# Possible strategies for the implementation of WHO program on the elimination of hepatitis C in Ukraine by 2030

## [1]I. Zaytsev, [2]V. Potii, [3]V. Kiriienko

[1]**National Medical University named after A.A. Bogomolets, Kyiv, Ukraine;** M.D., Professor, department of therapy, infectious diseases and dermatovenereology of postgraduate education; **Corresponding author -** e-mail: igor.a.zaytsev@gmail.com

[2]**Donetsk National Medical University, Liman, Ukraine;** Assistant, department of epidemiology, infectious diseases and laboratory diagnostics

[3]**National Medical University named after A.A. Bogomolets, Kyiv, Ukraine;** Ph.D., department of therapy, infectious diseases and dermatovenereology of postgraduate education

## Abstract

**Introduction.** The article describes the model of natural history of hepatitis C virus the use of which makes it possible to assess the dynamics of the infected population from 2015 to 2030 in natural history and under the influence of the strategies of antiviral therapy, namely, the changes in the number of infected populations, the progression of the diseases, patients' proportion with different stages of fibrosis and also the mortality which is associated with final stages of liver disease. In addition, there are estimated data on the number of the patients that are subject to annual diagnosing for treatment in accordance with specific therapy strategies which is necessary to achieve the results provided by the WHO program for the elimination of hepatitis C virus in Ukraine by 2030.

**Material and method.** The study included 897 patients with chronic hepatitis C virus in whom the activity and stage of the disease were determined by liver biopsy or non-invasive tests (FibroTest, FibroTest / ActiTest, FibroMax). All the patients were divided by sex and

age into the age groups with a 5-year interval: from 0 to 4 years, 5-9, 10-14, 15-19, 20-24, 25-29, 30-34, 35-39 , 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75 and more years.

**Results**. According to the model of natural history of hepatitis C virus the number of the infected population in Ukraine should be reduced by 30% by 2030 of which 80% of the patients will die from decompensated LC and HCC. To reduce the mortality from final stages of liver disease 42.2% of the infected population should be treated according to selected therapy strategies. In this connection from 2016 to 2030 it is necessary to identify 65% and 77% of the patients with fibrosis stages F0-F4 for Strategies No. 1 and 2 respectively.

**Conclusion.** To reduce the mortality from decompensated cirrhosis and hepatocellular carcinoma it's necessary to treat 42.2% of the infected population according to selected treatment strategies. To treat the required number of the patients according to Strategies No. 1 and 2 it is necessary to identify 65% and 77% of the patients from the estimated number of infected populations respectively.

**Keywords: hepatitis C virus, natural history of hepatitis C virus, elimination of hepatitis C virus, mathematical modeling, fibrosis stage, therapy strategies, population prediction.**

**Introduction**

Viral hepatitis C (VHC) is the second most frequent cause of liver cirrhosis (LC) and hepatocellular carcinoma (HCC) in the world [1]. Conducted pilot studies in Ukraine suggest that about 1.3 million of Ukrainians [2-4] are infected with hepatitis C virus (HCV) that makes VHC a serious problem for the health care system. In recent years a significant progress has been made in the investigation of the mechanisms of viral replication resulting in the emergence of the new generation of direct-acting antiviral drugs (DAA) that increased the efficacy of the therapy to 95%-100% (up to 85% -99% in patients with lC) and reduced its duration to 12-24 weeks [5-8]. Opened prospects in the management of HCV infection allowed WHO to propose "Viral Hepatitis Elimination Program" which is designed for 15 years and based on the principles outlined in the publication "Prevention and Control of Viral Hepatitis Infection: Framework for Global Action". The program was supported by 194 countries [9] including Ukraine. The program targets are to reduce the number of new cases by 90% by 2030 and the mortality rate from final stages of liver disease by 65%. In the then-issued WHO technical paper "Manual for the development and assessment of national viral hepatitis plans: a provisional document. World Health Organization 2015" [10] priority tasks

are to assess the burden of viral hepatitis in the country and determine the necessary resources for the implementation of the WHO program.

The aim of this study was to create a model of natural history of chronic HCV as a part of the national strategy for the elimination of HCV infection in Ukraine from 2015 to 2030 inclusive. With the help of the created model it is planned to determine the burden of VHC in Ukraine, to assess the effectiveness of different strategies for VHC patients' treatment in achieving the goals of the WHO program, to select the most preferred therapy strategies and in terms of the achievement of the WHO targets at minimum costs to determine the minimum number of the patients who is necessary to be diagnosed to have a possibility to treat the required number of the patients according to selected treatment strategies.

**Materials and methods**

From 2011 to 2014 897 patients with chronic hepatitis C (CHC) were enrolled in the study in whom the activity and stage of the disease were determined by liver biopsy (184) or non-invasive tests of FibroTest (8), FibroTest / ActiTest (396), FibroMax (309). All the patients were divided by gender and age into age groups with a 5-year interval: from 0 to 4 years, 5-9, 10-14, 15-19, 20-24, 25-29, 30-34, 35-39 , 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75 and more years.

The number of new cases of CHC was considered equal to 80% of the number of the reported cases of acute hepatitis C (ACH) [11]. The incidence of ACH was calculated on the basis of the regression equation obtained by nonlinear regression analysis of the dependence of the actual incidence of ACH in Ukraine from 2003 to 2014, from the observation year: $Z = \exp(121.796-0.0603 \times x)$, where Z - the incidence of ACH, $x$ – the observation year. The total number of the patients with ACH was considered equal to the calculated incidence multiplied by 7 [2].

In view of the absence of any data to assess the dynamics of fibrosis progression in VHC patients in Ukraine they were borrowed from the paper by H. Razavi in co-authorship [12]. The frequency of decompensation of LC in our model was 7.2% per year and the death rate from LC - 34.3% of the number of the patients with decompensated LC [13].

The minimum number of the patients who is necessary to be diagnosed in order to be able to treat the required number of patients according to selected treatment strategies were determined by formulas 1 (for Strategy No. 1) and 2, 3, 4 (for Strategy No. 2) for the periods from 2015 to 2022, 2023 and from 2024 to 2030 respectively.

X= 42000*100/A – B (1),

where X - the number of patients who is necessary to be diagnosed annually; A - the proportion of the patients with F3/4 in the population of patients with hepatitis C virus in the current year; B - the number of diagnosed patients in previous years with F0-2 in whom the disease was transformed into F3 the previous year.

$$X_{15-21} = \frac{\left(\frac{41000}{5} * 2 - F4_{15-21}^{3\to4}\right) * 100}{F4_{15-21}} \quad (2),$$

where $X_{15-21}$ - the number of the patients who is necessary to be diagnosed annually from 2015 to 2021; $F4_{15-21}$ - the proportion of patients with F4 in the population of patients with hepatitis C virus from 2015 to 2021; $F4_{15-21}^{3\to4}$ - the number of diagnosed patients in previous years with F0-3 in whom the disease was transformed into F4 the previous year

$$X_{22} = \frac{\left(\frac{41000}{14} * 7 - F4_{22}^{3\to4}\right) * 100}{F4_{22}} \quad (3),$$

where $X_{22}$ – the number of the patients who is necessary to be diagnosed in 2022; $F4_{F22}$ - the proportion of the patients with F4 in the population of patients with hepatitis C virus in 2022; $F4_{22}^{3\to4}$ - the number of diagnosed patients in previous years with F0-3 in whom the disease was transformed into F4 in 2022.

$$X_{23-29} = \frac{\left(\frac{41000}{21} * 15 - F4_{23-29}^{3\to4}\right) * 100}{F4_{23-29}} \quad (4),$$

where $X_{23-29}$ – the number of the patients who is necessary to be diagnosed annually from 2023 to 2029; $F4_{23-29}$ - the annual proportion of the patients with F4 in the population of patients with hepatitis C virus from 2023 to 2029; $F4_{23-29}^{3\to4}$ - the number of the patients diagnosed with F0-3 in previous years who had a disease progression from F3 to F4 last year.

**Results and discussion**

The initial data for building the model were the size of the population of HCV patients in Ukraine (about 1.5 million at the beginning of 2011), the distribution of fibrosis in the population in stages (the proportion of patients with fibrosis F0, F1, F2, F3, F4 was 23.5%, 21%, 24%, 13% and 18.5% respectively). The increase in the number of patients in the model is possible only due to new cases of infection with previously healthy people with ACH (Figure 1).
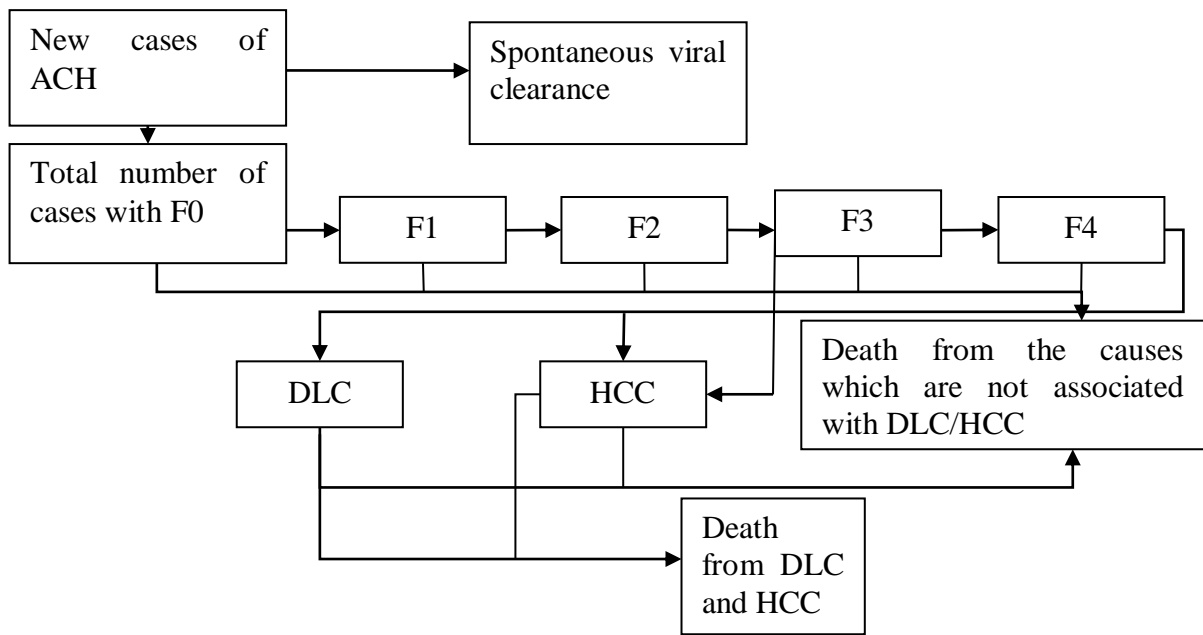
Figure 1. The model of natural history of the disease for the entire population of patients with chronic hepatitis C virus in Ukraine

The reduction the population is possible due to the death from the causes which are not associated with hepatitis (reaching the age of over 75 years) as well as from decompensation of LC and HCC.

According to the constructed model in natural history of the disease from 2011 to 2030 the number of patients with initial stages of fibrosis will be decreasing and with a severe form of fibrosis and LC - increase. As a result, it will lead to the increase in the number of patients with decompensated LC and HCC, and hence, the mortality which is associated with final stages of liver disease (Figure 2).

According to our prognoses by 2030 the number of VHC patients in Ukraine compared to 2016 (the year when the WHO Elimination Program began to be implemented) should be decreased by 381605 people of which 323427 patients will die from decompensated HC and HCC. During this time the population will be filled with 30745 new cases of chronic hepatitis. In this case the proportion of patients with F3/F4 will increase from 36.4% at the end of 2015 to 56.5% by 2030. In addition by 2030 the population of patients will "age": according to the results of modeling most of the lethal outcomes which are associated with end-stages of liver disease will be at the age of over 55 years, and from 2011 to 2030 the proportion of older patients among the dead will be increasing. So, if from 2012 to 2020 the proportion of the dead under 50 years will be 34%, then from 2021 to 2030 this index will

decrease by 14% and on the contrary, the proportion of the dead over the age of 60 will increase from 36% to 56%.
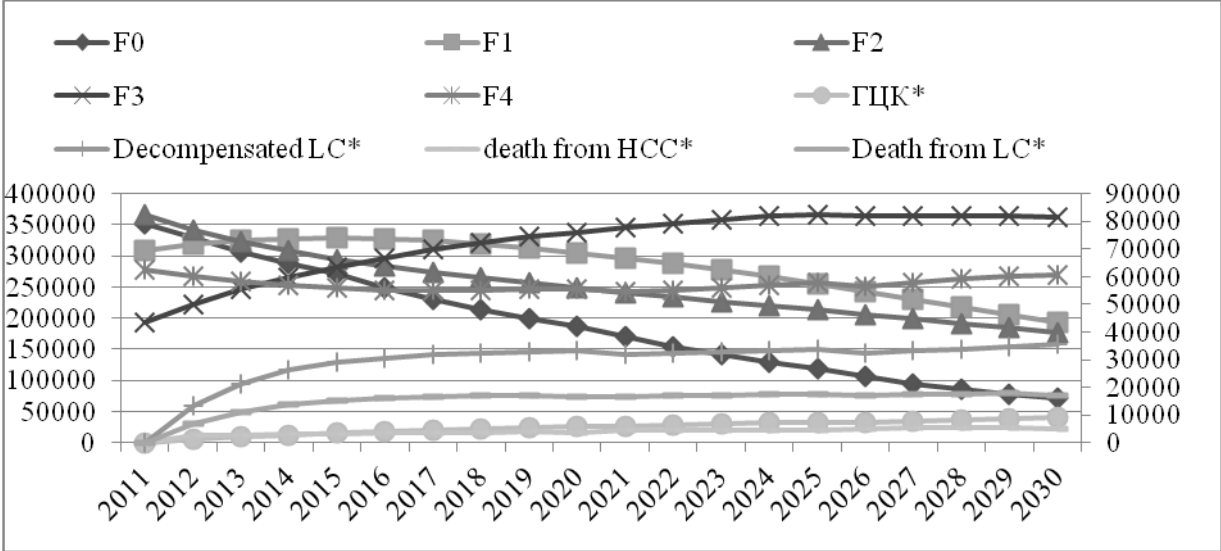


Figure 2. The dynamics of the population of CHC patients in Ukraine in natural history of the disease from 2000 to 2030 taking into account new cases of the disease (* - the data are projected onto the right axis)

Thus, these data clearly indicate the need to counteract natural history of the disease and make the implementation of the WHO Elimination Program in Ukraine urgent. If the latter is performed, a 65% mortality reduction over the period 2016-2030 will be equivalent to the survival of more than 100.000 patients (Figure 3).



Figure 3. The dynamics of the number of the dead from CHC in Ukraine for 2015-2030 in natural history of the disease and in the case of the implementation of the WHO Elimination Program

The only possible way to reduce the mortality from VHC is the antiviral therapy (AVT) of a sufficiently large number of patients. When modeling the impact of AVT on the population of CHC pa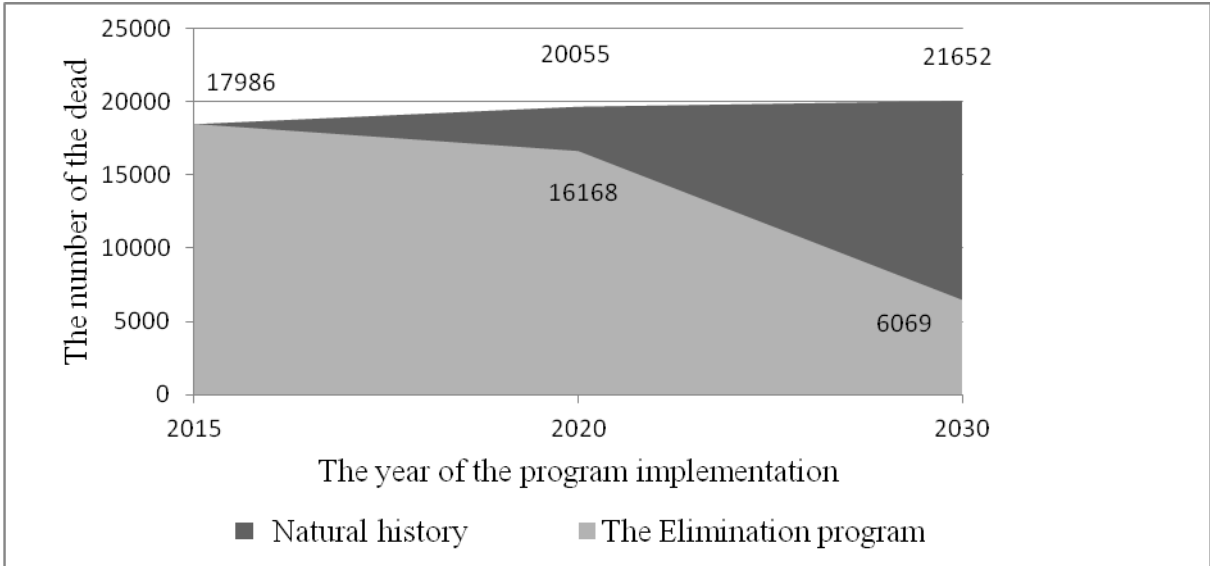tients we proceeded from the following initial assumptions (Strategy No. 1): a) only patients with severe fibrosis/LC will receive treatment in a proportion of 50% to 50%; b) the annual number of the patients who receive treatment from 2016-2030 will be the same; c) the treatment will be performed only with DAA (the effectiveness of the patients' treatment with LC in the model will be 90%, without LC - 95%).

The modeling showed that within the framework of Strategy No. 1 to reduce the mortality by 65% by 2030 it was necessary to provide treatment for 615 000 patients with F3/F4 that would amount to 42.2% of the total VHC population in Ukraine in 2015. At the same time, the number of the dead for the period from 2016 to 2030 will decrease by 123307 people compared to natural history of the disease (Table 1). However, despite the formal achievement of the goals of the elimination program there will be 691599 VHC patients in Ukraine by the end of 2030, and the progression of the disease to F3/F4 will occur in 478494 patients with F0-F2 as these patients will not receive any treatment. Obviously, the latter is the biggest shortcoming of Strategy No. 1. Based on this fact we considered other treatment strategies that would lack the drawbacks of Strategy No. 1 and achieve the goals of the WHO program at the same time. However, the costs of treatment should not increase, i.e. the total number of treated patients will be the same (41000 people annually).

By enumerating various therapies we first refused from the strategies in which the possibility of patients' treatment with F0 and then with F1 was suggested as it was impossible to achieve the goals of the Elimination Program, and the mortality was higher than in the implemention of Strategy No. 1 (*these data are not given in the article*). Therefore, while maintaining the costs of the therapy at the same level we can only talk about compromise strategies. In this regard we have developed an alternative strategy that involves the introduction of the patients with moderate fibrosis (F2) (Strategy No. 2) in Treatment Program. At the same time the distribution of the funds for treatment over the years and the degree of fibrosis should differ. In the first 7 years of the implementation of the Elimination Program (from 2016 to 2022) the number of the patients receiving treatment should be correlated with the fibrosis stage F2:F3:F4 as 2:1:2, in the last 7 years of the Program implementation (from 2024 to 2030) the patients' ratio with F2:F3:F4 receiving treatment should be changed by 1:5:15. The implementation of Strategy No. 2, on the one hand, will prevent the progression of the disease from F0-F2 to F3/F4 in 96265 people, on the other

hand, it will achieve the goal of the WHO Elimination Program: the number of deaths by 2030 will be reduced by 68.1% (target - 65%) (Table 1).

Table 1. The assessment of the effectiveness of possible strategies for the treatment of hepatitis C virus patients in Ukraine

| Datum | Natural history | Strategy | |
| --- | --- | --- | --- |
| | | No. 1 | No. 2 |
| The number of treated patients | 0 | 615000 | |
| The number of cured patients | 0 | 568875 | 566750 |
| The number of dead patients from decompensated LC and HCC | 323427 | 200120 | 212794 |
| The number of the patients with the progression of the disease from F2 to F3/F4 | 478494 | 478494 | 382229 |
| The patients' population by the end of 20130 | 1118530 | 691599 | 679058 |
| Of them F0/F1/F2/F3/F4/ decompensated LC/HCC (%) | 6.3/17.3/ 15.9/32.4/ 24.1/3.2/0.8 | 10.3/27.9/ 25.7/27.4/ 6.8/1.4/0.5 | 10.5/28.4/ 21.2/33.7/ 4.3/1.4/0.5 |
| Of them decompensated LC and HCC (abs.) | 35407/ 9021 | 9909/ 3447 | 4478/ 1253 |
| The number of saved lives | 0 | 123307 | 110633 |
| The number of the dead in 2015 | 17986 | 17986 | 17986 |
| The number of the dead in 2020 году abs./in % in relation to 2015 | 20055/ 111.5 | 16168/ 89.8 | 16977/ 94.3 |
| The number of the dead in 2030 abs./in % in relation to 2015 | 21652/ 120.3 | 6069/ 33.7 | 5731/ 31.8 |

The second goal of our study was to determine the number of the patients with F0-F4 who need to be identified from 2015 to 2029 in order to be able to treat the required number of the patients with F3/F4 according to Strategy No. 1 and F2-F4 according to Strategy No. 2 from 2016 to 2030.

According to the created model of natural history of VHC from 2015 to 2029 the number of VHC patients will decrease from 1471433 to 1163752 people due to the prevalence of the mortality from HC and HCC over the morbidity of ACH. In this case the proportion of the patients with severe fibrosis and LC will increase and with mild and moderate - decrease respectively (Table 2).

Table 2. The proportion of the patients with fibrosis stages F3/F4 and F2, F3, F4 in natural history of the disease

| Year | The number of infected population at the beginning of the year | The proportion of the patients with fibrosis stages (%) | | |
|---|---|---|---|---|
| | | F2 | F3 | F4 |
| | | | | |
| 2015 | 1471433 | 20.9 | 18.0 | 17.2 |
| 2016 | 1453867 | 20.2 | 19.3 | 17.0 |
| 2017 | 1437310 | 19.7 | 20.7 | 17.1 |
| 2018 | 1419893 | 19.2 | 21.9 | 17.2 |
| 2019 | 1401866 | 18.9 | 22.9 | 17.5 |
| 2020 | 1383372 | 18.5 | 23.9 | 17.8 |
| 2021 | 1350380 | 18.2 | 24.9 | 17.6 |
| 2022 | 1331602 | 18.1 | 25.9 | 18.1 |
| 2023 | 1312319 | 17.8 | 26.9 | 18.7 |
| 2024 | 1292547 | 17.6 | 27.8 | 19.3 |
| 2025 | 1272308 | 17.3 | 28.6 | 19.9 |
| 2026 | 1226832 | 17.0 | 29.5 | 19.7 |
| 2027 | 1206496 | 17.0 | 30.1 | 20.7 |
| 2028 | 1185463 | 16.8 | 30.7 | 21.7 |
| 2029 | 1163752 | 16.5 | 31.3 | 22.5 |

In this regard the need to diagnose new patients with VHC and F0-F4 fibrosis for the implementation of Strategy No. 1 will be steadily declining from 112691 patients in 2015 to 35,859 in 2029 (Figure 4).
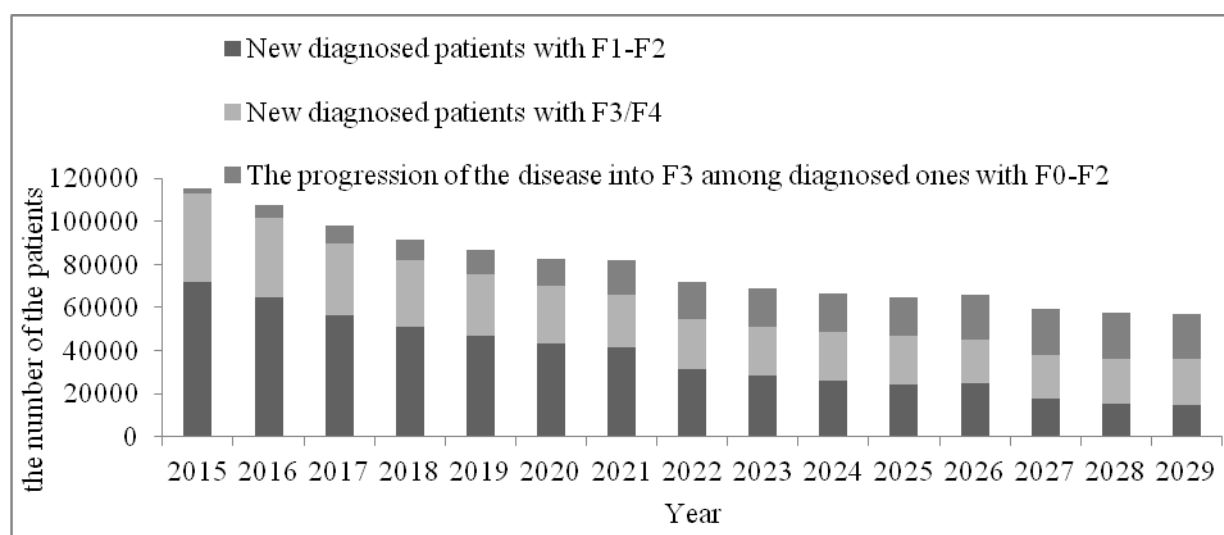


Figure 4. The annual number and structure of the population of new identified HCV patients that are sufficient to administer treatment to 41000 patients with F3/4 according to Strategy No. 1.

This is due to the increase in the proportion of the patients with severe fibrosis / cirrhosis in the general population (36% and 55% respectively in 2015 and 2029) (Table 2) and the increase in the number of the patients with the progression of the disease to F3 among previously diagnosed patients with F0-F2 (219415 patients for 2015-2029) (Figure 4). In total, 954954 patients with F0-F4 fibrosis stages (65% of the infected population at the beginning of 2015) should be diagnosed for treatment of 615,000 patients with F3/F4 fibrosis stage (41000 annually) from 2016 to 2030. In that case if during 2015-2029 it is possible to diagnose 955000 patients the number of undiagnosed population will be 516479000 people. For 15 years 30% of them (154368) will die from LC or HCC, another 3.5% - from other causes not related to liver disease. Thus, by 2030 the number of undiagnosed population will be 343517 patients or 29.5% of 1141416 people at the beginning of 2030 in natural history of the disease. This is 19.5% higher than the WHO target that makes it possible to conclude that the implementation of Strategy No. 1, although it will reduce mortality to the required level (65%), nevertheless does not guarantee the implementation of the WHO program in Ukraine in full. When implementing Strategy No. 2 the number of the patients who need to be diagnosed annually is determined by the proportion of the patients with HC: in the period from 2015 to 2022 their proportion is less than that of the patients with F2 or F3 (Table 2) and the ratio in which they should receive treatment during these years is 2:1:2. From 2024 to 2030 the majority of the patients who should receive treatment will be the patients with HC (the ratio F2:F3:F4 will be equal to 1:5:15). Therefore, their proportion in the population will also be of decisive importance in the total number of the patients who need to be identified in screening annually.

According to our calculations which were conducted in accordance with formulas 2-4 in order to implement Strategy No. 2 from 2016 to 2030 it is necessary to identify 1133572 patients with fibrosis stages F0-F4 that is in 178618 patients more in comparison with Strategy No. 1. 40.9% (138221) of 337861 undiagnosed patients during 15 years will die from HC or HCC, another 5.4% - from other causes which are not associated with liver disease. Thus, by 2030 the number of undiagnosed population will be 181332 patients or 15.8% of that in natural history of the disease. As a result of treatment 566750 patients will be cured that will reduce the mortality by 65% by 2030.

**Conclusion**

Our study has demonstrated that in order to achieve the goal of the WHO elimination program it is necessary to treat at least 42.2% of the population of VHC patients in Ukraine.

The treatment of the patients with extremely severe forms of fibrosis and LC allows achieving the goals of the program, but it does not prevent the progression of the disease in 32.8% of the patients from the number of infected population in 2015. The treatment of the patients regardless of fibrosis stage does not allow achieving the goals of the elimination Program and dramatically increases the number of deaths which are associated with final stages of liver disease. It is possible to achieve the goals of the elimination Program while reducing the number of the patients with fibrosis progression from F0-2 to F3/F4 by 20.1% and including the patients with moderate fibrosis in therapy program. The ratio of treated patients with fibrosis F2:F3:F4 in the first 7 years of the program should be 2:1:2, and in the last 7 years it should be 1:5:15. In addition, the implementation of the WHO program in Ukraine on Strategy No. 2 is more preferable. Formally, it brings us closer to achieving both targets: by 2030 the mortality will be reduced by 68.1% (target 65%), and the number of new cases - by 84.2% (target 90%). Simultaneously, Strategy No. 2 presupposes the treatment of a significant number of the patients with F2 that allows preventing undesirable progression of the disease in 20% of this category of the patients and thereby it favorably distinguishes Strategy No. 2 from Strategy No. 1.

### References

1. Mei-Hsuan Lee, Hwai-I Yang, Yong Yuan, Gilbert L'Italien, and Chien-Jen Chen Epidemiology and natural history of hepatitis C virus infection. J World J Gastroenterol 2014 Jul 28; 20(28): 9270–9280.

2. Gural A.L., Mariyevskiy V.F., Sergeyeva T.A.  The characteristics and trend of the epidemic process of hepatitis C virus in Ukraine. J Preventive medicine 2011; 1 (13): 9–17

3. Sergeyeva T.A. The characteristics of the epidemic process of hepatitis B and C in Ukraine in modern conditions and the system of epidemiological surveillance Extended abstract of Doctor's thesis.

4. https://index.minfin.com.ua/reference/people/

5. Sulkowski MS, Hézode C, Gerstoft J, Vierling JM, Mallolas J, Pol S, et al.. Efficacy and safety of 8 wks versus 12 wks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin in patients with HCV GT1 mono-infection and HIV/HCV coinfection (C-WORTHY): a randomised, open-label phase 2 trial. Lancet. 2015; 285(9973): 1087-97.

6. Zeuzem S, Mizokami M, Pianko S, Mangia A, Han KH, Martin R, et al. NS5A resistance-associated substitutions in patients with genotype 1 hepatitis C virus: Prevalence and effect on treatment outcome. J Hepatol. 2017; 66(5): 910-918.

7. Lawitz EJ, Gane EJ, Pearlman B, Tam E, Ghesquiere W, Guyader D, et al. Efficacy and safety of 12 wks vs 18 wks of treatment w/ GRZ and ELB w/ or without RBV for HCV GT1 infection in previously untreated pts w/ cirrhosis and pts w/ previous null response w/ or without cirrhosis (C-WORTHY), randomised, open-label phase 2 trial. Lancet. 2015; 385(9973): 1075-86.

8. Afdhal NH, Zeuzem S, Kwo PY, Chojkier M, Gitlin N, Puoti M, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med. 2014; 370(20): 1889-1898.

9. http://cdafound.org/polaris/

10. Manual for the development and assessment of national viral hepatitis plans: a provisional document. World Health Organization 2015.

11. Mohammed N. Al-Quaiz, Tariq A. Madani. The natural history of hepatitis C virus infection. J Saudi Med 2003; Vol. 24 Supplement 2: S67-S70.

12. H. Razavi, I. Waked, C. Sarrazin et al. The present and future disease burden of hepatitis C virus(HCV) infection with today's treatment paradigm.  J of  Viral Hepatitis, 2014; 21, (Suppl. 1): 34–59.

13. Fleming K. M., Aitha G. P., Card T. R.,  J. West. The rate of decompensation and clinical progression of disease in people with cirrhosis: a cohort study. Aliment Pharmacol Ther 2010; 32: 1343–1350.