks after treatment completion, multilevel logistic regressions
(for participants of the research on adherence to HCV infection treatment and retention barriers who completed the full course of treatment, were tested for HCV RNA 12 weeks after treatment completion, and received their result, N=857)

		Achieved		Did not achieve		OR (95% CI)	Adjusted OR* (95% CI)
		N	%	N	%		
Non-serious adverse reactions during the treatment (according to data provided by the HCF)	Present	78	97%	2	3%	2.23 (0.53-9.38)	-
	Absent	735	95%	42	5%	ref.	-
History of HIV	Yes	544	95%	31	5%	0.85 (0.44-1.65)	-
	No	269	95%	13	5%	ref.	-
History of HBV	Yes	70	95%	4	5%	0.94 (0.33-2.71)	-
	No	743	95%	40	5%	ref.	-
History of TB	Yes	172	95%	9	5%	1.04 (0.49-2.21)	-
	No	641	95%	35	5%	ref.	-
The result of the HCV RNA before treatment, IU/ml		821500 (2560000)		1600000 (4425000)		1.00 (1.00-1.00)	-
HCV genotype	Genotype 1	508	95%	25	5%	ref.	ref.
	Genotype 3	276	95%	14	5%	0.97 (0.50-1.90)	1.62 (0.66-3.95)
	Another genotype / not detected	29	85%	5	15%	**0.29 (0.10-0.80)**	0.77 (0.17-3.52)
Liver fibrosis	F3-F4	378	94%	25	6%	0.66 (0.35-1.23)	-
	F1-F2	435	96%	19	4%	ref.	-
History of pegIFN+RBV treatment	Yes	80	95%	4	5%	1.09 (0.38-3.13)	-
	No	733	95%	40	5%	ref.	-

OR = odds ratio.

CI = confidence interval.

IQR = inter-quartile range, the difference between the 75 and 25 percentiles.

ref. = reference category.

*Interpretation: OR>1.00, this was a positive ratio, the number of times the chances for the result in a particular group vs the reference category were higher (categorical factor), or how many times chances for the result increase if the factor value increases by one point on the scale (quantitative factor). OR<1.00, this was a negative ratio, the odds of the result in a certain group is (1-OR)*100 percent less than in the reference category, or the odds of the result is reduced by (1-OR)*100 percent if the factor value increases by one point on the scale (quantitative factor). If the CI is 1.00, the factor is not related to the result.*

* *Adjusted regression analysis is limited to statistically significant factors only, as well as key socio-demographic characteristics (age and sex) that may have the co-founding effect. Certain statistically significant factors are not included into the adjusted analysis due to the multicollinearity issue.*

RESEARCH ON THE RISKS OF HCV REINFECTION AFTER SUCCESSFUL TREATMENT

In general, the majority of the sporadic cases of HCV recurrence, revealed during the research, were observed among the participants who, after achieving SVR12, had high risks when injecting drugs, practiced sexual contacts in the state of alcohol or drug intoxication, or had surgical interventions due to complications of more intense injection drug use. The experience of participating in activities to prevent HCV reinfection in the framework of social support during treatment was one of statistically significant factors of reducing the risk of HCV reinfection, based on the research results. The relatively low incidence of detectable HCV RNA VL levels after achieving SVR12 and changes in patient behavior, in particular reduction of risky injections and sexual practices, both in the short and long term, prove effectiveness of reinfection prevention services.

Research on the risks of reinfection of the Project's participants at least 48 weeks after their achievement of SVR12 showed sustained positive changes in their behavioral practices, namely, formation of their adherence to safer behaviors. Upon completion of their participation in the Project (12 weeks after treatment completion), 5% of the participants had increased behavioral risks associated with alcohol use; in the research on the risks of HCV reinfection and fibrosis regression, those were 6% (see ***Table 17***). Among active PWID or PWID in remission, the prevalence of risky injection practices, in particular use of non-sterile needled, shared drug preparation devices, or injections in the state of alcohol intoxication was: for participants in the ***research on the risks of reinfection*** – 2%, in the ***research on adherence to HCV treatment and retention in treatment barriers*** – 4%.

At the same time, high-risk sexual behavior 12 weeks after treatment completion among participants in the ***research on the risks of reinfection*** was higher vs. participants in the ***research on adherence to HCV treatment and retention in treatment barriers***.

Among participants in the ***research on the risks of HCV reinfection***, a lower level of awareness about HCV at the stage of the SVR12 achievement test was recorded vs. participants in the ***research on adherence to HCV treatment and retention in treatment barriers***.

TABLE 17. Prevalence of behavioral risks and the awareness level of project participants at the stage of achieving SVR12 and 48 weeks or more thereafter, frequency and %		Research on adherence to HCV infection treatment 12 weeks after treatment completion (N=829)		Research on the risks of HCV reinfection at least 48 weeks after achieving SVR12 (N=456)	
		N	%	N	%
Alcohol addiction*	AUDIT≤7 points – no risk of alcohol addiction	790	95%	427	94%
	AUDIT 8-15 points – a simple counseling session is needed on reducing alcohol consumption	32	4%	23	5%
	AUDIT 16-19 points – counseling and follow-up required	5	1%	4	1%
	AUDIT≥20 points – referral to a specialist for diagnosis and treatment is required	2	0%	2	0%
	Total	829	100%	456	100%
Presence of high-risk injection practices: use of non-sterile needles, shared equipment for preparation of drugs, or injections in the state of alcohol intoxication (for active PWID or PWID in remission)**	Yes	25	4%	6	2%
	No	631	96%	344	98%
	Total	656	100%	350	100%
Anal or vaginal sex without a condom with partners from high-risk groups: casual or commercial partners, PWID partners, partners with HIV (for those who had sex during the period**)	Yes	46	8%	65	17%
	No	554	92%	315	83%
	Total	600	100%	380	100%
Sexual contacts in the state of alcohol intoxication (for those who had sexual contacts during this period**)	Yes	24	4%	60	16%
	No	576	96%	320	84%
	Total	600	100%	380	100%
Other risks: contact with someone else's blood, tattoo, piercing with non-sterile instruments, use of other people's personal hygiene items****	Yes	29	3%	38	8%
	No	800	97%	418	92%
	Total	829	100%	456	100%
Awareness level about HCV*	Insufficient awareness about HCV	315	38%	277	61%
	Correctly answered all the 10 questions about HCV transmission and prevention	514	62%	179	39%
	Total	**829**	**100**	**456**	**100**

* *Estimated at the time of the research.*

** *In the research on adherence to HCV infection treatment and retention barriers, they were asked about risks present in the past 3 months before the interview, while in the research on the risk of HCV reinfection and fibrosis regression – since the time the treatment was completed till the interview.*

*** *In the research on adherence to HCV infection treatment and retention barriers, they were asked about risks present in the past month before the interview, while in the research on the risk of HCV reinfection and fibrosis regression – since the time the treatment was completed till the interview.*

INVESTIGATIONS OF CASES OF DETECTABLE HCV RNA LEVELS 48 WEEKS AFTER TREATMENT OF HEPATITIS C VIRUS (ACHIEVEMENT OF SVR12)

Out of the 456 project participants involved into the research on the risk of reinfection, 15 (3%) had a detectable HCV RNA viral load at least 48 weeks after their achievement of SVR12.

Cases of detectable HCV RNA were mostly observed among active PWID (35 cases per 1,000 patient-years of follow-up), PWID in remission for 6 to 12 months (33 cases per 1,000 patient-years of follow-up), and PWID partners (30 cases per 1,000 patient-years of follow-up) (see ***Table 18***). There were no cased of detectable HCV RNA among SWs and MSM.

15 cases
of detectable HCV RNA levels 48 and more weeks after achievement of SVR12

20 cases per **1000** patient-years of follow-up

TABLE 18. Prevalence AND incidence of cases of HCV RNA detection, by key populations

	Detectable HCV RNA				Total patient-years of follow-up from the moment of HCV RNA testing, IU/ml (12th week after treatment completion) till repeated HCV testing within the research	Incidence of cases of **HCV RNA detection**, number of cases per 1,000 patient-years of follow-up
	Yes		No			
	N	%	N	%		
PWID, active	2	5.4%	35	94.6%	57.73	34.6
PWID in remission for up to 6 months	1	3.3%	29	96.7%	45.94	21.8
PWID in remission for 6 to 12 months	2	5.1%	37	94.9%	61.53	32.5
PWID in remission for more than 12 months	7	2.9%	235	97.1%	403.15	17.4
PWID on ST	1	3.3%	29	96.7%	47.95	20.9
MSM	0	0.0%	20	100%	29.95	0.0
PWID partner	2	5.1%	37	94.9%	66.54	30.1
SWs	0	0.0%	19	100%	28.2	0.0
Total	**15**	**3%**	**441**	**97%**	**741.0**	**20.2**

Out of the 15 participants who had detectable viral load of HCV RNA at least 48 weeks after achievement of SVR12:

- 4 patients showed a changed genotype;
- 1 patient – change of genotype 1 subtype – from 1b to 1a;
- 6 patients did not show changes in genotypes or subtypes;
- for 4 patients it was not possible to establish the genotype after detecting HCV RNA VL in blood plasma due to the low level of viral load and limitation of the laboratory equipment used for the testing – the low analytical sensitivity of the test kits to determine HCV genotype.

Thus, it can be stated that HCV reinfection was reported in 5 patients, who showed a change in the HCV genotype/subtype. In 10 other patients, in the absence of further laboratory data, it is only possible to state possible HCV reinfection.

TABLE 19.
Comparison of the HCV genotype before the start of treatment and within the investigation of reinfection cases

	Result of HCV genotyping in the context of the research on the risk of reinfection			**Total**
Result of HCV RNA genotyping before treatment	Genotype 1	Genotype 3	Not typeable	
Genotype 1	4	**3**	3	**10**
Genotype 3	**1**	3	1	**5**
Total	**5**	**6**	**4**	**15**

Based on results of the two-dimensional regression analysis, the key risk factors for possible HCV reinfection include presence of risky injection practices following SVR12 achievement (use of non-sterile syringes, shared drug preparation devices, or injections in the state of alcohol intoxication, HR=10.97, 95% CI: 1.30-92.50); sexual contacts in the state of alcohol/drug intoxication during this period (HR=4.14; 95% CI: 1.36-12.61); presence of risks associated with shared use of personal items and services for manicure and tattoo salons with damage to skin and mucous membranes during this period (HR=3.77; 95% CI: 1.12-12.72); presence of surgical interventions during this period (HR=8.60; 95% CI: 2.72-27.13), which may be due to more active injection practices (see ***Table 20***). In the unadjusted analysis, participants in the research who were members of non-governmental organizations in the field of HIV/HCV prevention had a higher risk of HCV reinfection after achieving SVR12 (HR=3.16; 95% CI: 1.05-9.53); this may be due to the fact that such participants were more likely to practice risky behavior. Sessions held for prevention of HCV reinfection within the treatment resulted in reduction in the risk of reinfection by 88% (HR=0.22; 95% CI: 0.06-0.83).

In the adjusted regression analysis by age, sex, and risky practices, only two factors had statistically significant differences with regard to cases of probable HCV reinfection after successful treatment: presence of risky injection practices after achievement of SVR12 (adjusted HR=24.87; 95% CI: 2.54-243.44) and presence of surgical interventions during this period (adjusted HR=7.62; 95% CI: 2.03-28.62), which may be due to more active injection behavior of the patients, which made necessary surgical care.

TABLE 20.
FACTORS OF HCV REINFECTION, MULTILEVEL COX REGRESSIONS
(among all the participants of the research on HCV reinfection, N=456)

		Detectable HCV RNA				OR (95% CI)	Adjusted OR (95% CI)
		Yes		No			
		N	%	N	%		
Sex	Male	13	4%	322	96%	2.29 (0.51-10.28)	1.89 (0.39-9.10)
	Female	2	2%	119	98%	ref.	ref.
Age	≤35 y.o.	1	2%	51	98%	0.59 (0.08-4.57)	0.86 (0.11-7.04)
	>36 y.o.	14	4%	390	97%	ref.	ref.
Employment	Work and/or study	11	3%	315	97%	0.99 (0.31-3.16)	-
	Do not study and do not work	4	3%	126	97%	ref.	-
Education	Completed secondary or lower	4	4%	94	96%	1.89 (0.47-7.64)	-
	Secondary vocational or incomplete higher	7	3%	201	97%	1.53 (0.44-5.27)	-
	Higher (Bachelor, Master)	4	3%	145	97%	ref.	-
Marital status	Married or an unregistered couple (live with a regular partner)	10	3%	318	97%	0.91 (0.28-2.92)	-
	Not married and have no regular partner	4	3%	119	97%	ref.	-
Individual monthly income	≤UAH 3,000	4	3%	122	97%	1.37 (0.41-4.61)	-
	> UAH 3,000	8	3%	276	97%	ref.	-
The median level of alcohol addiction based on AUDIT (IQR)		0 (6)		0 (1)		1.12 (1.00-1.26)	-
Injection drug use in the last 30 days (active PWID)	Yes	1	10%	9	90%	2.51 (0.29-21.54)	-
	No	14	3%	432	97%	ref.	-
Presence of risky injection practices after achieving SVR12 (use of non-sterile needles, shared equipment for preparation of drugs, or injections in the state of alcohol intoxication)	Yes	1	17%	5	83%	**10.97 (1.30-92.50)**	**24.87 (2.54-243.44)**
	No	14	3%	436	97%	ref.	ref.
Sexual contacts without a condom after achievement of SVR12	Yes	7	4%	183	96%	1.16 (0.41-3.28)	-
	No	8	3%	258	97%	ref.	-
Sexual contacts with high-risk group partners after reaching SVR12 (PWID, MSM, HIV+, random or commercial partners)	Yes	4	3%	127	97%	0.89 (0.28-2.81)	-
	No	11	3%	314	97%	ref.	-
Sexual contacts in the state of alcohol/drug intoxication after achievement of SVR12	Yes	5	8%	55	92%	**4.14 (1.36-12.61)**	2.88 (0.82-10.09)
	No	10	3%	386	98%	ref.	ref.

TABLE 20.
FACTORS OF HCV REINFECTION, MULTILEVEL COX REGRESSIONS
(among all the participants of the research on HCV reinfection, N=456)

		Detectable HCV RNA				OR (95% CI)	Adjusted OR (95% CI)
		Yes		No			
		N	%	N	%		
Other risks after achievement of SVR12: contact with someone else's blood, tattoo, piercing with non-sterile instruments, use of other people's personal items	Yes	4	11%	34	90%	**3.77 (1.12-12.72)**	1.95 (0.50-7.70)
	No	11	3%	407	97%	ref.	ref.
CLDQ – the general Quality of Life Index for patients with chronic liver diseases (IQR)		5.8 (1.0)		6.1 (1.3)		0.87 (0.51-1.47)	-
Member of a non-governmental organization providing harm reduction services	Yes	7	6%	119	94%	3.16 (1.05-9.53)	2.52 (0.67-9.52)
	No	8	2%	322	98%	ref.	ref.
Attending sessions on reinfection prevention during treatment	Attended	12	3%	425	97%	0.22 (0.06-0.83)	0.74 (0.13-4.33)
	Did not attend	3	16%	16	84%	ref.	ref.
Key population according to data provided by HCFs (at the time of the start of treatment)	PWID, active	2	5%	35	95%	2.79 (0.37-20.95)	-
	PWID in remission	10	3%	301	97%	1.17 (0.25-5.45)	-
	PWID on ST	1	3%	29	97%	1.46 (0.13-16.68)	-
	Other (PWID partners, SWs, MSM)	2	3%	76	97%	ref.	-
Duration of HCV treatment	12 weeks	13	4%	348	96%	0.64 (0.14-3.06)	-
	16 or 24 weeks	2	2%	93	98%	ref.	-
HCV treatment regimen	SOF+Peg-IFN+RBV	13	4%	314	96%	1.65 (0.36-7.51)	-
	SOF+RBV or SOF/DCV or SOF+DCV+RBV	2	2%	127	98%	ref.	-
HCV genotype before treatment	Genotype 1	10	5%	190	95%	ref.	-
	Genotype 3	5	2%	218	98%	5.03 (0.17-1.50)	-
	Another genotype / not detected	0	0%	29	100%	NP	-
The grade of fibrosis before treatment	F3-F4	13	4%	350	96%	1.54 (0.34-6.91)	-
	F1-F2	2	2%	91	98%	ref.	-
History of pegIFN+RBV treatment	Yes	3	5%	53	95%	1.88 (0.51-6.93)	-
	No	12	3%	388	97%	ref.	-
Body mass index at the time of the research (IQR)		22.5 (4.1)		24.5 (4.9)		0.92 (0.79-1.06)	-

TABLE 20.
FACTORS OF HCV REINFECTION, MULTILEVEL COX REGRESSIONS
(among all the participants of the research on HCV reinfection, N=456)

		Detectable HCV RNA				OR (95% CI)	Adjusted OR (95% CI)
		Yes		No			
		N	%	N	%		
HBV at the time of the research	Yes	1	4%	23	96%	0.88 (0.11-7.09)	-
	No	14	3%	418	97%	ref.	-
Diabetes mellitus at the time of the research	Yes	0	0%	12	100%	NP	-
	No	15	3%	429	97%	ref.	-
History of TB at the time of the research	Yes	2	2%	96	98%	0.59 (0.13-2.64)	-
	No	13	4%	345	96%	ref.	-
CVD at the time of the research	Yes	0	0%	24	100%	NP	-
	No	15	4%	417	97%	ref.	-
Chronic kidney disease at the time of the study	Yes	0	0%	19	100%	NP	-
	No	15	3%	422	97%	ref.	-
Blood transfusion at the time of the research	Yes	1	100%	0	0%	NP	-
	No	14	3%	441	97%	ref.	-
Surgical interventions at the time of the research	Yes	5	15%	29	85%	**8.60 (2.72-27.13)**	**7.62 (2.03-28.62)**
	No	10	2%	412	98%	ref.	ref.
HIV infection at the time of the research	Yes	13	4%	342	96%	0.88 (0.19-4.12)	-
	No	2	2%	99	98%	ref.	-

HR = hazard ratio.

CI = confidence interval.

IQR = inter-quartile range, the difference between the 75 and 25 percentiles.

ref. = reference category.

NP = no possibility to calculate the hazard ratio because of the zero values (no event in a certain category).

*Interpretation: HR>1.00, this was a positive ratio, the number of times the chances for the result in a particular group vs the reference category were higher (categorical factor), or how many times chances for the result increase if the factor value increases by one point on the scale (quantitative factor). HR<1.00, this was a negative ratio, the odds of the result in a certain group is (1-HR)*100 percent less than in the reference category, or the odds of the result is reduced by (1-HR)*100 percent if the factor value increases by one point on the scale (quantitative factor). If the HR is 1.00, the factor is not related to the result.*

* *Adjusted regression analysis is limited to statistically significant factors only, as well as key socio-demographic characteristics (age and sex) that may have the co-founding effect.*

FIBROSIS REGRESSION RESEARCH

According to research, SVR12 achievement significantly increases likelihood of improved liver status. The Project participants are no exception, most patients had fibrosis regression – a change from florid fibrosis (F3-F4) to F1-F2 – after 48 or more weeks after achieving SVR12. However, the Project participants who had HIV infection, previous experience of HCV treatment without DAAs (pegIFN+RBV), and/or another HCV genotype but for the first and second ones had a higher risk of absence of fibrosis regression one year after achieving SVR12.

BASED ON THE APRI METHOD

Of the 350 participants in the liver fibrosis regression research, 348 patients received laboratory data to assess the degree of liver fibrosis by the APRI method at the time of the fibrosis regression research. Of these, the overwhelming majority (87%) had indolent fibrosis (F1-F2) by APRI indicators at least 48 weeks after achieving SVR12.

In general, the incidence of fibrosis regression by the APRI was 383 cases per 1,000 patient-years of follow-up (see ***Table 21***). The replacement of florid fibrosis with indolent one was less frequently observed among PWID in remission for less than 6 months (367 cases per 1,000 patient-years of follow-up) and SWs (368 cases per 1,000 patient-years of follow-up).

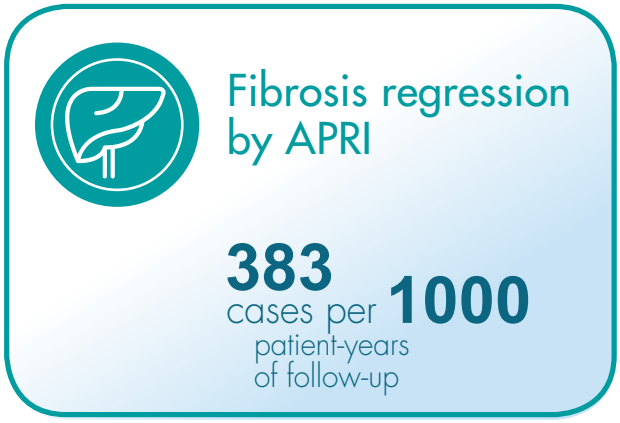


TABLE 21.
APRI-based prevalence and incidence of fibrosis regression, by key populations
(among all the participants in the fibrosis regression research having the data for APRI, N=348)

	Indolent fibrosis (F1-F2) by APRI at the time of the research on fibrosis regression cases				Total patient-years of follow-up from the achievement of SVR12 to the degree of fibrosis tests in the framework of the repeated research	Incidence of fibrosis regression by APRI, number of cases per 1,000 patient-years of follow-up
	Yes		No			
	N	%	N	%		
PWID, active	25	83%	5	17%	64.1	390.0
PWID in remission for up to 6 months	22	81%	5	19%	59.9	367.3
PWID in remission for 6 to 12 months	21	88%	3	13%	53.2	394.7
PWID in remission for more than 12 months	163	86%	27	14%	436.6	373.3
PWID on ST	17	94%	1	6%	39.3	432.6
MSM	13	93%	1	7%	33.9	383.5
PWID partner	29	97%	1	3%	68.4	424.0
SWs	12	80%	3	20%	32.6	368.1
Total	**302**	**87%**	**46**	**13%**	**788**	**383.2**

In the two-dimensional regression analysis, the following factors impacted the APRI-based statistically significant association with fibrosis regression (see ***Table 22***):

- Those participants who received harm reduction services from non-governmental organizations providing HIV and HCV prevention services had a better chance of improving their liver status (HR=1.42; 95% CI: 1.07-1.88).
- The history of pegIFN+RBV treatment reduced the likelihood of liver fibrosis regression by 52% (OR=0.48; 95% CI: 0.32-0.72).
- Patients with HIV had a lower likelihood of liver fibrosis regression (HR=0.50; 95% CI: 0.36-0.69).
- The fact of having neither the first nor the third HCV genotypes reduced the chance of fibrosis regression by 42% vs. the first HCV genotype (HR=0.58; 95% CI: 0.35-0.96).
- Frequent visits to the physician to assess the liver status after HCV treatment completion was most commonly observed for patients who did not have fibrosis regression (e.g. HR=0.51; 95% CI: 0.37-0.71 for the patients who visited the physician 2 or 3 times a year vs. those who did not visit the physician after treatment completion). Probably, this was due to the fact that patients with more severe fibrosis were more likely to seek medical care.

In the adjusted regression analysis by socio-demographic characteristics, the key population, and the frequency of visits to the physician after completion of HCV infection treatment the key risk factors for no fibrosis regression by APRI are as follows: presence of HIV infection (adjusted HR=0.48; 95% CI: 0.33-0.70) and pegIFN+RBV treatment history (adjusted HR=0.48; 95% CI: 0.31-0.75).

No statistically significant association between the likelihood of APRI-based fibrosis regression and the level of alcohol consumption, as well as other behavioral risks, including injection drug use, was found.

TABLE 22.
APRI-BASED FIBROSIS REGRESSION FACTORS, MULTILEVEL COX REGRESSIONS (among all the participants in the fibrosis regression research having the data for APRI, N=348)

			Indolent fibrosis (F1-F2) by APRI at the time of the repeated research				OR (95% CI)	Adjusted OR (95% CI)
			Yes		No			
			N	%	N	%		
Sex	Male		229	87%	34	13%	1.02 (0.77-1.36)	0.97 (0.71-1.34)
	Female		73	86%	12	14%	ref.	ref.
Age	≤35 y.o.		32	91%	3	9%	1.10 (0.75-1.62)	1.67 (0.72-1.64)
	>36 y.o.		270	86%	43	14%	ref.	ref.
Employment	Work and/or study		214	87%	31	13%	0.83 (0.64-1.09)	0.81 (0.60-1.10)
	Do not study and do not work		88	85%	15	15%	ref.	ref.
Education	Completed secondary or lower		71	90%	8	10%	**1.56 (1.12-2.18)**	**1.67 (1.14-2.43)**
	Secondary vocational or incomplete higher		134	84%	26	16%	1.31 (1.00-1.72)	**1.54 (1.14-2.09)**
	Higher (Bachelor, Master)		96	89%	12	11%	ref.	ref.
Marital status	Married or an unregistered couple (live with a regular partner)		226	89%	29	11%	1.13 (0.86-1.48)	-
	Not married and have no regular partner		74	81%	17	19%	ref.	-
Individual monthly income	≤UAH 3,000		81	83%	17	17%	1.15 (0.87-1.51)	-
	> UAH 3,000		192	89%	25	12%	ref.	-
The level of alcohol addiction based on AUDIT	0-7 points (no addiction)		227	57%	175	43%	0.98 (0.57-1.67)	1.47 (0.84-2.56)
	8+ points (addiction)		8	31%	18	69%	ref.	ref.
Injection drug use in the last 30 days		Yes	5	63%	3	38%	0.70 (0.27-1.67)	-
		No	297	87%	43	13%	ref.	-
Presence of risky injection practices after achieving SVR12 (use of non-sterile needles, shared equipment for preparation of drugs, or injections in the state of alcohol intoxication)		Yes	1	25%	3	75%	0.45 (0.06-3.26)	-
		No	301	88%	43	13%	ref.	-
Sexual contacts without a condom after achievement of SVR12		Yes	138	91%	13	9%	1.00 (0.79-1.28)	-
		No	164	83%	33	17%	ref.	-
Sexual contacts with high-risk group partners after reaching SVR12 (PWID, MSM, HIV+, random or commercial partners)		Yes	94	91%	9	9%	1.20 (0.93-1.54)	-
		No	208	85%	37	15%	ref.	-
Sexual contacts in the state of alcohol/drug intoxication after achievement of SVR12		Yes	30	71%	12	29%	1.40 (0.93-2.06)	-
		No	272	89%	34	11%	ref.	-
Other risks after achievement of SVR12: contact with someone else's blood, tattoo, piercing with non-sterile instruments, use of other people's personal hygiene items		Yes	24	89%	3	11%	1.17 (0.76-1.80)	-
		No	278	87%	43	13%	ref.	-

TABLE 22.
APRI-BASED FIBROSIS REGRESSION FACTORS, MULTILEVEL COX REGRESSIONS (among all the participants in the fibrosis regression research having the data for APRI, N=348)

		Indolent fibrosis (F1-F2) by APRI at the time of the repeated research				OR (95% CI)	Adjusted OR (95% CI)
		Yes		No			
		N	%	N	%		
CLDQ – the general Quality of Life Index for patients with chronic liver diseases		6.1 (1.2)		5.2 (2.0)		1.06 (0.93-1.21)	1.07 (0.93-1.24)
Member of a non-governmental organization providing harm reduction services	Yes	78	92%	7	8%	**1.42 (1.07-1.88)**	1.28 (0.93-1.76)
	No	224	85%	39	15%	ref.	ref.
Attending sessions on reinfection prevention during treatment	Attended	289	87%	45	13%	0.87 (0.49-1.54)	-
	Did not attend	13	93%	1	7%	ref.	-
The key population by clinical data	PWID, active	25	83%	5	17%	1.34 (0.80-2.25)	1.24 (0.70-2.19)
	PWID in remission	206	86%	35	15%	0.76 (0.55-1.04)	0.78 (0.55-1.10)
	PWID on ST	17	94%	1	6%	1.09 (0.62-1.91)	1.23 (0.84-2.56)
	Other (PWID partners, SWs, MSM)	54	92%	5	9%	ref.	ref.
Duration of HCV treatment	12 weeks	247	89%	30	11%	0.84 (0.62-1.16)	-
	16 or 24 weeks	55	78%	16	23%	ref.	-
HCV treatment regimen	SOF+Peg-IFN+RBV	227	91%	23	9%	0.97 (0.73-1.28)	-
	SOF+RBV or SOF/DCV or SOF+DCV+RBV	75	77%	23	24%	ref.	-
HCV genotype before treatment	Genotype 1	132	86%	21	14%	ref.	-
	Genotype 3	150	89%	18	11%	1.06 (0.83-1.35)	0.94 (0.73-1.76)
	Another genotype / not detected	19	79%	5	21%	**0.58 (0.35-0.96)**	0.68 (0.40-1.20)
History of pegIFN+RBV treatment	Yes	30	70%	13	30%	**0.48 (0.32-0.72)**	**0.48 (0.31-0.75)**
	No	272	89%	33	11%	ref.	ref.
Body mass index at the time of the research		24.6 (5.0)		24.5 (5.5)		0.99 (0.96-1.02)	-
HBV at the time of the research	Yes	12	80%	3	20%	0.82 (0.44-1.54)	-
	No	290	87%	43	13%	ref.	-
Diabetes mellitus at the time of the research	Yes	8	73%	3	27%	1.22 (0.59-2.52)	-
	No	294	87%	43	13%	ref.	-
History of TB at the time of the research	Yes	67	86%	11	14%	0.94 (0.71-1.25)	-
	No	235	87%	35	13%	ref.	-
CVD at the time of the research	Yes	15	83%	3	17%	1.11 (0.64-1.92)	-
	No	287	87%	43	13%	ref.	-

TABLE 22.
APRI-BASED FIBROSIS REGRESSION FACTORS, MULTILEVEL COX REGRESSIONS (among all the participants in the fibrosis regression research having the data for APRI, N=348)

		Indolent fibrosis (F1-F2) by APRI at the time of the repeated research				OR (95% CI)	Adjusted OR (95% CI)
		Yes		No			
		N	%	N	%		
Chronic kidney disease at the time of the study	Yes	13	81%	3	19%	0.85 (0.46-1.57)	-
	No	289	87%	43	13%	ref.	-
Blood transfusion at the time of the research	Yes	0	0%	0	0%	NP	-
	No	302	87%	46	13%	ref.	-
Surgical interventions at the time of the research	Yes	20	80%	5	20%	1.22 (0.77-1.95)	-
	No	282	87%	41	13%	ref.	-
HIV infection at the time of the research	Yes	237	87%	36	13%	**0.50 (0.36-0.69)**	**0.48 (0.33-0.70)**
	No	65	87%	10	13%	ref.	ref.
Frequency of attending the physician to assess the general health status after completing the treatment	Every month or more frequently	14	82%	3	18%	1.12 (0.59-2.10)	-
	Every 2-3 months	53	78%	15	22%	0.71 (0.46-1.08)	-
	2-3 times a year	79	90%	9	10%	0.73 (0.52-1.02)	-
	Once a year	43	86%	7	14%	0.72 (0.49-1.06)	-
	Less frequently than once a year	25	89%	3	11%	0.78 (0.50-1.23)	-
	Did not visit the physician during this period	84	90%	9	10%	ref.	-
Frequency of attending the physician to assess the liver status after completing the treatment	Every month or more frequently	8	89%	1	11%	1.00 (0.45-2.20)	1.72 (0.71-4.17)
	Every 2-3 months	61	79%	16	21%	**0.65 (0.44-0.96)**	0.70 (0.45-1.10)
	2-3 times a year	117	88%	16	12%	**0.51 (0.37-0.71)**	**0.63 (0.44-0.90)**
	Once a year	35	85%	6	15%	**0.47 (0.30-0.73)**	**0.56 (0.36-0.88)**
	Less frequently than once a year	15	100%	0	0%	0.82 (0.47-1.47)	0.74 (0.39-1.40)
	Did not visit the physician during this period	62	90%	7	10%	ref.	ref.

HR = hazard ratio.
CI = confidence interval.
IQR = inter-quartile range, the difference between the 75 and 25 percentiles.
ref. = reference category.
NP = no possibility to calculate the hazard ratio because of the zero values (no event in a certain category).
*Interpretation: HR>1.00, this was a positive ratio, the number of times the chances for the result in a particular group vs the reference category were higher (categorical factor), or how many times chances for the result increase if the factor value increases by one point on the scale (quantitative factor). HR<1.00, this was a negative ratio, the odds of the result in a certain group is (1-HR)*100 percent less than in the reference category, or the odds of the result is reduced by (1-HR)*100 percent if the factor value increases by one point on the scale (quantitative factor). If the HR is 1.00, the factor is not related to the result.*

* *Adjusted regression analysis is limited to statistically significant factors only, as well as key socio-demographic characteristics (age and sex) that may have the co-founding effect.*

BASED ON THE FIB-4 METHOD

In contrast to the APRI-based data, prevalence of fibrosis regression by FIB-4 was higher. Of the 350 participants in the research, 348 received their laboratory data to assess the degree of fibrosis with the FIB4 method at the time of the research. Of these, 94% had indolent fibrosis (F1-F2) by FIB4 indicators at least 48 weeks after achieving SVR12.

Incidence of fibrosis regression by the FIB4 was 414 cases per 1,000 patient-years of follow-up (see Table 23). Among the key populations, replacement of florid fibrosis with indolent one based on FIB4 was less frequently observed among PWID in remission for less more 12 months (399 cases per 1,000 patient-years of follow-up) and MSM (384 cases per 1,000 patient-years of follow-up).

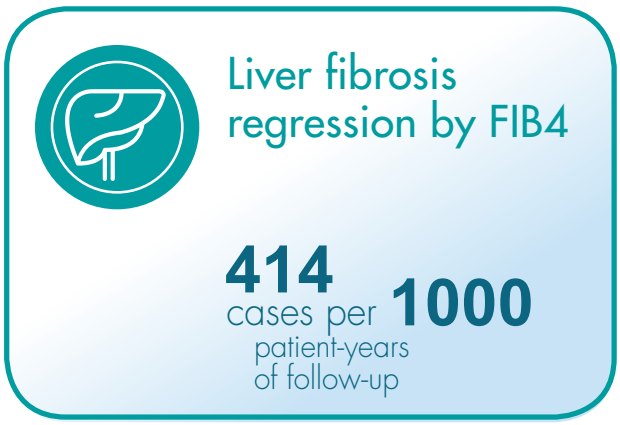


TABLE 23. FIB4-based prevalence and incidence of fibrosis regression, by key populations *(among all the participants in the fibrosis regression research having the data for FIB4, N=348)*	Indolent fibrosis (F1-F2) by FIB4 at the time of the repeated research				Total patient-years of follow-up from the achievement of SVR12 to the degree of fibrosis tests in the framework of the repeated research	Incidence of fibrosis regression by FIB4, number of cases per 1,000 patient-years of follow-up
	Yes		No			
	N	%	N	%		
PWID, active	28	93%	2	7%	64.1	436.8
PWID in remission for up to 6 months	26	96%	1	4%	59.9	434.1
PWID in remission for 6 to 12 months	24	100%	0	0%	53.2	451.1
PWID in remission for more than 12 months	174	92%	16	8%	436.3	398.8
PWID on ST	18	100%	0	0%	39.3	458.0
MSM	13	93%	1	7%	33.9	383.5
PWIDs' partners	29	97%	1	3%	68.4	424.0
SWs	14	93%	1	7%	32.6	429.4
Total	**326**	**94%**	**22**	**6%**	**788**	**413.9**

As with APRI indicators, in the two-dimensional regression analysis, FIB4 fibrosis regression factors were a low education level (vs. higher education, HR=1.60, 95% CI: 1.16-2.21 for completed secondary education and HR=1.42; 95% CI: 1.09-1.85 for secondary vocational or incomplete higher education); the fact of having not the first and not the third HCV genotype (HR=0.50; 95% CI: 0.30-0.84) vs. the first HCV genotype); pegIFN+RBV treatment history (HR=0.53; 95% CI: 0.37-0.77); presence of HIV infection (HR=0.54; 95% CI: 0.39-0.74); and frequent visits to the physician to assess the liver status after HCV treatment completion (e.g. HR=0.51; 95% CI: 0.37-0.71 for the patients who visited the physician 2 or 3 times a year vs. those who did not visit the physician after treatment completion) (see ***Table 24***).

In the adjusted regression analysis by socio-demographic characteristics, the key population, the frequency of visits to the physician, and the quality of life associated with health, the key risk factors for no fibrosis regression by FIB4 are presence of HIV infection (adjusted HR=0.52; 95% CI: 0.37-0.75), pegIFN+RBV treatment history (adjusted HR=0.52; 95% CI: 0.35-0.79), and other HCV genotypes, except for the first and third ones (adjusted HR=0.54; 95% CI: 0.32-0.92).

TABLE 24.
FIB4-BASED FIBROSIS REGRESSION FACTORS, MULTILEVEL COX REGRESSIONS (among all the participants in the fibrosis regression research having the data for FIB4, N=348)

		Indolent fibrosis (F1-F2) by FIB4 at the time of the repeated research				OR (95% CI)	Adjusted OR (95% CI)
		Yes		No			
		N	%	N	%		
Sex	Male	250	95%	13	5%	1.08 (0.82-1.43)	1.02 (0.75-1.39)
	Female	76	89%	9	11%	ref.	ref.
Age	≤35 y.o.	34	97%	1	3%	1.07 (0.74-1.55)	1.02 (0.69-1.51)
	> 36 y.o.	292	93%	21	7%	ref.	ref.
Employment	Work and/or study	232	95%	13	5%	0.86 (0.66-1.10)	0.86 (0.64-1.14)
	Do not study and do not work	94	91%	9	9%	ref.	ref.
Education	Completed secondary or lower	76	96%	3	4%	**1.60 (1.16-2.21)**	**1.65 (1.15-2.37)**
	Secondary vocational or incomplete higher	150	94%	10	6%	**1.42 (1.09-1.85)**	**1.58 (1.18-2.11)**
	Higher (Bachelor, Master)	99	92%	9	8%	ref.	ref.
Marital status	Married or an unregistered couple (live with a regular partner)	242	95%	13	5%	1.09 (0.84-1.41)	-
	Not married and have no regular partner	82	90%	9	10%	ref.	-
Individual monthly income	≤UAH 3,000	90	92%	8	8%	1.18 (0.91-1.54)	-
	> UAH 3,000	205	95%	12	6%	ref.	-
The level of alcohol addiction based on AUDIT	0-7 points (no addiction)	306	94%	19	6%	1.14 (0.70-1.86)	-
	8+ points (addiction)	20	87%	3	13%	ref.	-
Injection drug use in the last 30 days	Yes	8	100%	0	0%	1.03 (0.50-2.11)	-
	No	318	94%	22	7%	ref.	-
Presence of risky injection practices after achieving SVR12 (use of non-sterile needles, shared equipment for preparation of drugs, or injections in the state of alcohol intoxication)	Yes	4	100%	0	0%	NP	-
	No	322	94%	22	6%	ref.	-

TABLE 24.
FIB4-BASED FIBROSIS REGRESSION FACTORS, MULTILEVEL COX REGRESSIONS (among all the participants in the fibrosis regression research having the data for FIB4, N=348)

		Indolent fibrosis (F1-F2) by FIB4 at the time of the repeated research				OR (95% CI)	Adjusted OR (95% CI)
		Yes		No			
		N	%	N	%		
Sexual contacts without a condom after achievement of SVR12	Yes	148	98%	3	2%	1.00 (0.79-1.27)	-
	No	178	90%	19	10%	ref.	-
Sexual contacts with high-risk group partners after reaching SVR12 (PWID, MSM, HIV+, random or commercial partners)	Yes	98	95%	5	5%	1.14 (0.90-1.45)	-
	No	228	93%	17	7%	ref.	-
Sexual contacts in the state of alcohol/drug intoxication after achievement of SVR12	Yes	39	93%	3	7%	1.71 (1.20-2.43)	-
	No	287	94%	19	6%	ref.	-
Other risks after achievement of SVR12: contact with someone else's blood, tattoo, piercing with non-sterile instruments, use of other people's personal hygiene items	Yes	25	93%	2	7%	1.11 (0.73-1.69)	-
	No	301	94%	20	6%	ref.	-
CLDQ – the general Quality of Life Index for patients with chronic liver diseases		6.1 (1.3)		5.1 (1.9)		1.06 (0.93-1.20)	1.04 (0.91-1.20)
Member of a non-governmental organization providing harm reduction services	Yes	79	93%	6	7%	1.28 (0.97-1.68)	-
	No	247	94%	16	6%	ref.	-
Attending sessions on reinfection prevention during treatment	Attended	312	93%	22	7%	NP	-
	Did not attend	14	100%	0	0%	ref.	-
The key population by clinical data	PWID, active	28	93%	2	7%	1.48 (0.90-2.43)	1.45 (0.85-2.49)
	PWID in remission	224	93%	17	7%	0.81 (0.59-1.10)	0.86 (0.61-1.20)
	PWID on ST	18	100%	0	0%	1.11 (0.64-1.91)	1.34 (0.73-2.44)
	Other (PWID partners, SWs, MSM)	56	95%	3	5%	ref.	ref.
Duration of HCV treatment	12 weeks	264	95%	13	5%	0.81 (0.60-1.09)	-
	16 or 24 weeks	62	87%	9	13%	ref.	-
HCV treatment regimen	SOF+Peg-IFN+RBV	243	97%	7	3%	0.95 (0.73-1.24)	-
	SOF+RBV or SOF/DCV or SOF+DCV+RBV	83	85%	15	15%	ref.	-

TABLE 24.
FIB4-BASED FIBROSIS REGRESSION FACTORS, MULTILEVEL COX REGRESSIONS (among all the participants in the fibrosis regression research having the data for FIB4, N=348)

		Indolent fibrosis (F1-F2) by FIB4 at the time of the repeated research				OR (95% CI)	Adjusted OR (95% CI)
		Yes		No			
		N	%	N	%		
HCV genotype before treatment	Genotype 1	144	94%	9	6%	ref.	-
	Genotype 3	162	96%	6	4%	1.06 (0.84-1.34)	0.95 (0.75-1.21)
	Another genotype / not detected	18	75%	6	25%	**0.50 (0.30-0.84)**	**0.54 (0.32-0.92)**
History of pegIFN+RIB treatment	Yes	35	81%	8	19%	**0.53 (0.37-0.77)**	**0.52 (0.35-0.79)**
	No	291	95%	14	5%	ref.	ref.
Body mass index at the time of the research		24.6 (4.9)		25.9 (5.9)		0.84 (0.46-1.53)	-
HBV at the time of the research	Yes	13	87%	2	13%	0.84 (0.46-1.53)	-
	No	313	94%	20	6%	ref.	-
Diabetes mellitus at the time of the research	Yes	9	82%	2	18%	1.29 (0.65-2.56)	-
	No	317	94%	20	6%	ref.	-
History of TB at the time of the research	Yes	72	92%	6	8%	0.97 (0.73-1.27)	-
	No	254	94%	16	6%	ref.	-
CVD at the time of the research	Yes	14	78%	4	22%	0.93 (0.53-1.62)	-
	No	312	95%	18	6%	ref.	-
Chronic kidney disease at the time of the study	Yes	13	81%	3	19%	0.77 (0.42-1.41)	-
	No	313	94%	19	6%	ref.	-
Blood transfusion at the time of the research	Yes	0	0%	0	0%	NP	-
	No	326	94%	22	6%	ref.	-
Surgical interventions at the time of the research	Yes	20	80%	5	20%	1.23 (0.71-1.79)	-
	No	306	95%	17	5%	ref.	-
HIV infection at the time of the research	Yes	258	95%	15	6%	**0.54 (0.39-0.74)**	**0.52 (0.37-0.75)**
	No	68	91%	7	9%	ref.	ref.

TABLE 24.
FIB4-BASED FIBROSIS REGRESSION FACTORS, MULTILEVEL COX REGRESSIONS (among all the participants in the fibrosis regression research having the data for FIB4, N=348)

		Indolent fibrosis (F1-F2) by FIB4 at the time of the repeated research				OR (95% CI)	Adjusted OR (95% CI)
		Yes		No			
		N	%	N	%		
Frequency of attending the physician to assess the general health status after completing the treatment	Every month or more frequently	15	88%	2	12%	1.13 (0.62-2.08)	-
	Every 2-3 months	61	90%	7	10%	0.79 (0.53-1.18)	-
	2-3 times a year	84	96%	4	5%	0.74 (0.53-1.02)	-
	Once a year	47	94%	3	6%	0.74 (0.51-1.06)	-
	Less frequently than once a year	26	93%	2	7%	0.77 (0.49-1.19)	-
	Did not visit the physician during this period	89	96%	4	4%	ref.	-
Frequency of attending the physician to assess the liver status after completing the treatment	Every month or more frequently	9	100%	0	0%	1.04 (0.49-2.20)	NP
	Every 2-3 months	69	90%	8	10%	0.70 (0.48-1.02)	0.71 (0.47-1.08)
	2-3 times a year	124	93%	9	7%	**0.51 (0.37-0.71)**	**0.59 (0.42-0.83)**
	Once a year	39	95%	2	5%	**0.49 (0.32-0.75)**	**0.57 (0.37-0.88)**
	Less frequently than once a year	15	100%	0	0%	0.83 (0.46-1.48)	NP
	Did not visit the physician during this period	66	96%	3	4%	ref.	ref.

HR = hazard ratio.

CI = confidence interval.

IQR = inter-quartile range, the difference between the 75 and 25 percentiles.

ref. = reference category.

NP = no possibility to calculate the hazard ratio because of the zero values (no event in a certain category).

*Interpretation: HR>1.00, this was a positive ratio, the number of times the chances for the result in a particular group vs the reference category were higher (categorical factor), or how many times chances for the result increase if the factor value increases by one point on the scale (quantitative factor). HR<1.00, this was a negative ratio, the odds of the result in a certain group is (1-HR)*100 percent less than in the reference category, or the odds of the result is reduced by (1-HR)*100 percent if the factor value increases by one point on the scale (quantitative factor). If the HR is 1.00, the factor is not related to the result.*

* *Adjusted regression analysis is limited to statistically significant factors only, as well as key socio-demographic characteristics (age and sex) that may have the co-founding effect.*

DATA LIMITATION

- **Not all Project participants were included into the operational research.** ***The research on adherence to HCV infection treatment and retention in treatment barriers*** began at the second phase of patient enrollment, so participants in the first phase of the Project were not admitted for the research. Since the different stages of patient enrollment were different in the composition of key populations, results of the analysis are not representative for all participants in the HCV infection treatment Project.

- **The limitation of comparison of different OR components.** The research on adherence to HCV infection treatment and retention barriers, the research on the risk of HCV reinfection, and the research on the cases and factors of fibrosis regression include different categories of participants that differ in their socio-demographic and clinical profiles. In contrast to the ***research on adherence to HCV infection treatment and retention barriers***, patients from the first enrollment phase were participants in the ***research on the risk of HCV reinfection*** and the ***research on the cases and factors of fibrosis regression***. They were characterized by a higher level of well-being, and the group did not include patients receiving DAA-based treatment without pegIFN and RBV (SOF/LDV regimen). This limits comparison of the same indicators across the different components of the research, for example, regarding behavioral practices.

- **Limitations of determining the risks of HCV reinfection.** In the ***research on the risk of HCV reinfection***, cases of detectable levels of HCV RNA viral load were considered at least 48 weeks after the patients' reaching SVR12. Reinfection with HCV can be confirmed in cases of replacement of one HCV genotype (or subtype) with another. During the research, it was found that for some of the patients the same genotype (subtype) as they had before the treatment was identified, therefore, considering the diagnostic limitations, these cannot be interpreted with certainty as reinfection cases. These cases were identified as likely HCV reinfection, given the high predictive value of SVR12 as an indicator of HCV infection treatment, and with use of DAAs – as an indicator of complete HCV eradication. If the detected cases of HCV RNA with the same HCV genotype are the result of absence of the long-term effect of hepatitis C treatment, the estimates of the prevalence and incidence of HCV reinfection may be overestimated.

- **Limitation of the definition of fibrosis regression.** At the start of treatment, in most of the research participants the degree of fibrosis was determined with the Fibroscan device, which is more accurate than the APRI and FIB4 index methods. In the framework of the ***fibrosis regression research***, no Fibroscan examination was held. The APRI and FIB4 indicators before the start of HCV infection treatment among the research participants did not always correspond to the degree of liver fibrosis as

determined with the Fibroscan method. The following definition of fibrosis regression was used in the framework of the research data analysis: presence of indolent fibrosis (F1-F2, corresponding to APRI≤0.70 and FIB-4≤3.25) at least 48 weeks after achievement of SVR12 and absence of HCV RNA at the time of the research among all the participant with florid fibrosis (F3-F4) diagnosed at the start of treatment by any method. Given this definition, the estimations of fibrosis regression prevalence and incidence may be somewhat overestimated.

- **Statistical analysis limitations.** Estimation of multidimensional models and determination of adjusted odds ratios and hazard ratios were limited by the small size of the available sample and low prevalence of the result or the control group. On average, inclusion of more than ten factors into the multidimensional models led to the impossibility of evaluating model parameters due to the problem of a large number of zero cells. Due to this, the adjusted effect of all the potential factors could not be estimated. The small size of the sample affected a significant amount of confidence intervals for a number of factors. Since the individual factors strongly correlated with each other, this cause the issue of multicollinearity. The multidimensional analysis included only one of the correlating factors to avoid shifts of parameter estimates. Thus, the joint contribution of a number of factors into the multidimensional models could not be estimated.

CONCLUSIONS AND DISCUSSION

Operational research results have supported high effectiveness of hepatitis C community-based treatment using DAAs for key patient groups in resource-constrained Ukraine. Patients in all the key populations showed a high level of satisfaction with MDT work and with the quality of Project services due to friendly attitude, no stigma or discrimination, comfort, attention to the patient's individual needs and provision of high quality care services.

- **Availability of social support is a critical component of successful HCV infection treatment among key populations.** As results of the research prove, both patients and medical staff recognize social support as an extremely important tool for achieving success in treatment and high adherence (98% of patients completed a full course of treatment).
- As to their general awareness about hepatitis C virus, **patients mostly lacked information about HCV transmission risks**. In patient counseling, there should be a greater focus on this information.
- The low level of welfare and **significant costs of pre-treatment diagnostic tests are the key barriers at the stage of engagement for treatment**.
- **Active PWID are the most vulnerable group among those who took part in the Project.**
- There were only rare cases of HCV RNA detection 48 weeks after SVR12 achievement. **The relatively low incidence of detectable HCV RNA VL levels after achieving SVR12 and changes in patient behavior, in particular reduction of risky injections and sexual practices, both in the short and long term, prove effectiveness of reinfection prevention services.**
- **SVR12 achievement significantly increases likelihood of improved liver status.** Vast majority of patients improved their liver status after HCV eradication.

REPORT ON RESULTS OF THE PROJECT
"Scaling Up Accessible and Effective Hepatitis C Virus Treatment through Community-Based Treatment Model for Most Vulnerable Populations in the Resource-Constrained Ukraine"

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