
# Hepatitis C in Russia: an epidemic of negligence

**The Andrey Rylkov Foundation for Health and Social Justice**

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## Abbreviations

| | |
|---|---|
| AASLD | American Association for the Study of Liver Diseases |
| AHC | Acute hepatitis C |
| AIDS | Acute Immune Deficiency Syndrome |
| ALAT | Alanine aminotransferase |
| ART | Antiretroviral therapy |
| AspAT | Aspartate aminotransferase |
| CDC | Centers for Disease Control and Prevention |
| CHCV | Chronic hepatitis C virus |
| EECA | Eastern Europe and Central Asia |
| EVR | Early virologic response |
| FDA | U.S. Food and Drug Administration |
| FSEP | Federal Service for Execution of Punishment |
| FSMC AIDS | Federal Scientific and Methodological Centre on AIDS Treatment and Prevention (the Federal AIDS Center) |
| HCV | Hepatitis C virus |
| HIV | Human Immunodeficiency Virus |
| ELISA | Enzyme-linked immunosorbent assay |
| IFN | Interferon |
| MoH | Ministry of Health |
| MSM | Men who have sex with men |
| PNP | Priority National Program |
| PCR | Polymerase chain reaction |
| PEG-INF | Pegylated interferon |
| PWID | People who inject drugs |
| RBV | Ribavirin |
| RHRN | All-Russian Harm Reduction Network |
| RNA | Ribonucleic acid |
| SVR | Sustained virologic response |
| UNODC | United Nations Office on Drugs and Crime |
| WHO | World Health Organization |

## Table of contents

## Executive summary

Although the incidence of hepatitis C virus (HCV) in Russia is extremely high, posing one of the biggest threats to the national public health, access to treatment of hepatitis C in the country remains limited. On the one hand, the government acknowledges hepatitis C as a socially significant disease and commits to providing free treatment for those in need, but on the other hand, treatment programs receive minimal funding at the federal and local levels, and the country does not even attempt to lobby for reduced prices for medications. In the absence of a special governmental treatment program, patients have to pay for their treatment, although not many people can actually afford a full course that significantly exceeds an average salary.

Despite the urgency of the problem, Russia has yet to conduct a systematic research that would assess hepatitis C prevalence, treatment needs, availability of medications, legal provisions and the level of access to HCV treatment. Such research is needed if the country wants to harmonize its approaches to achieve exponential growth of access to hepatitis C treatment and optimize its advocacy priorities.

**The aim of this research** is to describe processes around access to HCV treatment in the Russian Federation.

**Research methods:** review of scientific papers, collection of epidemiology data, in-depth interviews held in three regional centers (Yekaterinburg, Barnaul, Togliatti) and at the federal level with patients who started and/or finished hepatitis C treatment (n=21), as well as with doctors who prescribe and manage treatment (n=5) and experts (n=4).

**At least 5 million people in Russia are infected with hepatitis C (approximately 4.4% of the whole adult population), of which, according to various estimates, 1–2 million people urgently need treatment.** Despite the lack of official statistics on HCV prevalence and treatment needs in the population, one can estimate approximate proportions of the problem based on available data. According to the Central Scientific Research Institute of Epidemiology, Russia is home to 5 million people who live with hepatitis C. Even following the most conservative estimates, a total of people who tested positive to hepatitis C antibodies in the country is over 1.5 million. Similar figures (1.1–2 mln people) are reported by the Federal Service for Protection of Consumer Rights and Personal Wellbeing. According to international sources, 20–40% of people with hepatitis C may develop cirrhosis or cancer of the liver, and these patients should be treated in the first place. Already now, 1–2 million people out of the 5 million affected need to start treatment as soon as possible, while others should be treated as their disease progresses. Apart from high HCV prevalence, the spread of chronic hepatitis C is another concern, with figures as high as 40.2 per 100,000 reported for 2010 (a three-fold increase compared to 1999), prevailing in people under 40 years of age.

**Hepatitis C in Russia mostly affects people who inject drugs (PWID), among which, according to the most conservative estimates, as much as 1.3 million people are infected.** Sentinel surveillance data show extreme HCV prevalence rates among PWID, in some cities ranging from 45% to 90% (mid-range estimate – 69%). According to UN Reference Group, estimates of the number of IDUs living with HCV in Russia range from 985,500 to 1,770,250 (2008), with a mid-range estimate of about 1.3 mln (2011).

**According to the Central Scientific Research Institute of Epidemiology, up to 30–40% of Russian patients are infected with hepatitis C genotypes 2 and 3, which better respond to treatment with**

**pegylated interferon and ribavirin.** About 50% are infected with genotype 1b. Genotype determines treatment effectiveness and its outcomes. Patients with genotype 2 and 3 are prescribed 24-week courses of treatment, while genotype 1b requires a 48-week course.

**According to international guidelines, treatment should be provided to all HCV-infected people with detectable virus activity.** To identify clinical indicators and address them properly and in due time, all patients should be offered preliminary examination: an ELISA test (to detect HCV antibodies), a clinical blood analysis (total bilirubin, ALAT, AspAT, total protein, amylase, blood urea nitrogen, glucose, etc.), an ultrasound investigation, RNA tests (qualitative and quantitative), HCV genotype test, puncture biopsy and elastography of the liver.

**Russia doesn't have an integrated registry of patients in need of hepatitis C treatment.** Until now, full clinical examination has not been offered to patients registered in infectious clinics, regardless of the region. As a result, treatment needs have not been assessed on the basis of clinical indications. Russia's system of epidemiological monitoring and surveillance is underdeveloped, which makes it near impossible to realistically evaluate the total number of chronic hepatitis C (CHCV) cases and treatment needs in this respect. Until 2011, Russia's system of monitoring was segmentary and failed to incorporate the whole of laboratory data, so it was difficult to give adequate national estimates related to treatment needs for more than a million of registered HCV patients. To improve the situation, a special Reference Center was created in 2011, tasked with functions of HCV diagnostics, prevention, provision of technical support to the regions in the sphere of disease control, and a situation analysis held on the basis of an integrated computerized patient registry (in several regions this project is still at a pilot stage).

**The main source of funding is the Priority National 'Health' Program that offers HCV treatment for people living with HIV.** Currently, no federal program exists in Russia that would cover clinical examination and diagnostics needed to prescribe treatment to all patients who need it. The main source of funding for hepatitis C treatment of the Priority National 'Health' Program that involves several activities in the field of diagnosis, prevention and treatment of viral hepatitis B and C, but only for people living with HIV. In 2008–2012 Russia allocated 8.4 billion rubles to purchase pegylated interferon, linear interferon and ribavirin, which provided for 18,881 48-week treatment courses with pegylated interferon. In 2012, HCV treatment program was downsized, which led to reduced amounts of procured medications and a 30% decrease in treatment coverage (ITPCru, 2012). Indicators for HCV treatment availability beyond 2012 have not been set, as the national program has yet to be updated, and no short- or long-term plans in this respect are currently available.

**The Priority National 'Health' Program provides treatment to less than 10% of PLHIV who need treatment for Hepatitis C.** Even though people living with HIV is a priority group for this national project, HCV treatment coverage remains extremely low. According to quantitative data published at research websites (as federal-level data is not available), from 2008 to 2011 only 5% of patients with HIV/ HCV co-infection received treatment in Togliatti, and 8% – in Altay region and Yekaterinburg.

**Injecting drug users are excluded from treatment programs.** Low treatment coverage of patients with HIV/HCV co-infection is related to the fact that people who use injecting drugs are often refused treatment. In all the surveyed regions, internal regulations prohibited AIDS Centers from enrolling people with drug dependency into treatment programs. This is common practice in Russia, although such an approach is not based on any scientific evidence. As a result, treatment is not provided to those patients who need it most. When dealing with people who use drugs, doctors usually offer them

hepatoprotectors or advise to stay off drugs for 6 or 12 months. But in the absence of effective drug treatment programs, up-to-date rehabilitation centers and support mechanisms, this requirement is not feasible for most PWID in Russia.

**Legal ban on methadone and buprenorphine substitution therapy programs leads to exclusion of people who use drugs from treatment programs.** All over the world, opioid substitution treatment programs involve people with drug addiction in hepatitis C treatment programs and help encourage adherence to treatment. In Russia, OST programs are officially prohibited. As a result, doctors fail to prescribe antiviral treatment to CHCV patients who use drugs, on the grounds that they won't be able to follow their treatment regime.

**High cost is the main barrier to expansion of CHCV treatment.** Pegylated interferon is in general a very expensive medication due to oligopoly of two original brand drugs. Yet, several countries (such as Egypt and Brazil) successfully lobbied ten-fold reductions in prices, while others introduced compulsory licensing to produce biosimilar medications (India and Vietnam). In Russia, HCV treatment drugs are purchased at high cost, and the government does little to advocate for reductions. According to the federal procurement documents for 2012, the price for a standard 48-week treatment course varied from 292,402 rubles (9,366 USD) to 419,199 rubles (13,427 USD).

**Health facilities in Russia are not ready for expanded hepatitis C treatment.** Within the Priority National 'Health' Program, people living with HIV/HCV are usually treated by AIDS Centers, although in some cases patients are referred to local polyclinics. Regional activities aimed at strengthening and maintaining human resource capacities are basically non-existent, which results in the health system failing to address HCV treatment burden even in the context of minimal access to treatment. Infectious diseases specialists often lack adequate training to manage HCV patients: when piloted, PNP did not involve staff enhancement, and additional training was offered only to small proportion of medical specialists. Besides that, the system fails to determine officially at which level hepatitis C treatment should be provided. HCV treatment in some regions is considered a highly specialized medical intervention owned by in-patient hepatology facilities, whereas in other regions HCV care is an outpatient service provided by local polyclinics.

**Medication control is a complex and bureaucratic procedure, therefore many doctors refuse to deal with HCV treatment.** Medical staff have to fill in numerous forms that are part of the medication control procedure, and some hepatology centers have refused to provide treatment to avoid these complications. Moreover, medications are usually stored at AIDS Centers, and not in pharmacies, to be distributed by doctors personally. On the grounds of medication storage conditions and rules against unauthorized use, some facilities require that patients receive their weekly injections in the clinic, which is inconvenient and even problematic for some of them.

**Doctors fail to inform patients about the recent HCV treatment methods, which results in low treatment uptake.** Few people living with hepatitis C know about availability of up-to-date antiviral treatment. Post-test counseling for patients with HCV is usually a mere statement of diagnosis. Most respondents haven't heard about any treatment options from their doctors. In most cases, doctors only prescribe hepatoprotectors, the use of which is not scientifically grounded and financially burdensome.

**Treatment demand is limited by high cost of preliminary tests required for the prescription of treatment.** As stated in the PNP 'Health' guidelines, preliminary clinical examination for future participants of treatment programs should be paid from the regional budgets, but due to severe underfunding most patients have to pay for the testing themselves. The standard package of specific

laboratory tests costs from 3500 to 8000 rubles (depending on the test), and another 4000–6000 rubles is required to have elastography of the liver.

**Russia does not have clinical protocols for hepatitis C treatment.** Although in March 2013 clinical guidelines were approved, absence of official clinical protocols makes it impossible to develop unified patient selection criteria and provide quality treatment. With no federal-level treatment protocols available, the regions develop local regulations, define their own treatment eligibility criteria or refer patients to the local treatment commissions to decide on patient selection.

**Patient selection criteria are very subjective, the most common requirement being 'treatment should be provided only to socially reliable citizens'.** The process of patient selection varies from region to region is managed by individual doctors, thus lacking objectivity. AIDS Center specialists often add their own criteria of 'urgent treatment need', which exclude patients who have other problems besides CHCV (hepatitis B, tuberculosis) from the full clinical examination required for the prescription of comprehensive treatment. Thus, doctors select only among patients 'worthy of treatment' who, in their opinion, are capable of adhering to complex medication schemes. The lists of contraindications used by healthcare specialists are not always in agreement with international recommendations.

**Instead of reflecting the actual treatment needs, regional requests for certain amounts of therapy kits submitted to PNP 'Health' are based on the assumed federal budget and limited capacities of the AIDS Centers.** Regional healthcare authorities take various approaches to preparing annual requests for medications as part of the national 'Health' program. Some regions report that they divide between medical facilities the quotas set at the federal level, and local doctors then prepare estimates of how many patients would be sent for preliminary examination this year. Other regions are reportedly able to obtain as many medications as they request, and their doctors decide themselves on how many patients they can treat the coming year.

In both cases, therapy lists are based not on the number of tested patients in need of treatment, but on various subjective factors.

**Hepatitis C treatment is basically not available to HIV-negative patients.** While patients with HIV at least theoretically have a chance to get HCV treatment, the situation for HIV-negative individuals looks quite bleak. Russia does not have a federal program to treat HCV, and although some regions initiate their own treatment programs that address mono-infections, they are able to treat very few patients, whereas the demand is calculated in thousands or even tens of thousands. In the absence of governmental funding, HCV treatment often has to be paid by patients. To treat genotypes 2 and 3, doctors sometimes offer simple interferon to patients who cannot afford pegylated interferon – a sub-standard according to international approaches.

**Recommendations**

1. Develop federal-level clinical protocols for treatment of viral hepatitis C, mandatory for all regions of the Russian Federation.

2. Develop and approve a separate federal program for treatment of viral hepatitis C as a socially significant disease, including the provision of therapy, all the necessary pre-examinations, treatment monitoring and medications against side-effects.

3. Develop standards of outpatient treatment, including detailed description of the procedure and the levels of service provision, as well as workload standards for doctors and other healthcare specialists.

4. Facilitate inclusion of people who use drugs in hepatitis C treatment programs. Reverse regional norms excluding drug users from treatment programs. Provide client management services for people with drug dependency (social and psychological support, self-help groups) to improve adherence to treatment, enhance patient motivation and address other specific needs.

5. Legalize methadone/buprenorphine substitution therapy programs in Russia in order to safeguard treatment adherence in patience with opioid dependency.

6. Reduce the cost of pegylated interferon procured by the government through implementation of adequate price reduction mechanisms: modifying procurement procedures, negotiating with manufacturers, reducing initial auction prices – or introducing compulsory licensing and local production of medications that have social relevance and the lack of which can be catastrophic for public health.

7. Introduce an integrated registry of patients with hepatitis C as a tool to evaluate treatment needs, and register all patients with HCV, irrespective of their social status, risk factors or co-infections.

8. Enable training possibilities for the medical staff in order to decentralize treatment provision: from infectious diseases doctors in specialized institutions to infectious diseases doctors within the primary network, including the delivery of medications through pharmacies.

9. Scale up demand and raise patient awareness through the provision of quality counseling (including post-test counseling) by specialists and peer educators, as well as through the creation and maintenance of patient schools.

10. Expand harm reduction projects (needle and syringe exchange, outreach-programs) to ensure timely diagnosis and involvement of people who use drugs in treatment programs.

11. To patient organizations and groups: actively advocate for increased access to treatment, including through strategic litigation and peer education.

## Introduction

Although the incidence of hepatitis C virus (HCV) in Russia is extremely high, access to treatment of hepatitis C in the country remains limited. HCV treatment is regulated by the federal targeted program 'Prevention and control of socially significant diseases (2007–2011)', but it is provided on the leftover principle: medications for treatment of hepatitis C may be purchased only if funds are left after HIV antiretroviral drugs have been procured in the needed amount. Out of 89 Russian regions, only 30 allocate at least some local funding to address the problem. In 2009–2010, HCV treatment budgets have been reduced all over the country, and community-based monitoring networks reported instances of discontinuation of patient enrollment into treatment programs.

Despite the urgency of the problem, Russia has yet to conduct a systematic research that would assess hepatitis C prevalence, treatment needs, availability of medications, legal provisions and the level of access to HCV treatment. Such research is needed if the country wants to harmonize its approaches to achieve exponential growth of access to hepatitis C treatment and optimize its advocacy priorities.

## Research methods

This research was designed to employ mixed methods of data collection and analysis: review of scientific papers, collection of epidemiology data and in-depth interviews in three regional centers (Yekaterinburg, Barnaul, Togliatti) and at the federal level.

**The aim of this research** is to describe processes around access to HCV treatment in the Russian Federation.

**Objectives of this study were set to analyze:**

- decision-making processes related to needs assessment and distribution of funds for HCV diagnostics and the required amount of medications at the federal and regional levels;
- experiences of healthcare professionals in the sphere of HCV treatment and patient evaluation;
- decision-making processes related to the prescription of treatment and priorities in resource-limited situations;
- health promotion activities of patients with hepatitis C;
- experiences of patients associated with lack of access to hepatitis C treatment;
- interaction between patients and service providers.

**Qualitative research sample**

- patients who started and/or finished hepatitis C treatment (n=21)
- doctors who prescribe and manage treatment (n=5)
- healthcare experts at the regional and federal levels (n=4)

**Patients with hepatitis C**

'Patients with hepatitis C' are patients whose diagnosis has been confirmed. In this group, the following sampling criteria were used: treatment background (7 respondents), age (3 respondents under 30), gender (8 women, 13 men), drug-using experience (18 active or former drug users, 2 medical workers, 1

sexual partner of an IDU), monoinfection (9 respondents), co-infections (12 HIV-positive respondents). For more detail, see Annex 1.

**Doctors**

'Doctors' are infectious disease specialists who have prescribed and managed evidence-based hepatitis C treatment in the past two years.

**Experts**

'Experts' are people with experience in and knowledge of healthcare policy, in particular related to decision-making in the sphere of hepatitis C.

**Ethical issues**

Research protocols have been reviewed and approved by the Ethics Committee of Pavlov's State Medical University in St. Petersburg. To avoid conflict of interests for medical workers participating in the study, the protocols were also approved by the healthcare authorities in all the three regions. All interviews were anonymous and confidential, conducted with informational consent from participants.

All respondents received incentives in the form of food packages or telephone cards priced at 500 rubles. If necessary, transportation costs and other expenses were also reimbursed. Incentive gifts were not provided to decision-makers and doctors.

**Interviews**

Interviews were held at homes or offices of respondents (and sometimes at other places suggested by respondents) and were digitally recorded. Each interview lasted 30–60 minutes and was based on a semi-structured thematic guide with open questions, so that respondents had a chance to say everything they saw proper. At the beginning of each interview, researchers wrote down a short summary of respondents' background. Interviews were held by Anya Sarang and Tatiana Ivanova (The Andrey Rylkov Foundation for Health and Social Justice). A coordinator was assigned in each city to select respondents and organize interviews.

**Data analysis**

All recorded interviews were thoroughly transcribed. The project team performed thematic coding and categorizing of data obtained during interviews. The interviews were transcribed and analyzed with Max QDA 2M software for qualitative data analysis. The study involved review of Russian and international research publications, unpublished federal documents, data available at websites of the Ministry of Health and the Federal Service for Protection of Consumer Rights and Personal Wellbeing, as well as some other sources and materials.

Quantitative epidemiology data from the regions were processed through descriptive analysis, as there was no possibility to standardize or compare them due to insufficient quality of primary data.

## Review of HCV epidemiology

Since hepatitis C virus was detected in 1989, HCV prevalence has been growing steadily all over the world, reaching, as estimated by the World Health Organization (WHO), 130–200 million cases globally. Around 350.000 people die from conditions associated with hepatitis C on an annual basis. The HCV epidemic is one of the most significant public health threats, the consequences of which are to be felt by many countries for several decades (WHO 2011).

Hepatitis C virus is transmitted through contact with the blood of an infected person. Before the detection of the virus in late 1980s, HCV was often transmitted through the transfusion of blood or its products, and through medical paraphernalia and invasive medical procedures. These cases are rare now, as all donor blood is tested for hepatitis C, and medical facilities follow strict rules to control infections – including by using disposable and sterile equipment. Yet, infection risks increase for cases of damaged skin, where medical workers ignore the requirement to wear gloves for all medical procedures, or violate other universal infectious control precautions.

The most common way of HCV transmission is through sharing of syringes and other injecting equipment for using drugs. From 2 to 7 per cent of all cases are attributed to mother-to-child transmission, conditioned by health status of a pregnant woman (high viral activity, HIV co-infection) and some other factors. In most cases, hepatitis C virus cannot spread through sexual intercourse and breastfeeding, with some exceptions related to contact with blood. Thus, a high risk group for HCV infection includes blood recipients (before mandatory HCV screening of all donated blood was introduced), active or former drug users who have limited access to sterile syringes and other drug injecting equipment, medical workers, people living with HIV, people born to mothers living with hepatitis C and patients on hemodialysis.

Currently there is no vaccine for hepatitis C. In more than 80% of cases HCV infection does not show any symptoms. Infection becomes chronic in about 60–70% of patients (chronic hepatitis C, CHCV), and, if left untreated, leads to cirrhosis or cancer of the liver in 5–20% of cases (WHO 2011). The risk of liver cirrhosis or cancer is higher for people living with HIV (PLHIV) and people suffering from alcohol abuse; it is higher among men (10–15%) than among women (1–5%) (Yu 2009). Hepatitis C infection is often referred to as ‘the silent epidemic’, and the virus – ‘the silent killer’, because a typical cycle of the disease from infection to symptomatic liver disease may take many years.

Hepatitis C virus is a complex virus with a heterogeneous genome: it has as much as 11 genotypes and subtypes affecting different countries of the world to varying extents. Its high heterogeneity limits opportunities for the development of a vaccine and impacts virologic response to treatment. The most common genotypes are 1a and 1b: they account for about 60% of global infections and are widespread in Northern Europe, North America, Southern and Eastern Europe. Type 3 is endemic for South-East Asia (Simmonds 1999). It is important to determine HCV genotype, as different subtypes respond differently to treatment. For type 1, treatment with interferon is less successful, while for type 3 interferon-based treatment usually gives a sustainable clinical response (Mondelli 1999).

## HCV epidemiology in the Russian Federation

### HCV incidence

Official registration of acute hepatitis C in Russia was initiated in 1994 (Patsuk 2010), while registration of new cases of chronic viral hepatitis (B and C) commenced only in 1999. From 1995 to 2008, Russia followed epidemiological screening procedures that registered 'HCV carriers' – people with hepatitis C antibodies but without clinical or laboratory confirmation of hepatitis virus (Pimenov 2012). In 2000 alone, 156,000 carriers of hepatitis C were identified, and this figure increased by 38.9% in the following year (Shakhanina 2001). In 2001, a dramatic growth of registered HCV cases was seen: chronic hepatitis C incidence in Moscow, for example, increased 15-fold for the first time in five years. Drug-users under 30 accounted for 80% of all deaths from hepatitis B (according to the State Statistics Form # 2). Back in 2001, researchers already described social aspects of the epidemics of viral hepatitis in Russia and associated the incidence with injecting drug use (Brico 2001).

According to the Federal Service for Protection of Consumer Rights and Personal Wellbeing (2011), CHCV incidence in 2010 rose three-fold compared to 1999, reaching 40.2 per 100,000 of the population, which accounted for 73.8% of all cases of chronic hepatitis. In 2010, the highest CHCV incidence was in North-Western and Ural federal regions of Russia (Pokrovskiy, Zhebrun 2011). Among the most affected regions were Yamalo-Nenetsk Autonomous Region, St. Petersburg, Sakhalin region, Novosibirsk region, Lipetsk region, Murmansk region and Altai Republic. More than half of the cases were registered among people under 40 years of age (Rospotrebnadzor 2011).

From 1994 to 2001, the amount of 'carriers' increased from 30 to 127 per 100,000, then the incidence gradually decreased, reaching 87.5 per 100,000 in 2008. On the one hand, the 'HCV carrier' diagnosis based on antibodies alone led to hyperdiagnostics of hepatitis C, especially among children under 1 year of age who still had antibodies from their mothers. On the other hand, in 2009, after the line about 'HCV carriers' was removed from the law, a significant number of CHCV cases appeared to be unrecorded, and therefore antibodies-registered 'carrier' cases should have added to CHCV rates through the clinical and laboratory testing (Pimenov et al. 2012). Yet, CHCV incidence hasn't changed much over the last years, indicating that such cases are most likely ignored by the official statistics.

### Ways of HCV transmission and most-at-risk groups

According to international epidemiologic research, sexual transmission of HCV is unlikely, yet Russian official statistics shows the contrary, indicating that the structure of known ways of HCV transmission changed significantly from 1997 to 2010: the number of infections attributed to injecting drug use and medical procedures decreased, while the amount of transmissions through sexual or everyday contact rose (Pokrovskiy, Zebrun 2011) (Table 1). With that, official figures reflect ways of transmission only for acute HCV cases, and don't include data on transmissions related to chronic hepatitis C.

From the epidemiological point of view, such interpretation of transmission routes has serious limitations. Firstly, since the acute form of the disease is asymptomatic in 70–90% of cases, and in 60–80% of cases chronic HCV develops, and also given that medical and blood donor institutions apply strict safety requirements to prevent transmissions, most cases of hepatitis C will be detected in their chronic form. This assumption is confirmed by official statistics: in 2010, CHCV incidence in Russia was 20 times higher than incidence of acute hepatitis C (40.2 and 2.1 per 100,000 respectively) (Pokrovskiy, Zhebrun

2011). Therefore, data on ways of transmission and development of acute hepatitis C alone may not be sufficient to show the full picture of the epidemic.

Secondly, HCV is mostly transmitted parenterally, whereas sexual transmission of the virus is not common. US Centers for Disease Control and Prevention consider the statement about risks of HCV sexual transmission as highly controversial: according to CDC, not more than 15–20% of people with acute HCV reported situations associated with sexual transmission in the absence of other risk factors (Centers for Disease Control 2011). Therefore, high rates of sexual HCV transmission in Russia may rather be indicative of the gaps in data collection mechanisms, whereby initial data collection forms do not include standard lists of risk factors to allow for objective analysis of possible risky situations and routes of HCV transmission.

Thirdly, existence of a high proportion of cases with unknown way of transmission further limits possibilities for adequate data analysis.

**Table 1: Possible ways of transmission of acute hepatitis C in 1997 and 2010**

| Transmission route | 1997 | 2010 |
|---|---|---|
| **Injecting drug use** | 40.0 | 21.5 |
| **Sexual contact and everyday contact** | 11.0 | 35.3 |
| **Medical procedures** | 12.8 | 2.8 |
| **Not known** | 36.2 | 40.6 |

According to information from the Rospotrebnadzor website, a sharp growth of HCV incidence in late 90-s in Russia was related to transmissions through injecting drug use (about 70–80 per cent). Infection with hepatitis C through the use of non-sterile injecting equipment is a key factor driving the epidemic in several Russian regions, also determining certain incidence levels in different age groups. The epidemic mostly affects adolescents aged 15–17 years, and 18–29-aged youth: these groups represent high risk communities for HCV transmission. According to available data, 38–56% of all HCV cases occurred through injecting drug use, 2–10% through blood transfusion, and 1% – through hemodialysis. The risk of HCV transmission among health care workers who frequently come into contact with blood amounts to approximately 2–6% (Patsuk 2010).

Sentinel surveillance shows that injecting drug users account for the highest CHCV rates: from 45% in Naberezhnye Chelny to 90% – for example, in St. Petersburg. Same research demonstrates high proportion of HIV/HCV co-infection in St. Petersburg, Togliatti, Irkutsk and Ekaterinburg, as well as high levels of anti-HCV among sex workers (that in 2008 reached 12% in Irkutsk and 40% in Chelyabinsk), most likely associated with injecting drug use (NGO ‘Stellit’ 2010, WHO in Russia, Federal AIDS Center, NGO ‘Stellit’ 2008, Rhodes 2005) (Table 2).

**Table 2: HCV prevalence in most-at-risk groups in Russia (sentinel surveillance data)**

| Region, Year | Risk group | Researcher | HCV, % | HIV, % |
|---|---|---|---|---|
| **Moscow, 2011** | Injecting drug users (IDUs) | ESVERO, 2011 | **69** | 18 |
| **Екатеринбург, 2011** | IDUs | ESVERO, 2011 | **79** | 59 |
| **Omsk, 2011** | IDUs | ESVERO, 2011 | **78** | 17 |
| **Oryol, 2011** | IDUs | ESVERO, 2011 | **42** | 6 |
| **St. Petersburg, 2009** | IDUs | UNODC, 'Stellit' | **90** | 62 |
| **Voronezh, 2008** | IDUs | WHO, Federal AIDS Center, 'Stellit' | **63** | 4 |
| **Irkutsk, 2008** | IDUs | WHO, Federal AIDS Center, 'Stellit' | **81** | 49 |
| **Ekaterinburg, 2008** | IDUs | EHRN, 'Stellit' | **90** | 64 |
| **Naberezhnye Chelny, 2007** | IDUs | WHO, Federal AIDS Center, 'Stellit' | **45** | 13 |
| **Oryol, 2007** | IDUs | EHRN, 'Stellit' | **61** | 15 |
| **Chelyabinsk, 2007** | IDUs | WHO, Federal AIDS Center, 'Stellit' | **51** | 16 |
| **Moscow, 2003** | IDUs | Imperial College London | **67** | 14 |
| **Volgograd, 2003** | IDUs | Imperial College London | **70** | 3 |
| **Barnaul, 2003** | IDUs | Imperial College London | **54** | 9 |
| **Togliatti, 2003** | IDUs | Rhodes, 2005 | **87** | 56 |
| **Irkutsk, 2008** | SWs | WHO, Federal AIDS Center, 'Stellit' | **40** | 19 |
| **Chelyabinsk, 2008** | SWs | WHO, Federal AIDS Center, 'Stellit' | **14** | 6 |

| | | | | |
|---|---|---|---|---|
| **Moscow, 2006** | MSM | WHO, Federal AIDS Center, 'Stellit' | **2** | 1 |
| **St. Petersburg, 2006** | MSM | WHO, Federal AIDS Center, 'Stellit' | **3** | 4 |

According to UN Reference Group, estimates of the number of IDUs with HCV in Russia range from 985,500 to 1,770,250 (2008), with a mid-range estimate of about 1.3 mln (in 2011). This figure is higher only in China and USA (Mathers 2008, Nelson 2011).

According to data from sentinel surveillance, the number of IDUs living with HCV ranges between 0.4 and 1.6 million, with a mid-range estimate of 900,000 people.

**Table 3: Estimate numbers of injecting drug users carrying HCV in Russia**

| HCV prevalence among IDUs, % | | Estimates of IDU population, mln | | |
|---|---|---|---|---|
| | | **Low** | **Inter-mediate** | **High** |
| | | 1 | 1.3 | 1.8 |
| **Conservative estimates** | 45% | 0.4 | 0.6 | 0.8 |
| **Intermediate** | 69% | 0.7 | 0.9 | 1.2 |
| **High** | 90% | 0.9 | 1.2 | 1.6 |

Official data demonstrates high rates of anti-HCV among inmates (5.2% in 2010) and children born to mothers with confirmed HCV (2.6% in 2010), while figures for other population groups subject to respective screening are quite low (Pokrovskiy and Zhebrun 2011). Another sampling study in Novosibirsk found the highest HCV rates among IDUs in drug treatment (48.0%) and PLHIV (35.8%). Hepatitis C prevalence in the general population was also reported as high: 5.6% among clients of outpatient clinics and 4.6% among health care workers (Shustov 2004).

**HCV prevalence in the general population.** Although there is no overview of data on HCV prevalence in the population of Russia, experts estimate that it varies significantly between regions. For example, a study held in 1999 showed that prevalence varied from 0.7% in central regions of Russia to 3.8% in central-southern regions and 5–7% in Siberia and the Far East (Lvov 1997).

Following estimates of the Central Scientific Research Institute of Epidemiology, Russia is home to about 5 million people living with HCV. According to the same source, realistic prevalence rates are twice as high (90 per 100.000 of the population – compared to 40.2) (Pimenov et al 2012). Even the most conservative estimates indicate that in 1999–2009 Russia had more than 500,000 people with chronic hepatitis C, and over 1,500,000 people with HCV antibodies (Pokrovskiy, Zhebrun 2012). Similar figures

are found in reports by Rospotrebnadzor, where the number of people infected with viral hepatitis is estimated between 1.1 and 2 mln people.

An alternative way is to use sampling studies as a source of hepatitis C prevalence in Russia: for example, screening for markers of chronic viral infections organized as part of the Priority National 'Health' Program showed that 3.6% out of 16.3 mln people who underwent testing were infected with HCV (Alekseyeva 2010).

Circumstantial evidence of HCV prevalence in the general population may also be found in blood donor testing: in 2006–2008, from 1% to 1.5% of donors were identified as anti-HCV-positive (Kodenev 2010). According to another source, HCV prevalence among blood donors was as high as 7% (Patsuk 2010). Another group regularly screened for hepatitis C is pregnant women – from 1999 to 2001 HCV incidence in this group increased 4-fold and reached 1.3% (Rospotrebnadzor 2011).

To summarize the above, Russia may be home to 1.5–5.7 million people carrying HCV (mid-range estimate – 5 million, which is 4.4% of the total adult population in the country).

**Table 4: Estimated numbers of people living with HCV in the population, according to different sources**

| **Sources that estimated the number of HCV carriers** | **Adult population living with HCV** | |
|---|---|---|
| | mln | % of adult population |
| Pokrovskiy, Zhebrun 2011 | 1.5 | 1.30% |
| Rospotrebnadzor 2011 | 2 | 1.80% |
| Alexeyeva 2010 | 4.1 | 3.60% |
| **Pimenov 2012** | **5** | **4.40%** |
| Shustov 2004 | 5.7 | 5.00% |

**HCV genotypes in Russia**

Defining the distribution of HCV genotypes in Russia is extremely important for the outcomes of treatment and resource planning, as types 2 and 3 require 24-week treatment courses, versus 48 weeks for types 1 and 4.

According to official data, the most prevalent in Russia are type 1b (about half the cases) and 3a (30–40%), although their distribution varies per region. For example, in some region genotype 3a is prevalent (in some territories of the Southern Federal District) (Rospotrebnadzor 2011). According to the Central Scientific Research Institute of Epidemiology, based on representative sample of 1928 isolates, the most dominant in Russia are subtypes 1a, 1b, 2 and 3a; most prevalent of these is type 1b (52.8%), followed by 3a (36.3%), 2 (8.1%) and 1a (2.1%) (Pimenov et al. 2012).

An earlier research showed similar genotype distribution: 1b (50.3%), 3a (44.8%), 2 (4.,4%), with subtype 1b more prevalent amont people over age 50. Genotype 3a was more frequent among young people

(Shustov 2005). A St. Petersburg research among people who use drugs demonstrated prevalence of subtype 3a in this social group (Paintsil 2009), as confirmed by another research held by the Institute of Epidemiology among people aged 15–35 and men infected with HCV through injecting drug use (Pimenov et al. 2012).

## Current approaches to hepatitis C treatment

Treatment approaches to chronic hepatitis C have changed significantly in the last 15 years. In 1998, the U.S. Food and Drug Administration (FDA) approved the first combination therapy with interferon α-2b and ribavirin, three times a week subcutaneously. It became a standard treatment scheme that gave a sustained viral response (SVR)[1] in 38–43% of cases, with significant genotype-related differences in outcomes: 66% for types 2 and 3, 29% for type 1 (Keeffe 2003). Clinical recommendations of the World Health Organization included standard interferon in doses more than 3 mln units three times weekly, in a course of 24 weeks (SVR in 50% of cases, later reduced to 15–25%) (WHO, 2002). Since combination therapy with pegylated interferon and ribavirin was introduced, treatment with conventional interferon has been considered substandard.

In 2001–2002, new forms of pegylated interferon were developed by two pharmaceutical companies: interferon α-2b (brand name PegIntron) from Schering-Plough, and pegylated interferon α-2a (brand name Pegasys) from Roche, which allowed to increase SVR to 42–51% for genotypes 1 and 4, and 78%–88% for genotypes 2 and 3, and to reduce the number of injections to once weekly (Manns 2001, Fried 2002, Hadziyannis 2002).

In 2002, independent experts studied the evidence base for CHCV treatment that regulated indications and contraindications for treatment, required diagnostic tests and treatment monitoring, and issued their first results (National Institutes of Health 2002). A combination scheme with pegylated interferon alpha-2a or alpha-2b (PEG-IFN) and ribavirin (RBV) was approved as the gold standard of treatment. These recommendations were first standardized in USA and later endorsed at the international level, with most remaining valid up till now.

In 2011, new protease inhibitors were introduced that showed significant improvement in treatment outcomes, and were quickly approved by FDA through their fast-track program. In the same year, the American Association for the Study of Liver Diseases (AASLD) published a new practical guidance recommending a combination of protease inhibitors (boceprevir and telaprevir) with PEG-IFN and RBV (Ghany 2011) as an optimal therapy for CHCV genotype 1. It should be noted, however, that boceprevir-based schemes cost up to 1,100 USD per week, and telaprevir schemes – up to 4,100 USD per week, and this is excluding the costs for pegylated interferon and ribavirin. Nevertheless, in their research published in February 2012 in USA, the authors claim these schemes to be cost-effective (Liu 2012).

The most significant predictors of a successful treatment response are considered to be the genotype and the viral load before treatment < 600 000 IU/ml (Manns 2001, Fried 2002, Hadziyannis 2002). Therefore, according to AASLD recommendations, **all carriers of the virus** are candidates for CHCV treatment (Ghany 2009).

[1] Sustained virologic response is defined as undetectable HCV RNA in the patient's blood six months after completing therapy and afterwards.

According to the 2001 Clinical Manual of the European Association for the Study of Liver (EASL), key prognostic factors defining the success of treatment are the IL28B gene polymorphism[2], the genotype and the stage of fibrosis. Not less important are the initial results of the RNA load, medication doses, duration of treatment, and, from the patient's side, – weight, insulin resistance, gender and manifestations of the liver disease, such is the stage of fibrosis, co-infection with other hepatotropic viruses or HIV, and levels of alanine aminotransferase (ALT) and gamma-glutamyl transferase (Manns 2006; European Association for the Study of the Liver 2011).

Both EASL and AASLD conclude that all treatment-naïve patients with the compensated liver disease, who wish to receive therapy and having no contraindications to PEG-IFN and RBV, should be granted access to HCV therapy. Absolute contraindications include: uncontrolled depression, autoimmune diseases and decompensated liver cirrhosis; pregnancy and refusal to use contraception; serious associated diseases, such as hypertonic disease, heart failure, diabetes, and chronic obstructive pulmonary disease (European Association for the Study of the Liver 2011).

As of this writing, WHO is developing clinical recommendations for screening, care and support of patients with chronic hepatitis C, expected to be published in 2013.

**The U.S. National Institutes of Health**

**Consensus statement on management of hepatitis C (2002)**

- **All patients with chronic hepatitis C are potential candidates for antiviral therapy. Treatment is especially recommended for patients with an increased risk of developing cirrhosis (detectable HCV RNA levels higher than 50 IU/mL, and at least moderate inflammation and necrosis).**
- **Experience has demonstrated the feasibility and effectiveness of treating chronic hepatitis C in people who use injection drugs. This is potentially important because injection drug use is the most common risk factor for new HCV infections, and successful treatment may reduce transmission.**
- **A history of alcohol abuse is not a contraindication to therapy; however, continued alcohol use during therapy adversely affects response to treatment, and alcohol abstinence is strongly recommended before and during antiviral therapy.**
- **For patients with genotypes 2 and 3, a reduced ribavirin dosage of 800 mg daily appears to be adequate; a standard dosage of 1000 to 1200 mg daily is recommended for patients with genotype 1.**
- **Among patients with genotypes 2 or 3, SVRs with standard interferon and ribavirin were comparable to those with pegylated interferon and ribavirin, and a 24-week course of PEG-IFN and ribavirin was found to be as effective as a 48-week course, but not in patients with genotype 1 who require 48 weeks of treatment.**

[2] The IL28B genotype also determines treatments outcomes. It has three sub-types: CC CT and TT. In patients with CT and TT, sustained virologic response is about 30%, therefore they require triple therapy that increases chances for successful treatment to 70%.

- **Early virologic response (EVR), defined as a minimum 2 log decrease in viral load during the first 12 weeks of treatment, is predictive of SVR and should be a routine part of monitoring patients with genotype 1.**
- **Patient adherence is critical to the success of treatment of hepatitis C. Physicians should discuss the importance of adherence with patients before embarking on therapy and regularly assess and take steps to help their patients maximize their adherence. Such measures include management of side effects, depression, and substance abuse.**

**CHCV treatment in people who use injecting drugs**

Even though injecting drug use is the main route of HCV transmission in the U.S., people who use drugs have been excluded from clinical research, except clients of substitution treatment programs with methadone or buprenorphine. Exclusion of drug users from clinical research creates a vicious circle: lack of clinical data is used as a pre-requisite for refusal to treat representatives of the population associated with the highest CHCV prevalence, without any account to clinical research or willingness of drug users living with hepatitis C to receive treatment (Treatment Action Group 2011). However, at least three clinical studies have been conducted in the communities of people who use drugs, where researchers found no significant differences in treatment outcomes among drug using patients and those who don't use drugs (Cournot 2004; Hellard 2009; Robaeys 2006). According to clinical protocols of the WHO Regional Office for Europe, opioid substitution treatment should not be viewed as an obstacle to HCV treatment, and the issue of CHCV treatment for people who use drugs should be resolved on an individual basis, whereby all those in need should have access to comprehensive medical, psychological and social care (WHO 2006).

The AASLD manual provides special recommendations for managing treatment in active PWID and PLHIV. According to these, many active PWID are not willing to be treated, their adherence to treatment regime is low and they do not often seek medical care. At the same time, some active drug users wish to be treated from CHCV and are quite capable of undergoing treatment. There are certain factors that predetermine advantages and risks of CHCV treatment. Ideally, such therapy should be integrated with drug treatment and be managed by multidisciplinary teams that also provide counseling on mental issues and addictions. From 2009, AASLD recommends to view people who use injecting drugs and patients of OST programs as potential candidates for treatment – if they wish to receive it and are able and willing to maintain regular appointments and use contraception. PWID should have access to care and support, drug treatment counseling and consultations of a psychiatrist. People with CHCV and accompanying mental disorders should also be seen as candidates for antiviral treatment (Ghany 2009).

According to EASL guidelines, there is not enough data to develop recommendations for treatment of active PWID due to a widespread opinion that patients should abstain from drugs or take substitution therapy (methadone or buprenorphine) 6–12 months before the start of CHCV treatment.

Similar to AASLD, EASL recommends an individual approach to treatment and access to multidisciplinary teams of liver and addiction specialists (Edlin 2002, European Association for the Study of the Liver 2011). Clinical protocols of the World Health Organization's Regional Office for Europe (WHO/ROE) practically reiterate AASLD and EASL recommendations pertaining to treatment criteria for active PWID and people with HIV/HCV co-infection (WHO 2006).

It should be noted that in many European countries (such as France, Czech Republic, the Netherlands, and Switzerland) drug use is not considered as contraindication to treatment (Reimer et al 2005, Correlation network 2010, Central and Eastern European Harm Reduction Network 2007).

**CHCV treatment and problem alcohol use**

Following the WHO/ROE clinical protocols, active alcohol use is considered as relative contraindication to PEG-IFN-based treatment (Samet 2007; BO3 2006). According to WHO/ROE recommendations, SVR is lower among patients who use alcohol (Anand 2006). Yet, almost two-thirds of patients fully abstain from alcohol when they start treatment. As there is no sufficient data on their response to standard treatment, therefore WHO/ROE recommends not to exclude patients who use alcohol from treatment programs, but to offer them mandatory counseling about the benefits of reducing or stopping alcohol use. Such patients may need additional support in maintaining and improving adherence to treatment (European Association for the Study of the Liver, 2011).

**CHCV treatment in patients with co-infections (HIV/HCV)**

Despite the high prevalence and severe consequences of CHCV and HIV co-infection, patients with co-infections have limited access to treatment compared to patients with HIV monoinfection due to weaker clinical response, presence of other co-morbidities, mental disorders or unwillingness of doctors to prescribe treatment (Butt 2009; Hall 2004; Mehta 2006). To build the evidence about CHCV treatment in patients with HIV/HCV, several extensive randomized research studies were held. According to the outcomes, the urgency of CHCV treatment in HIV-positive patients may be even higher than for CHCV monoinfection, as co-infection is associated with faster progression of liver disease and a two-fold risk of cirrhosis (Graham 2001; Sulkowski 2007). Besides that, effective CHCV treatment improves tolerability of ART by reducing hepatotoxicity (Sulkowski 2000).

A randomized study APRICOT compared the effectiveness of three different 48-week schemes and showed the following results: linear interferon alpha-2a plus RBV achieved SVR in 12% of cases; PEG-IFN and placebo – in 20%; and PEG-IFN with RBV – in 40% of cases (Torriani 2004). Treatment results (SVR) for the PEG-INF plus RBV scheme was 29% in patients with HIV/HCV genotype 1, and 62% for genotypes 2 and 3 (Carrat 2004).

Based on the above, AASLD recommends the following:

- All HIV-positive patients should be tested for HCV.
- Qualitative PCR-based measurement of HCV RNA is recommended for HIV-positive patients with HCV antibodies, including if ELISA is negative but there are signs of liver disease.
- People with HIV/HCV co-infection should be offered treatment if the likelihood of serious liver impairment and treatment response may be higher than possible negative consequences related to side effects.
- HCV treatment in people with HIV/HCV co-infection should include PEG-IFN plus RBV for 48 weeks in the doses recommended for HCV monoinfection.

(Ghany 2009).

## Clinical recommendations for hepatitis C treatment in the Russian Federation

At the time of this writing and field studies, various groups of authors have attempted to develop their own clinical manuals, but none of them was successful, and not a single document was sent for approval

at the federal level. Some regions had been using methodologies obtained at conferences. Clinical recommendations were approved by Russia's Ministry of Health (MZ RF 2013) only when this report was being finalized, and their implementation is not reflected in this document. According to these recommendations, all treatment-naïve patients with CHCV, regardless of drug use, are candidates for antiviral treatment. Depending on the degree of liver impairment, treatment should either be prescribed immediately or delayed for a certain period of time. Treatment decisions should be made on an individual basis, taking into account, besides clinical indications, 'analysis of treatment success likelihood and potential risks of adverse AVT outcomes' and 'patient's readiness to start treatment', which makes treatment-related decision making a somewhat subjective process. These recommendations provide for the possible use of standard interferon instead of PEG-IFN, conditioned by the state of economic resource, in patients with genotypes 2 and 3, aged under 40, having no manifestations of liver fibrosis and upon condition that early virologic response is reached soon (MZ RF 2013).

The Ministry of Health recommendations also provide for triple therapy with protease inhibitors boceprevir and telaprevir for patients with genotype 1 who are previously untreated or who have failed therapy with two medications (MZ RF 2013).

Unlike many other countries, Russia bans substitution therapy programs, which substantially limits Hepatitis C treatment opportunities for people who use drugs.

## CHCV treatment needs assessment in the Russian Federation

According to the international epidemiology data, about 10–15% of people with CHCV may develop liver cirrhosis within the first 20 years after infection (Chen and Morgan 2006), and about 20–30% may develop decompensated liver cirrhosis and cancer of the liver (Afdhal 2004, Lauer Walker 2001) if untreated. Irrespective of the age at infection, most patients are expected to develop cirrhosis before 65 years (Pradat et al 2007). Given this data and the number of people with HCV which is estimated at 5 million in Russia, one might assume that 2 million of them are in need of immediate treatment.

To assess treatment needs, Russia uses the following approach: a full medical examination and regular medical check-ups on the basis of infectious clinics at the place of residence. The full medical examination includes an ELISA test (a test that detects antibodies to HCV and other hepatitis), a clinical blood analysis (total bilirubin, ALAT, AspAT, total protein, amylase, blood urea nitrogen, glucose, etc.), an ultrasound investigation, RNA tests (qualitative and quantitative), HCV genotype test, puncture biopsy or elastography of the liver (Yuschuk et. al 2010). Yet, this method hasn't helped Russia collect official estimates of its treatment needs, as it is impossible to organize medical check-ups for all people undergoing regular medical observation in all regions. Thus, it is fair to say that treatment needs assessment in Russia is not based on any clinical indications.

Moreover, until 2011 Russia did not have an integrated monitoring system that would collect and analyze all laboratory data, therefore it is impossible to give a realistic estimate of treatment needs for more than a million of registered HCV carriers at the national level, either. In 2011, to improve monitoring of viral hepatitis, a Reference Center was established and tasked to develop methods of diagnosis and prevention, and to provide advisory support to Russian regions in the sphere of computerized HCV surveillance (Rospotrebnadzor 2011). As long as the system of epidemiological

monitoring and surveillance of parenteral hepatitis is underdeveloped, the government is not able either to give estimates of the total number of CHCV patients, or to assess realistic CHCV treatment needs. In 2011, Rospotrebnadzor admitted that significant variations in incidence registered in different regions of Russia are related to the gaps in epidemiological monitoring: HCV infection is registered at different levels of the system, with varying procedures for confirming diagnoses. For example, only 67 Russian regions (89%) conduct ELISA to diagnose hepatitis A, B and C, but only 45% provide for the broad-spectrum ELISA. Hepatitis A, B and C are diagnosed through PCR only in 31 regions (43%) (Rospotrebnadzor 2011).

Other gaps in epidemiologic monitoring are related to the fact that not all positive ELISA tests are registered through a centralized database. According to reports from one of Russian regions, clinical monitoring of patients is irregular throughout the year, and client records that assign patients to medical check-ups are kept carelessly. Less than 50% of people with chronic hepatitis are covered by regular medical ('dispensary') observation. Medical facilities often fail to follow the current standard of post-diagnosis care in patients with chronic viral hepatitis. According to 2010 overview data, only 41.1% of cases of CHCV infection had been confirmed through PCR. In most cases, chronic hepatitis C infection is confirmed only through total anti-HCV antibodies, without screening for additional markers of viral hepatitis (Republic of Sakha 2011).

An integrated patient registry is currently under development in Russia, to be piloted in late 2012 in ten Russian regions.

## Barriers to HCV treatment

**High cost of treatment is the main barrier. How do other countries address this problem?**

Universal access to the standard HCV therapy worldwide is far from being a reality due to prohibitive costs of PEG-IFN under patent monopoly of two pharmaceutical companies. Patent for PEG-IFN alpha 2a expires in 2016, for PEG-IFN alpha 2b in 2017, and for combined use with ribavirin even later. These patents are registered in Russia (Amin 2012). Currently in Eastern Europe and Central Asia the annual cost of HCV treatment per patient is as high as 15–20 thousand USD for a yearly course, although some countries managed to reduce this price.

- Brazil, Russia's partner in the BRICS initiative, managed to provide treatment through an extended program to 10,000 patients from 2006 to 2010, with yearly cost of treatment around 10,000 USD. Brazil continues direct negotiations with producers in order to reduce treatment costs further (Vallini 2010).

- Egypt achieved a 6-fold reduction in the cost of the PEG-IFN course: 2000 USD for 48 weeks of treatment with local generic drugs or 2500 USD with Merck and Roche medications. This was made possible through market competition and direct negotiations with Merck and Roche. According to the Coordinator of the National HCV Treatment Program in Egypt, only after a local company started to produce pegylated interferon, the costs of patent drugs started to go down (Right to Health 2012, Ford 2012). Thanks to the established agreements and local production, an original ampoule now costs 41 USD. Reduced treatment costs allowed Egypt to provide treatment to 240,000 people with HCV since 2006.

- In Georgia, procurement procedures and international tenders created competition between two pharmaceutical companies and an unprofitable international supplier. As a result, the country was able to purchase 500 treatment courses for five years at the price of 8700 USD, or 125 USD per ampoule.

Cost reduction measures are limited because pegylated interferon is a biological product, and it is more difficult to produce a proper biosimilar medicines and to test its quality and obtain approval from regulatory services (for chemical products, it is sufficient to prove its bioequivalence[3]). Lack of biosimilar products limits opportunities for using flexibilities in the protection of intellectual property rights and following suit in the field of HIV where generics and drug competition drastically decreased the cost of treatment – from 10,000 in 2000 to 130 USD per year for the cheapest course (MSF 2012).

Alongside with that, patent on pegylated interferon is a barrier for the development of analogue drugs at the country level. However, the current patenting landscape may change soon – for example, a recent court decision in India has revoked the patent on pegylated interferon alpha-2a. India has a highly efficient pharmaceutical industry – this country is the 'world pharmacy for generic drugs', primarily for antiretroviral treatment. This is thanks to India's careful patenting policy, especially on medications. The court ruled that since the main active ingredient is interferon, which is unpatented, and pegylated interferon is not a substantial innovation, it fails to meet patenting criteria. This decision gives opportunities both to India – to produce pegylated interferon locally, and to other countries – to be able to import generic drugs from India. Yet, most countries, including Russia, can get around Merck's and Roche's patents only through compulsory licensing or announcing 'public interest' in certain drugs.

**Other factors limiting access to treatment**

The high cost of medications is not the only barrier to treatment. Other limiting factors are unpreparedness of the system, prejudices of healthcare workers and side effects of drugs (especially depression).

Serious side effects undermine adherence to treatment and often lead to interruption or discontinuation of therapy. To address this, patients should be prepared for treatment in advance, and medical staff should be taught in managing side effects.

Another barrier to treatment is unwillingness of the government, medical facilities or healthcare staff to provide treatment to PWID. This continuing reluctance to treat active drug users is driven by concerns about the risk of reinfection and low treatment compliance (due to concomitant alcohol abuse, drug use and mental health issues), although evidence shows that there are no significant differences in treatment outcomes among PWID and people who don't use drugs (Hellard 2009).

In EECA, hepatitis C treatment is considered a very costly and intensive procedure from the point of view of human and administrative healthcare resources. Access to HCV treatment is provided in specialized institutions and requires a multi-disciplinary approach. As in case with HIV, quality hepatitis C treatment calls for reforms of healthcare systems, 'de-verticalization' and integration of treatment with other services.

[3] In Egypt, pegylated interferon alpha was registered as a generic drug, as the country did not have official requirements regulating generic copying of biological drugs. Currently, patients who received treatment with the local drug are being monitored.

**Hepatitis C treatment in Russia: costs and funding**

Even though pegylated interferon is included in the List of Essential Medicines, its cost is not covered by compulsory medical insurance. The government determines priorities and socially significant diseases and allocates additional funding to address these through targeted federal programs. However, although hepatitis C is considered a socially significant disease, the government still hasn't produced a federal program that would provide for a full clinical examination and diagnostic procedures required to prescribe treatment to all patients who need it.

Currently, the main source of funding is the Priority National 'Health' Program that allocates finances for HIV and CHCV treatment (only for HIV-positive patients). In 2008–2012, this program was the main source of funding of CHCV treatment in Russia. In 2011 it was discontinued, to be launched again in 2012 with reduced funding. The future of this program remains uncertain. So far, the program includes the following activities in the field of diagnosis, prevention and treatment of viral hepatitis B and C:

1. Screening of the population to identify HIV and HBV/HCV infections. Planned coverage: 22 mln people per year. Estimated budget: 48 bln rubles; deposited to the federal budget: 31 bln rubles for 2009–2011.

2. Treatment for PLHIV infected with HBV/HCV and for patients with hepatitis B and C who urgently need treatment. Planned coverage: 26.5 mln people in 2009–2011; estimated budget: 46 bln rubles; deposited to the federal budget: 30 bln rubles for 2009–2011.

3. Prevention of HIV and hepatitis B and C; planned budget – 0.4 bln rubles per year.

   (Presidential council for the Implementation of Priority National Projects and Demographic Policy, 2008)

Medications for hepatitis treatment are purchased on the leftover principle: the federal program may procure these drugs only after HIV and hepatitis testing expenses have been covered, and HIV antiretroviral drugs have been ordered in the needed amount.

Besides the Priority National 'Health' Program, another federal targeted program is functioning in Russia, with a 2007–2012 'Viral Hepatitis' component covered by a separate budget: about 247.29 mln USD, including 95.79 mln USD from the federal budget and 138 mln USD from regional budgets. This program involves 'capital investments' in research and development technologies, as well as 'other needs', and does not provide for diagnosis and treatment of viral hepatitis (Federal targeted programs in Russia, 2012). In practice, in the past four years only 58.87 mln USD have been allocated from the federal budget for the implementation of this component.

Some local regional programs provide additional resources for diagnosis and treatment hepatitis C monoinfections, but mostly for social benefit holders and healthcare workers. According to a qualitative study, the National Program provides treatment for hundreds of patients per year, whereas regional programs are able to support only tens of patients who are placed on years-long waiting lists before they can receive treatment.

In order to compare the expected and actual drug procurement indicators, the authors have submitted an official request to the Ministry of Health, which they have never received an official response to. However, ITPCru collects annual information with auction results available from open sources and the public procurement website. According to this data, from 2008 to 2012 Russia spent a total of 8.4 bln

rubles to purchase pegylated interferon, linear interferon and ribavirin, and prescribed 18,881 PEG-INF treatment courses and 827 linear interferon regimens (standard 48-week courses with 1 weekly injection of PEG-IFN or 3 weekly injections of linear interferon), as well as 17,695 courses of ribavirin (800 mg daily) (ITPCru 2012) (Table 5).

According to the official statistics, from 2006 to 2010, treatment was provided to 38,628 people living with HIV, of these, 17,074 were treated as part of the National Priority 'Health' program (Rospotrebnadzor 2011). It is not known how many HIV-positive individuals out of the registered 589,581 PLHIV (by the end of 2010) were able to undergo a full medical examination necessary for the prescription of HCV treatment.

According to ITPCru, in 2012, the federal budget for the procurement of specific drugs as part of the 'Health' program was reduced 1.5 times compared to 2011, amounting to approximately 45 mln USD (S. Golovin 2012). This led to reduced amounts of procured medications and a 30% decrease in treatment coverage (3,625 PEG-IFN regimens, as opposed to 5,513 in 2011).

**Table 5: Actual budget and spendings of the PNP 'Health' on the procurement of antiviral drugs for CHCV treatment, 2002–2012**

| | 2008 | 2009 | 2010 | 2011 | 2012 | 2008–2012 |
|---|---|---|---|---|---|---|
| **Actual procurement budget (in rubles)** | 987,913,358 | 1,595,988,791 | 2,297,089,608 | 2,155,677,838 | 1,358,064,526 | 8,394,734,120 |
| **A total of PEG-IFN regimens** | 1,555 | 2,925 | 5,343 | 5,447 | 3,612 | 18,881 |
| **A total of interferon regimens** | 207 | 283 | 258 | 66 | 13 | 827 |
| **A total of regimens for all types of interferon** | 1,762 | 3,207 | 5,601 | 5,513 | 3,625 | 19,708 |
| **A total of ribavirin regimens (average dose – 800 mg)** | 2,261 | 3,308 | 6,106 | 6,020 | N/A | 17,695 |

Source: International Treatment Preparedness Coalition in Eastern Europe and Central Asia (ITPCru)

**Cost of CHCV treatment in Russia**

Procurement price of standard antiviral schemes for CHCV treatment remains extremely high in Russia, because the government procures only the original PEG-IFN medications, and even though prices offered for public procurement are lower than retail pharmacy prices, public procurement does not involve a significant reduction of costs. Based on the comparison of actual prices of state purchases and retail prices in Moscow pharmacies (2011), the authors calculated that the average retail cost of a standard 48-week treatment course with PEG-IFN was 460,000 rubles (or 360,000 rubles if procured by the government as part of the 'Health' program in 2011), while the Pegasys-based regimen cost 550,000 rubles in Moscow pharmacies, and 430,000 rubles for public procurement (Table 6).

**Table 6: Estimated comparative cost of standard treatment regimens – retail and public procurement prices**

| Standard regimen 1 | Retail price | Actual price for public procurement | Difference |
|---|---|---|---|
| **PEG-IFN, 100 mcg/week** | 412,351 | 346,931 | 16% |
| **Ribavirin, 800 mg/day** | 46,502 | 11,183 | 76% |
| **Cost of regimen** | **458,854** | **358,113** | **22%** |
| **Standard regimen 2** | | | |
| **Pegasys, 180 mcg/week** | 500,341 | 419,199 | 16% |
| **Ribavirin, 800 mg/day** | 46,502 | 11,183 | 76% |
| **Cost of regimen** | **546,844** | **430,382** | **21%** |

The cost of CHCV treatment is mostly determined by the price of pegylated interferon, as ribavirin is produced by numerous pharmaceutical companies, including by local ones. As demonstrated in Table 6, the price of pegylated interferon for a once-weekly injection varies significantly among the regions. For example, public procurement prices, retail prices in Moscow pharmacies and retail prices in Ekaterinburg and Togliatti may vary on a scale up to several thousand rubles per dose. One PEG-IFN ampoule cost 7228 rub as part of public procurement (2011), 10,200 rub in Ekaterinburg pharmacies and 9,974–12,236 rub in Togliatti pharmacies (January 2013).

**Table 7: Comparative cost of pegylated interferon in Russian regions – retail an public procurement prices**

| Medication | dose | Price per dose, 2012, rubles | | Retail price per dose, local pharmacies, 2013, rubles | | |
|---|---|---|---|---|---|---|
| | | **Public purchase** | **Online pharmacy** | **Moscow** | **Ekaterinburg** | **Togliatti** |
| **PEG-IFN** | 100 mcg | 7,228 | 8,591 | 8,240–10,640 | 10,400 | 9,974–12,236 |
| **Pegasys** | 180 mcg | 8,733 | 10,424 | 9,500–10,200 | 10,600–11,550 | ... |

It should be noted that in 2013 antiretroviral drug procurement was decentralized, which may lead to a subsequent increase in prices. It will also be more difficult to monitor costs and control transparency of regional procurement procedures.

In February 2013, a local drug 'Cepeginterferon alpha-2bC' was registered in Russia under a brand name 'Algeron'. As of this writing, this medication has not been included in the List of essential medicines or public procurement lists, and it is not clear whether the new drug will contribute to the reduction of prices.

In addition to standard treatment regimens, Russian doctors tend to prescribe various hepatoprotectors to their patients. Not proven effective or mentioned in international guidelines, these medications

increase the cost of treatment by several thousands, sometimes even tens of thousands of rubles, and these additional expenses are not covered by governmental budgets.

**Cost of the new protease inhibitors for CHCV treatment**

In line with international recommendations, new regimens that include protease inhibitors boceprevir and telaprevir – recommended as optimal for treatment of CHCV genotype 1 – are based on the combination with PEG-IFN and RBV, yet these schemes are extremely expensive and unaffordable in many countries, including Russia, where these medications have been recommended in March 2013 and registered in July 2013. Based on prices offered by online pharmacies, the 48-week triple therapy with boceprevir costs about 1.72 mln rub, and with telaprevir – up to 3.58 mln rub.

**The cost of clinical tests required for the prescription and monitoring of hepatitis C treatment**

When funding for HCV treatment was budgeted, it was expected that the PNP 'Health' would provide funds for ELISA-tests that determine anti-HCV antibodies, whereas full examination required for the prescription of treatment would be covered by local programs and budgets. Yet, in reality, with some exceptions, local programs cannot pay for clinical tests, leaving it in the responsibility of patients. Some local budgets provide for a limited amount of PCR and genotypic testing, although these are usually not sufficient even for patients who already receive treatment. Thus, in order to collect all the necessary data for the clinical commission that prescribes treatment, patients have to pay for the tests themselves, even though they are entitled to receive free-of-charge diagnostic procedures according to the law (see **'Maxim's case'** below). The cost of clinical tests significantly influences demand for treatment and results of needs assessment.

> 'To diagnose viral hepatitis we need test systems. So far we have been performing only screening procedures. I think we haven't had any supplies of test systems for about two years now. How can we treat patients without diagnosing them? And what about our 240 patients who already completed treatment – they should be monitored every six months for three years, where will I get these tests? They won't come here for testing if they have to pay for it.'
>
> *Doctor-infectionist*

According to the general laboratory prices, the needed set of tests costs from 3,500 to 8,000 rubles. Besides specific tests, liver elastography is required (one FibroScan procedure costs 4,000–8,000 rub) or, alternatively, patients may apply to hepatology centers for liver biopsy. Interviews with respondents showed that elastography is not available at every medical facility – sometimes patients have to travel to another town or region to get it, or agree to be treated without it.

> 'We don't have FibroScan here in our town, and not at the regional center, either, although the regional clinical hospital plans to buy it. So the arrangement is as follows: every three months a FibroScan is brought from Moscow, and patients make appointments for the procedure. It costs 3,000 rubles. Patients can also apply for liver biopsy (for free, covered by mandatory health insurance). If we suspect that a patient has fibrosis, we send them to have liver biopsy and analyze the results.'
>
> *Expert*

Therefore, besides expenses for treatment that may be covered by the national program, patients have to spend an average of 20,000 rubles for laboratory testing and treatment monitoring, which significantly exceeds the minimum wage (6,050 rub). In the regions, the cost of diagnostic procedures is even higher, as limited supply of these services leads to their commercialization.

**Table 8. The cost of clinical tests required for the prescription of CHCV treatment**

| Laboratory diagnostics | Moscow | Ekaterinburg |
|---|---|---|
| **Hepatitis C virus, qualitative RNA detection (biopsy)** | 400–500 | 380–480 |
| **Hepatitis C virus, qualitative RNA detection (blood plasma)** | 400–500 | 480 |
| **Hepatitis C virus, quantitative RNA (blood plasma)** | 2000–3000 | 2300 –8000 |
| **Hepatitis C virus, genotype test (types 1, 2, 3) – (performed only together with the quantitative RNA test)** | 600–900 | 700 |
| **Hepatitis C Virus, advanced genotypic test** | 1500–2500 | 2400 |
| **Elastography of the liver (FibroScan)** | 4000–6000 | 4000 |

**Maxim Malyshev**
**Fighting for our rights: a quest to obtain free-of-charge HCV diagnostics in Russia**

In March 2011 I decided to apply for hepatitis C treatment, which should be provided free-of-charge to people living with HIV in Russia. In the Tver AIDS Center, I was told upfront that although the treatment is indeed free, I would have to pay for all the tests and doctor consultations in the course of treatment. By my conservative estimate, these additional costs would have cost about five thousand rubles. I was outraged – I have always thought that diagnostics was an integral part of treatment.

With the help from Mikhail Golichenko (senior associate at the Canadian HIV/AIDS Legal Network), I have filed the complaint – first to the Regional AIDS Center, and then higher up, to prove that this approach to treatment practiced in Tver region is unlawful. In March 2011, I sent a complaint to the chief of the regional AIDS Center. One month later I received an official response: written in bureaucratic language and full of links to various articles, it said that there was no money for the purchase of test kits in the region.

The next step was **to appeal the actions of chief physician to the then Department of Health of Tver region**. By law, the answer to the complaint must come within 30 days. However, it arrived only after three months. I called them, came by, listened to their promises and excuses. In September, when I visited them yet again, I filed another complaint – for inaction and non-compliance with procedures. And only in October, when I visited the Department one more time, have I received **a long awaited response** that only confirmed unavailability of free testing.

Then we went to the District Court to apply to the Ministry of Health of Tver region. In December 2011, the first hearing in court was held. Luckily, Mikhail Golitchenko was able to be there and represent me as claimant. From the defendant's side, there were lawyers from the Ministry of Health and the AIDS Center, as well as a doctor-infectionist from the AIDS Center. Unfortunately, the hearing had to be postponed, because I hadn't submitted a copy of court order to the defendant. The court heard our position and assigned the next hearing to 23 December. Yet, the first hearing already triggered some positive changes. The Ministry of Health confirmed in writing that before December 2011 they would purchase the tests for quantitative analysis of HCV RNA and test me free of charge. I am not sure how my previous application influenced the processes in the Department of Health (currently – the Ministry of Health), so that they began moving in the right direction and included quantitative tests in their procurement plans. I believe that our application played an important role, because during unofficial talks with the MoH officials and employees of the AIDS Center we learned that each of our statement had been discussed at the ministry, and the problem of the lack of hepatitis C diagnostics became a little clearer in the bureaucrats' heads. They realized that it wasn't enough to purchase qualitative tests, and that the patients were willing to sue them in court. It seemed that at that point the ministry should have accepted the complaint and concluded the trial. However, they kept on insisting that the rights of the applicant had not been violated.

On 23 December, at the court session, we expected the defendant's side to accuse me of being a 'bad patient', so we prepared a **convincing speech that I delivered at the hearing**. We expected to win and were really surprised when the court ruled that the applicant's claim to the Ministry of Health and the AIDS Center was… unlawful!

This didn't stop us, though. Having received a motivation report from the court, we submitted a **cassation complaint** to the Regional Court of Tver region. The third trial session was held on April 12, and this time it was different: the Regional Court reversed the decision of the District Court and fully upheld my claim! I could not believe my ears, so happy I was!

It took us more than a year to achieve this: thanks to Mikhail Golitchenko, Anya Sarang, the Andrey Rylkov Foundation and other people who supported us. We won! It means that we are strong, and we can make a difference!

The appellate resolution of the court and other relevant documents are available at our website: http://rylkov-fond.org/blog/health-care/hepatitis/hcv-treatment-max/

## Treatment rationing at the regional level as part of the PNP 'Health'

With no federal-level clinical protocols available, some regions have developed and approved their own treatment regulations. Various local norms for the implementation of HCV treatment programs have been introduced, that include diverse lists of indications and contraindications. However, these lists are usually not formulated clearly, and facilities make their own decisions about treatment – with reference to official documents and through special 'clinical commissions' – possibly established in order to reduce individual responsibility and counter prejudiced attitudes of some medical specialists.

> 'We have a commission at the level of the regional healthcare administration that selects patients for treatment. This commission is comprised of the deputy chairman of the regional health department, head of the hepatology department, deputy head of the academic department, our chief doctor, head of the treatment department. Together, they decide about providing treatment to patients. So after we, doctors-infectionists, conduct preliminary examination and send medical histories with all the test results to the commission, they decide collegially about the prescription of treatment. Usually, the commission presides once a month. It takes time before all the testing is done, anyway.'
>
> *Doctor-infectionist*

Some specialists still use clinical standards approved by the Ministry of Health, even though these guidelines do not include pegylated interferon (the RF Ministry of Health and Social Development, 2006).

> 'We use the 2006 standard approved by our Ministry of Health. It only covers in-patient treatment, though. All infectious diseases are regulated by standards, and those for hepatitis treatment are precise and strict. We treat patients the same way as they do it around the world.'
>
> *Expert*

The stage of liver fibrosis and indications to treatment are also interpreted differently. Some doctors consider cirrhosis a contraindication, while others perceive the risk of cirrhosis as an indication to treatment.

> 'Do they prescribe treatment to patients with liver cirrhosis?'
>
> 'Very, very carefully. Depending on the stage of cirrhosis. First, decompensated cirrhosis should be reversed back to a state of compensation. So, in cases of compensated cirrhosis – yes, treatment could be prescribed, but really carefully. And only in big hepatology centers, as advised in our guidelines. As for patients with a decompensated state – your so called 'treatment' may quickly move them closer to their last breath…'.
>
> *Expert*
>
> 'Yes, I give priority to patients with the risk of cirrhosis. We do place everyone on the waiting list, but first of all I'll take those who suffered more damage against those with zero fibrosis, as they may not even need treatment.'

*Expert*

## Individual approach to selecting patients living with HIV for CHCV treatment

In the absence of official clinical protocols for CHCV treatment for people living with HIV, which is the only group of patients distinctively supported by the state – they can receive treatment regardless of any medical commissions – decision-making mechanisms are localized and depend on the regional context and subjective opinions of doctors. Even in the AIDS Centers there are additional criteria for selecting patients 'in immediate need of treatment', according to which patients with HCV/HIV co-infection may be denied laboratory testing required for considering possibilities of treatment. For example, in one region HIV-infected people with a CD4 count less than 400 cells/$mm^3$ were not even viewed as candidates for treatment, while in another region similar threshold was set at 350 cells/$mm^3$.

> 'For patients with a CD4 count less than 350, HIV treatment should be provided, but few of them agree to ART – they still feel fine and you have to persuade them into treatment.'
>
> *Doctor-infectionist*

Another problem is that because of the gaps in the monitoring system and the absence of harm reduction projects, substitution therapy and contact with patients, most AIDS Center patients, having been diagnosed, return for a follow-up only at advanced stages, with a CD4 count so low that HIV treatment becomes a priority.

> 'It's very difficult to work with HIV-infected patients. I have checked the figures: out of the confirmed HBV and HCV diagnoses, more than 70% require HIV treatment. Those who start treatment here are at their lowest CD4 count, and most of them fail to reach the normal immune values, while I can't accept patients at 250. So, providing treatment within the system of AIDS Centers, to people with co-infections, is a very complicated and dangerous process.'
>
> *Doctor-infectionist*

In some regions patients with HBV are excluded from groups viewed as candidates for treatment. There is no clarity at which point HCV therapy should be prescribed in cases when ART is also an indication. Some doctors prefer to start ART, monitor its success and, based on results, estimate whether a patient would be able to adhere to hepatitis C treatment.

> 'About 40% of people with HCV who need treatment should first of all receive antiretroviral therapy. So, for almost half of patients the first step is HIV treatment, adjustment to it, establishing adherence, and only after that, if they are ready to cooperate with their doctor, they can start hepatitis C treatment. So it's not exactly true that there are too many cases of HCV and too little treatment – we don't have waiting lists for HCV treatment, because half of the patients need antiretroviral therapy to strengthen their immunity, which may increase their chances to clear hepatitis C.'
>
> *Doctor-infectionist*

People registered at psychiatric facilities are also excluded from treatment, as are patients with suspected TB, confirmed TB and undergoing TB treatment.

'If a patient has a history of tuberculosis, or has TB now, what kind of HCV treatment are we talking about? I understand that there are global guidelines, all those standards, but somehow they forget the problem of tuberculosis… These cases are very difficult to manage. They get anemia, opportunistic infections, and what not. So every month they should come back and have things controlled – laboratory issues, clinical issues, etc.'

*Doctor-infectionist*

Medical specialists in the regions have confirmed that active drug users or people with a recent drug using history are either not viewed as candidates for treatment at all, or considered as eligible patients only after longer remission. Some regions require 6 months off drugs, others – 12 months. Most doctors explain this by personal experience, when in the absence of adequate adherence support (such as substitution therapy) PWID stopped treatment after several injections. Some healthcare providers mentioned that such treatment is a waste of expensive medicines that could help other, more 'reliable' patients.

'If a patient is an active drug user, I don't see any sense in prescribing therapy. I will first convince them to resolve this problem. First deal with your problem, then we'll deal with other issues.'

*Expert*

'The law, the standards, the international recommendations, the global scientific evidence – they all recommend at least six months of abstinence. Any type of abstinence – from drugs or alcohol. Otherwise what's the point? Treatment is counter-indicative to such patients.'

*Expert*

Patients' wish to be treated is quite a weighty factor in decision-making about treatment: doctors tend to offer treatment to 'reliable' patients or those who they think will adhere to their therapy. Many doctors act upon their personal preferences – some take in married couples, thinking that parallel treatment may improve adherence in both, others prioritize treatment of medical workers.

**Estimating treatment needs as part of the Priority National 'Health' Project**

In the absence of standardized clinical recommendations and protocols, the regions develop their own approaches to preparing annual requests for medications as part of the national 'Health' program. In some regions, healthcare providers reported that they divide between medical facilities the quotas set at the federal level, and local doctors then prepare estimates of how many patients would be sent for preliminary examination this year.

'When the 'Health' program was launched, Rospotrebnadzor announced the regional quotas. Our region was part of the 14 territories who received quotas, and we were able to obtain test-systems and medications. Our quota was 100 patients per year. Every year, probably depending on availability of funds, we were told how much we could apply for. This quota was approved back in 2008. If it every changed, it changed downwards: initially we also included HIV-negative patients, but then received orders that we could only treat people with co-infections, so in the end we were left with the minimum quotas.'

*Expert*

In other regions, experts and doctors said that they were able to obtain as many medications as they requested on the basis of estimates made by doctors-infectionists on how many patients they would treat the coming year. These estimates included not just the number of patients who had been tested and were found eligible, but also the expected workload of doctors.

> 'We try to map out the approximate number of patients we may treat the following year, depending on how many HIV-infected patients had been tested for hepatitis. Not in 100% of cases they are able to conduct PCR tests needed for decisions about treatment eligibility.'
>
> *Expert*
>
> *« – How do you assess treatment needs – for example, as part of the national project?*
>
> – Every polyclinic is able to take a certain amount of patients. Their doctors make estimates of how many patients are eligible for treatment. Such-and-such number of patients for this medication, such-and-such number – for that medication.'
>
> *Expert*

Preferences and opinions of doctors about treatment eligibility criteria for patients with HIV/HCV are confirmed statistics published by several research sites *(see Annex 2)*. For example, by the end of 2011 in Ekaterinburg, out of 11,767 people registered as HIV-positive and 4,046 with the laboratory-confirmed CHCV, 256 had completed CHCV treatment, and 70 more were receiving therapy. That said, the AIDS Center doctor still considered that HCV treatment coverage was as high as 50%: 3,468 out of 4,046 patients had a CD4 count at 350 cells/$mm^3$ and were not on ART, therefore the potential treatment group was estimated at 578 patients – the remaining part of people HIV/CHCV.

In 2008–2011 in the Altay Region, treatment was provided to 282 patients out of 9,171 registered PLHIV and 3,700 people with HIV/HCV, which is less than 10% of PLHIV with laboratory-confirmed HCV. In Togliatti, as of 1 January 2011, 14,167 people were registered as HIV-positive, out of whom 5,177 were patients with HIV/HCV co-infection, and 6,368 – with HCV / HBV co-infection. Only 278 patients received CHCV treatment, which is about 5% of PLHIV with the documented HCV.

According to the data provided by the research sites, in the period 2007–2011, not more than 5–8% of the registered PLHIV who were also HCV carriers received treatment.

**Table 9: HCV treatment needs assessment and the provision of treatment by the end of 2011**

| Site | Number of registered PLHIV | Number of people with HCV | Number of patients who received HCV treatment | % |
|---|---|---|---|---|
| **Ekaterinburg** | 11,767 | 4,046 | 326 | 8% |
| **Altay region** | 9,171 | 3,700 | 282 | 8% |
| **Togliatti** | 14,167 | 5,177 | 278 | 5% |

**Readiness of healthcare systems to provide HCV treatment, and how treatment is organized**

The system of education and staff training to provide hepatitis C treatment at the federal and regional levels has multiple gaps, and healthcare systems are not prepared for expanded treatment. Even though the annual number of patients on treatment is minimal, the surveyed doctors reported that the burden of HCV treatment at AIDS Centers is already almost critical. HCV treatment is often prescribed and monitored by the same doctors who manage HIV cases. In several other AIDS Centers, patients with hepatitis are managed by physicians.

> 'It's really hard for our infectionists, who already have 5000 people on the prophylaxis HIV registry, plus 500–600 patients on ART, to take up cases of viral hepatitis. The clinical follow-up is almost the same as for PLHIV – examination within one month, then within 3, 6 and 12 months. The patients should also be referred for testing. The doctors' workload increases manifold, which is physically impossible – especially since our doctors are already overbooked with their main group of patients. That is why cases of hepatitis are currently being managed by our physician, although she is also very busy – 356 patients on regular dispensary observation.'
>
> *Doctor-infectionist*

Infectious diseases specialists often lack adequate training to manage HCV patients: when piloted, PNP did not involve staff enhancement, and additional training was offered only to small proportion of medical specialists – some of them were trained through financial support of pharmaceutical companies, others attended various educational events. In most cases, treatment is being prescribed and monitored by self-taught doctors.

> 'Try and visit any ordinary polyclinic, ask any physician what they think about HCV treatment. No one will tell you how to treat patients with hepatitis. I can only name five or six specialists who are treating patients with hepatitis (and have professional competence to do so). They are the ones who use every chance they get to visit presentations or conferences, as they want to stay tuned.'
>
> *Expert*

We don't have working hours regulations for infectionists (how many patients they should see, whether they are hospital cases or outpatient clients).

> 'Sometimes I see up to 40 people in one day. I'm working from early morning till late evening. Besides that, I have other tasks: reporting, lectures for medical staff, etc. A doctor-infectionist is responsible for educating everyone. We also get assignments to raise awareness among the general population. So, we've really been snowed under with work. That is why specialists seldom apply for this position.'
>
> *Doctor-infectionist*

Moreover, the doctors don't get paid enough.

> 'Have you seen our wage rates? The first salary step for a doctor is four thousand rubles, not more. Later, if you have worked for many years, you get your track record, category and all that. But the initial rate is lower than the minimum wage.'

*Doctor-infectionist*

Doctors' workload is also influenced by the local system of distributing medications. In some regions, doctors hand out medications to patients (once a month, or less frequently). In other regions, to avoid the risks of unauthorized use or breach of storage conditions, doctors prescribe injections under observation, which significantly increases the burden on the procedure rooms.

The hierarchy and stages of hepatitis C treatment are also not defined. In some regions, HCV treatment is considered a highly specialized medical intervention owned by in-patient hepatology facilities, whereas in other regions HCV care is an outpatient service provided by local polyclinics. In some places, specialized hepatology centers were established – normally, all patients in treatment should be managed by these. However, experts think that to achieve the task of expanded treatment and improved patient coverage, maximum decentralization is required.

> 'Are there good specialists in HCV treatment in the regions? No. Who can diagnose hepatitis properly? Only the specialized high-level hospitals, with PCR, FibroScan and liver biopsy readily available. Big cities have it all, but 'the masses' live in the regions. We do see here patients from the regions who are willing to be treated, but they are here for their own money. Very dedicated people, they are.'

*Expert*

In particular, in Samara region and Togliatti, hepatitis treatment was decentralized from the start at the level of polyclinics: doctors-infectionists manage all patients from their district.

> 'Of course, treatment should be provided in polyclinics. It is an outpatient procedure. These patients cannot all be placed in a clinic. That would require a big facility, but here in Togliatti we don't have one. So we decided to do it in polyclinics.'

*Expert*

Managing medications is a huge bureaucratic burden. Bulk purchases made by PNP 'Health' are transferred to the regional AIDS Centers, which, in their turn, send medications to the local medical facilities. Doctors not only have to hand out medications, which is unusual for them, but are also obliged to fill in numerous reporting forms.

> 'I wish I just knew that the drug is available and is stored in the pharmacy, and that I don't have to fill in three dozens of reports for one PEG-IFN package. We report to Rospotrebnadzor monthly, and I'm like a non-stop counting machine for this national project. When we decided not to divide medications and send them to the hospital, they were very relieved – no more reporting for them. These twenty ampoules, they said, don't make a difference here, while you have to report to everyone and everybody.'

*Doctor-infectionist*

**Hepatitis C treatment for people without co-infections**

While there is progress in treating HCV in people living with HIV, and doctors and healthcare administrators at least have a feeling that they are moving in the right direction, HCV as a monoinfection is still a problem. In the absence of a federal program of universal HCV treatment, some regions are

designing their own programs to treat HCV monoinfection – but their coverage is minimal: out of the estimated thousands or even tens of thousands of patients, treatment is provided only to tens of patients per year, and these patients have to pay for diagnostic procedures out of their own pockets. People with absolute indications for treatment are placed on patient registries and waiting lists. They have to wait for years, as there are several hundreds of patients in front of them.

> 'The targeted regional program has a strictly defined budget: for example, in 2011 treatment budget was 103 mln rubles, which covered 430 patients. This figure was divided between all the towns and districts. We have many polyclinics, but only five of them are part in the program. And the waiting list is huge, it has been there since 2007. When the national project started, and people found out that you could get treatment for free, we started to put them on the waiting list. Not everyone – just the patients with clinical indications for therapy. Currently, we have around 300 people on our waiting list.'
>
> *Expert*

Some doctors have found a way to provide additional CHCV treatment as part of the compulsory medical insurance – to beneficiaries of federal subsidies who apply for a disability status. During the first years, the Priority National Health Program also covered treatment for medical workers, but later this component was limited to PLHIV only.

As governmental funding for HCV monoinfection is insufficient, patients often have to pay for treatment themselves. To treat genotypes 2 and 3, doctors sometimes offer linear interferon to patients who cannot afford pegylated interferon, which is considered sub-standard according to international approaches.

> 'We have patients who pay for their treatment – the biggest group is with genotype 3, as the prices are more or less affordable. The first genotype is a real issue – treatment costs way too much, our people cannot pay for it, only the very few. Genotypes 2 and 3 are sometimes treated with the ordinary interferon produced in Russia, and there are forms of ribavirin that are also produced here. Such treatment costs about 5–7 thousand rubles per month.'
>
> *Expert*

In doctors' opinion, the patients who receive treatment as part of governmental programs show higher levels of adherence to treatment, especially if compared to treatment compliance among PLHIV: since hepatitis C therapy became more available for this group, they no longer consider it exceptional.

> 'Every patient who got free treatment is still in the program. Their fortune has finally smiled at them, of course they don't miss the chance. They stay on treatment.'
>
> *Expert*

## Factors determining patients' demand for HCV treatment

Apart from gaps in the healthcare system, low levels of HCV treatment uptake are associated with patients' demand for treatment. Theoretically, as demand grows, doctors get a clearer picture about

treatment needs in their area. The authors of this report, having analyzed responses from patients both in and outside of treatment programs, have summarized factors influencing demand.

Treatment-naïve people with HCV knew little about their disease, antiviral treatment and possibilities to get it in their region. One would think that patients would be at least minimally informed about their condition after they had been diagnosed. Yet, most respondents noted that they did not get *any* information about hepatitis C after the doctor announced that they had HCV.

> ' – Have you spoken to your doctor about hepatitis?
> – No, she just said I had HCV, that's it.'
>
> *Ekaterinburg, female, 28 y.o.*

A person diagnosed with hepatitis in a penitentiary reported the following:

> ' – Naturally, there is no echo-scan in prison. The doctor just told me – ok, you have hepatitis C, you won't live much longer. They scared me to death, actually. He said I had five to ten years to live, not more. That's how they give you counseling in prison. They don't care if you live or die here – it's prison, man.'
>
> *Togliatti, male, 40 y.o.*

Most people diagnosed with hepatitis C did not know anything about treatment possibilities.

> ' – Have you heard about hepatitis C treatment?
> – No, I haven't. I heard it's almost incurable. You can treat it, but it's difficult, and there are few drugs available. I don't really know about it, and I have never tried to find out, to tell the truth.'
>
> *Togliatti, male, 39 y.o.*

One of the respondents noted that the level of awareness among people living with hepatitis is extremely low, except for people with HIV co-infection who are in regular contact with the AIDS Centers.

> 'I think that people don't know anything about their condition. I mean, those who have hepatitis but don't have HIV. I think many people, if not everyone, are unaware of what's going on. They don't know that treatment is available.'
>
> *Togliatti, male, 29 y.o.*

**Drug dependence as a barrier to treatment**

Drug dependence is a key formal factor limiting access to treatment of hepatitis C and other socially significant diseases in Russia. In the absence of effective drug treatment and support systems tailored to the needs of patients with addictions, hepatitis C treatment is almost unavailable to this group of the population.

> ' – Was it a special requirement, that you should stay off drugs?

– Yes, they required it. They said that I should not use drugs. Active drug users were not even viewed as candidates for the treatment program. Allegedly, there is no point in treating them. Why should you treat a junkie if he shoots up every day'.

*Ekaterinburg, male, 30 y.o.*

However, none of the surveyed sites could offer adequate drug treatment services. Most respondents repeatedly sought drug treatment assistance, but available treatment was far from the evidence-based standards and did not have the intended effect.

' – Yes, I was on drug treatment. If you can call it treatment. They [the governmental drug treatment clinic] had a 18-day course, with work therapy.

– Work therapy to treat drug dependence? That's how doctors called it?

– It was like an additional method to enhance effectiveness of treatment. We had to wash windows in our ward. It looked like prison, actually. I was there two times [for treatment], and later I wanted to go there again, but they didn't take me, as free-of-charge drug treatment courses are only available once a year.'

*Togliatti, female, 29 y.o.*

In the absence of effective drug treatment services, many patients are on the verge of despair because of the multiple problems they face.

'I wanted to kill myself, as I couldn't get off drugs. I didn't understand how to continue, and I couldn't constantly live on drugs. I hoped I would die, but I survived.'

*Togliatti, female, 29 y.o.*

People with drug dependence get into an endless circle of hopes and problems, and they cannot struggle out of it on their own.

'I had occasional problems with drugs, and there are periods when I'm using regularly, so it doesn't make sense to start treatment then. It's like an ongoing cycle. I had short remissions, managed to stay clean from six to ten months, took care of my health, tried to be responsible, my immune status grew and I was ready to start treatment. And then – boom! – something happens. And I cannot think of treatment anymore, maybe I don't even want to live. My only problem is how and where I will find drugs. It's an endless circle: you have hopes and aspirations, your health gets better – and then something happens, and you are back to feeling worse again. And so on...'

*Ekaterinburg, male, 30 y.o.*

Stigma and discrimination against people who use drugs not only lock them out of treatment programs, but also block access to the basic information about hepatitis C. Our respondents described cases of abuse and degrading treatment in health facilities, and examples of doctors' refusal to provide treatment:

'Somewhere in 2002 it [hepatitis] started to bother me a lot, I felt really awful. I tried to go to doctors, but they told me I should prepare for the worst, because there's no life ahead of me. They said I'd killed everything inside me with poisonous drugs. Well, I did feel terrible, that's true. And the doctors said they would not treat me and that I was on my own. Once I came out after such a visit to an infectionist and realized that I would not set foot in there again, ever.'

*Togliatti, male, 44 y.o.*

Another patient mentioned that the only attitude he had ever seen from doctors is that of insults and contempt:

'They either start offending you directly, or show disgust. Sometimes they don't even say anything, but you can tell from their attitude. Their faces change when they see you: like you are a bastard, a dirty dog. We've been through wars, and who are you?'

*Togliatti, male, 38 y.o.*

Naturally, with such attitudes from medical staff drug users tend to avoid healthcare institutions and do not seek medical assistance or treatment. They fear the system and do not trust it. Many people with HCV mentioned that their communication with doctors made them think they did not deserve any treatment. In the patients' community there is a perception – encouraged by doctors – that HCV treatment is a disciplinary incentive for the 'proper' and 'moral' lifestyle: for not using drugs, starting a family or keeping up with good behavior.

'When I applied [for treatment] – not married, not anonymous – they said no way, because they obviously did not consider me socially approvable. Why would they give me expensive therapy if I would only start it and fail. They did not believe in me. The government allocates money for it, and why should they waste it.'

*Ekaterinburg, female, 28 y.o.*

Stigma from doctors gradually transforms into self-stigma in patients. Some of them mentioned that they never sought HCV treatment because they did not think they were worthy of it:

'I called [the doctors] in February when I already knew about HCV treatment. The doctor had said that treatment was available, but nobody offered me anything. So I thought I didn't deserve it yet, as it's very expensive. She prescribed me some pills, but I said I was taking oats. She said I should continue with it for a month, then take the pills.'

*Barnaul, female, 39 y.o.*

**The cost of treatment**

Hepatitis C treatment for HIV-negative individuals is practically not available. Only a very small proportion of patients are eligible to get treatment from the state budget, while others cannot afford it.

' – Have you ever thought about getting HCV treatment?

– Sure I have, but it's way too expensive – you need a fortune to get cured. So I won't even bother: I cannot afford it. I don't have many relatives, only my mother, grandmother and sister, so I don't count on anyone's help. I know that it is an ordinary disease, but we, simple working class people, do not have any chances to get treatment.'

*Barnaul, male, 37 y.o.*

Most patients on waiting lists of the hepatology center hope to get free-of-charge treatment, but they have to wait for years. One patient said that he was hoping that new, less expensive drugs will appear, making treatment more affordable.

'Yes, once I had a conversation about treatment – that I should improve my health, save up some money and buy those pills. I've heard that there are good medications and the therapy that works, and that new drugs have appeared, but they are extremely expensive, while taking cheaper drugs will not be good for your health. So we always postponed it, hoping that new medications would appear soon – those that are better tolerated and are not so unbelievably expensive.'

*Ekaterinburg, female, 28 y.o.*

**Scientifically ungrounded methods of HCV treatment**

Left without access to HCV therapy, patients start thinking about other treatment strategies, and many of them resort to 'alternative medicine'.

' – So you tried to treat it yourself?

– Yes, I tried to maintain some stability, at least… by using herbs. You know, old ladies and inmates always have their ways, and some of their advice is quite good. To use dried burdock root or celandine, for example. My grandmother cured herself from cancer like this.

– And which holy grass did you use to treat hepatitis?

- I used holy thistle. I've read that it's good for renewal of liver cells. I didn't really believe in it, but I took it as a prevention measure. My mother also bought me some herbal pills. I took them as well.'

*Barnaul, male, 37 y.o.*

'Once in the diagnostic room a man was saying that he had had cirrhosis, but he took oats instead of pills – he ate, like, five sacks of oats (he said he would soon be laughing like a horse!). Yes, I know about oats. When I was little and had jaundice, my grandmother made me drink boiled oats. People who are a bit older, they all tell me I should take oats, not pills.'

*Barnaul, female, 39 y.o.*

Patients often take various hepatoprotectors, effectiveness of which is not proven – on the contrary, some of them have been recognized as negatively affecting the liver. Many doctors prescribe these drugs, and patients have to buy them out of their own pocket:

> 'The doctor prescribed 'Heptral' that I had to buy myself. I took a course of 'Heptral', now I'm taking 'Sufodex'. But it's all expensive, you know. Two ampoules of 'Heptral' daily, it's 4,500 rubles for the course. Then I had to take other pills for ten days, which is another 3,500 rubles. And I still have to buy 'Sufodex'. Before that I took 'Ursan' – it was around 1,500 per package.'
>
> *Ekaterinburg, male, 37 y.o.*

Thus, antiviral treatment is not available to most patients with Hepatitis C, and people with drug addiction are almost fully excluded from treatment. Limited access to treatment for drug users results from widespread stigma and the lack of adequate drug treatment and support services (in particular, rehabilitation programs, social and psychological support services, and methadone / buprenorphine substitution therapy). As the quality of counseling and education of patients is low, many people resort to scientifically ungrounded and ineffective methods of treatment.

**Conclusion**

The system of hepatitis C treatment in Russia is extremely underdeveloped and is unable to have a significant impact on the epidemic. Treatment is available to very limited numbers of patients, the reason for this being high cost of medications and poor organization of the healthcare system: absence of clinical protocols and an integrated patient registry, inadequate management of treatment processes (centralized treatment, unprepared medical staff) and insufficient efforts aimed at identifying patients and enrolling them in treatment programs. Low treatment uptake is a result of poor education of patients and absence of quality pre- and post-test counseling services. Treatment is prescribed based not on unbiased indications, but on arbitrary decisions of doctors. The group of the population most affected by the hepatitis C epidemic – people who use injecting drugs – are excluded from treatment on the basis of normative requirements approved by most doctors. The main barriers to the expansion of hepatitis C treatment are lack of adequate drug treatment services and widespread stigma towards people who use drugs. The national and regional treatment programs have limited funds, and treatment is provided to a very small proportion of patients: even among people with HIV co-infection, the population officially eligible for HCV treatment, less than 10% of those in need receive treatment.

Expanding access to and improving quality of HCV treatment programs should be acknowledged as one of key priorities for the Russian healthcare system. Based on the analysed data and interviews, the authors of this report have developed recommendations for the expansion of treatment programs (see Recommendations in the 'Executive summary' section).