



Eliminating Viral Hepatitis in Turkey: Achievements and Challenges

Türkiye’de Viral Hepatitin Ortadan Kaldırılması: Başarılar ve Zorluklar

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ABSTRACT

After the declaration Global Health Sector Strategy on Viral Hepatitis by the World Health Organization in 2016, the Turkish Government defined a national strategy covering 2018-2023 to reach goals by 2030. Following a participatory decision process and a series of workshops, the strategy was built on eight separate subheadings. Apart from the official Prevention and Control Program, two separate road maps for hepatitis B and C were developed to obtain targets accessible with the cooperation of the Viral Hepatitis Society and the Turkish Association for the Study of the Liver in 2018 and 2020, respectively. Up to 2023, achievements and the current situation of the National Viral Hepatitis Prevention and Control Program and the hepatitis B virus and hepatitis C virus road maps were assessed in detail on June 28th, 2022, by the subject matter experts in Turkey. Besides the officially reported achievement rate (42%) of the Program in 2021, participants mentioned undesirable effects of the coronavirus disease-2019 pandemic, unregulated migration, low levels of professional and public awareness, and barriers to access to anti-viral treatment. Recommendations focused on increasing the efficiency of screening and surveillance by integrating the viral carrier identity of individuals into the national health information system, simplifying the drug supplement and treatment initiation process and insisting on education to raise awareness.

Keywords: COVID-19, HBV, HCV

ÖZ

2016 yılında Dünya Sağlık Örgütü tarafından Viral Hepatite İlişkin Küresel Sağlık Sektörü Stratejisi ilan edildikten sonra Türk Hükümeti, 2030 yılına kadar hedeflere ulaşmak için 2018-2023’ü kapsayan ulusal stratejiyi tanımladı. Katılımcı bir karar süreci ve bir dizi çalıştayın ardından strateji sekiz ayrı alt başlık üzerine inşa edildi. Resmi Önleme ve Kontrol Programı dışında, sırasıyla 2018 ve 2020 yıllarında Viral Hepatitle Savaşım Derneği ve Türk Karaciğer Araştırmaları Derneği iş birliği ile (sırasıyla; 2018 ve 2020) Türkiye’de de hedeflerin erişilebilir hale getirilmesi için hepatit B ve C’ye yönelik iki ayrı yol haritası geliştirilmiştir. Ulusal Viral Hepatit Önleme ve Kontrol Programı ile hepatit B virüs ve hepatit C virüs yol haritalarının 2023 yılına kadar elde edilen kazanımları ve mevcut durumu 28 Haziran 2022 tarihinde Türkiye’nin önde gelen kanaat önderleri tarafından detaylı olarak değerlendirilmiştir. Programın 2021’de resmi olarak bildirilen başarı oranının yanı sıra (%42), katılımcılar koronavirüs hastalığı-2019 pandemisinin istenmeyen etkilerine, düzensiz göçe, düşük düzeyde profesyonel ve kamu bilincine ve anti-viral tedaviye erişimin önündeki engellere dikkat çekti. Öneriler, bireylerin viral taşıyıcı kimliğinin ulusal sağlık bilgi sistemine entegre edilerek tarama ve süreyansın etkinliğinin artırılmasına, ilaç takviyesi ve tedaviye başlama sürecinin basitleştirilmesine ve farkındalığın artırılmasına yönelik eğitimde ısrar edilmesine odaklandı.

Anahtar Kelimeler: COVID-19, HBV, HCV

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Introduction

Viral hepatitis continues to be a global health problem despite innovative health technologies and improving living conditions. It seems to have a priority for health policymakers in the next several years. In Turkey, the prevalence of hepatitis B and C were reported as 4.0% and 0.3-1.0% (1,2). The seropositivity rates also indicate that the total amount of hepatitis B virus (HBV) carriers might be more than 3.5 million actually. But only 12% of these HBV carriers are aware of their status (3) (Figure 1). Despite prevention policies, unregulated migration, changing demographic features, and persistent awareness challenged the achievement of predicted goals (4,5).

Global Health Sector Strategy on Viral Hepatitis (GHSS) was declared by the World Health Organization (WHO) in 2016 for the sake of moving toward a world where viral hepatitis transmission has stopped and barriers to access to safe and effective treatment have been removed. For this, it is aimed to prevent the transmission of hepatitis viruses, reduce complications and deaths related to viral hepatitis, improve patient care, and reduce the socio-economic negative effects of viral hepatitis in social areas. Also, WHO set targets to eliminate viral hepatitis as a public health risk by 2030. By this, 90% reduction in the risk of new infections, 80% of eligible people with chronic hepatitis B and C infections treated, and 65% reduction in hepatitis-related mortality were declared as goals to be achieved (6).

In Turkey, prevention efforts have been implemented since 2013 before the declaration of GHSS (Table 1). Epidemiologic data point out a demonstrable reduction in seropositivity in the last decades as an indicator of the success of existing national health care policy in the manner of prevention and treatment (7). In a study, where 26,001 adult patients were included, hepatitis B surface antigen (HBsAg) and anti-HBs were positive in 4.2% and 16.8% of patients, respectively. When the 20 years included in the study are divided into three periods namely 1995-2002, 2003-2009, and 2010-2015 and each period is analysed separately. It was reported that the rate of HBsAg positivity decreased from 5.3% to 4.8% and 3.1% (8).

Although there is a decrease in the prevalence of HBV in the country, people who migrate to Turkey are in a position to affect the prevalence of HBV in the country. A huge amount of immigrants from Syria (3.6 million) live in Turkey (4). In addition, Turkey also stands on the road of immigration from Afghanistan and other Central Asian countries as well as from East-European countries placed in the former Soviet Union. The aforementioned people are employed informally in household services and the care of children and disabled people. Moreover, the higher prevalence of viral hepatitis in these countries (9-12) (Table 2) and persistent low-level awareness remain a threat to the program's success (4). From this standpoint, it can be stated; that viral hepatitis continues to remain high in the long term (13).

Methods

1. Defining the Strategy

Turkish Health Authority has been handling the issue in a detailed and extended manner consistent with a global strategy soon after its declaration. For this issue, workshops were held in Istanbul and Ankara before the final workshop on April 3rd, 2018. The Turkish Viral Hepatitis Prevention and Control Program were announced by The Ministry of Health on September 12th, 2018. In this program, eight strategies were planned to be implemented in long term (Table 3).

Apart from the comprehensive "Turkish Viral Hepatitis Prevention and Control Program" managed by Ministry of Health, two road map projects were carried out to facilitate the national program and determine achievable, smart targets. The first of which was to target the elimination of hepatitis C virus (HCV) in June 2018 with the cooperation of Viral Hepatitis Society (VHSD) and Turkish Association for the Study of the Liver (TASL), "Hepatitis C Elimination Roadmap Recommendations and Workshop in Turkey" (14) was created. Then, in 2020, the "National Hepatitis B Elimination Roadmap" (15) was created in cooperation with VHSD and TASL.

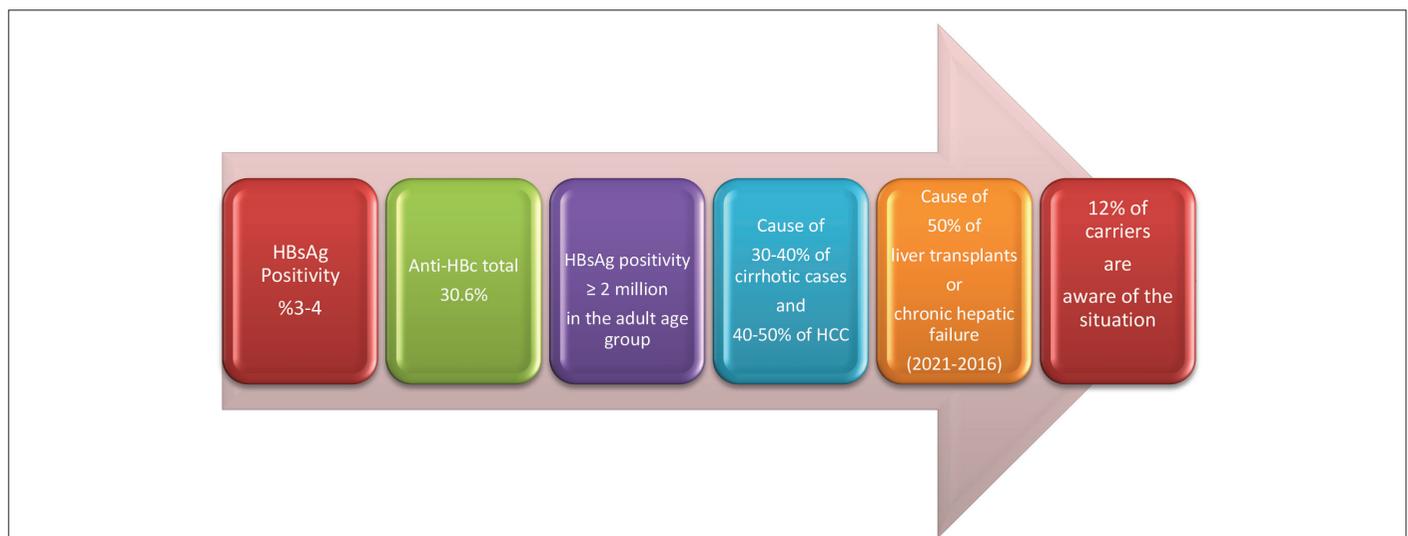


Figure 1. Epidemiologic features of hepatitis B virus infection in Turkey

Elimination of Hepatitis C Virus

At the workshops of “Hepatitis C Elimination in Turkey, Roadmap Recommendations and Workshop Reports” held in Ankara, İstanbul, and Izmir. The practical applications of the countries having a national elimination plan were reviewed. The content of the national hepatitis C elimination plan specific to Turkey was discussed and local recommendations were outlined. The resulting reports were prepared based on especially treating physicians’ opinions about the current situation and recommendations for solutions under the title of a roadmap. Especially, Professor Jeffrey V. Lazarus explained how the idea of HCV elimination emerged in the world, the WHO’s proposed targets for HCV elimination, the micro-elimination approach and its benefits, and the best practices to date in HCV elimination in other countries. Moreover, Professor Lazarus shared the results

of the research conducted in 2017, which includes the current status of HCV in Turkey and solution suggestions on which topics it should be under if an elimination plan is to be carried out. The attending physicians shared their ideas about how these solution proposals can be transferred to Turkey. The status of HCV infection in Turkey and the recommended approach steps for HCV elimination are grouped under seven strategies as listed below (Figure 2).

1. Establishing a national HCV elimination plan

a. A specific, quickly applicable, traceable national HCV elimination plan should be implemented as soon as possible.

b. The targets of the program need to be adopted by The Ministry of Health and specialized associations operating in the field of HCV. Responsible units and teams should be determined and assigned.

Table 1. Achievements of national hepatitis program before the declaration of GHSS

Definition of achievements
1. Inclusion of hepatitis B vaccine in the childhood vaccination program in 1998
2. Development of the surveillance system and inclusion of acute hepatitis in the scope of compulsory notification
3. Inclusion of hepatitis A vaccine in the childhood vaccination program in 2012
4. Inclusion of nucleic acid test in the blood transfusion safety panel as well as serological tests.

GHSS: Global Health Sector Strategy on Viral Hepatitis

Table 2. Prevalence of hepatitis in some countries where immigrants originate

Geographic region	Hepatitis B	Hepatitis C	Reference
Syria, country estimated, (%)	5.6	2.8	Bashour and Muhjazi (9)
Aleppo, (%)	10.5	10.14	-
Hassakeh, (%)	10.6	-	-
European part of Russia, (%)	-	0.7-3.8	Lovo et al, (10)
North Caucasian of Russia, (%)	-	2.1	-
Far-East part of Russia, (%)	-	2.5	-
Mongolia, (%)	-	10.7	-
Middle East, (%)	2-7	-	MacLachlan and Cowie (11)
Eastern and Southern Euro, (%)	2-7	-	-
Central Asia, (%)	≥8	-	-
Kazakhstan, (%) (0.95 CI)	-	0.7 (0.7-0.8)	Botheju et al. (12)
Kyrgyzstan, (%) (0.95 CI)	-	2.0 (1.7-2.4)	-
Uzbekistan, (%) (0.95 CI)	-	9.6 (5.8-14.2)	-

CI: Confidence interval

Table 3. Eight Strategies announced by The Turkish Ministry of Health for implementing prevention and control program

Strategy	Targeted achievements
Strategy 1.	Raising awareness
Strategy 2.	Increasing immunization
Strategy 3.	Strengthening viral hepatitis surveillance
Strategy 4.	Reducing vertical transmission
Strategy 5.	Increasing access to treatment
Strategy 6.	Providing safe blood products
Strategy 7.	Prevention of viral hepatitis transmission in injecting drug users
Strategy 8.	Prevention of healthcare-associated transmission

c. Subpopulations available for immediate improvements should be allocated to micro-elimination projects.

2. Increasing awareness

a. Public announcements could be prepared for conceiving that HCV infection is an easily recognizable and easily treatable disease.

b. Develop training activities by Provincial Health Directorate to raise the contribution of family physicians or internal medicine specialists to the process of diagnosis, treatment, and follow-up of HCV infection.

3. Getting screening to be more effective and comprehensive

a. It could be developed software warning physicians before interventional/surgical procedures (surgical services, dental clinics, etc.) about positive patients and compelling them to consult with relevant departments/specialists.

b. Cases defined as anti-HCV positive in donor screening should be registered to the national health informatics system.

c. Anti-HCV positive cases could be periodically directed to the treatment and follow-up process.

d. Population-based screening programs could be conducted in regions with high HCV prevalence (eg. Hatay, Ordu, Nevşehir, Manisa, Kütahya).

e. Encouraging family physicians to evaluate for HCV. In this context, the cost of HCV assessment might be kept out of the physician's predefined budget.

f. Integration of the Ministry of Justice into the health information system could allow screening of prisoners to have priority.

g. Diagnosis, treatment, and follow-up procedures of HCV in outpatients and inpatients in people who inject drug (PWID) centers can be standardized.

h. Anti-HCV screening can be included in the routine pregnancy follow-up program.

i. Previous gastrointestinal cancer screening projects successfully implemented such as "faecal occult blood screening" can serve as a reference point.

j. Defining subpopulations with priority for assessment.

- Existing liver disease patients,
- Intravenous drugs users,
- Prisoners,
- Having a history of liver or renal transplantation,
- Haemodialysis patients,
- Infected with HIV.

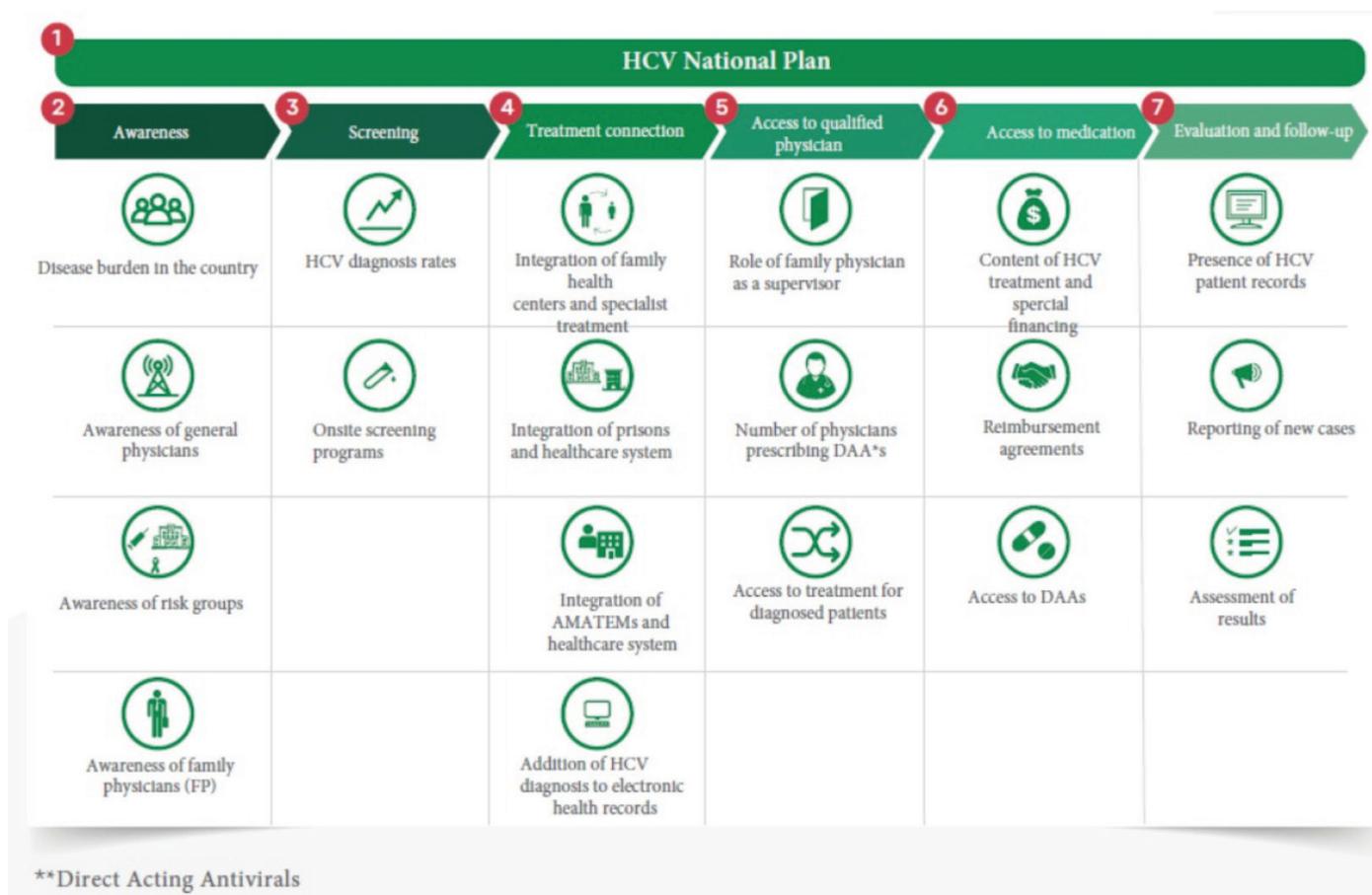


Figure 2. Roadmap for elimination of hepatitis C virus infection
HCV: Hepatitis C virus

4. Improving treatment connection

a. Information systems can be developed to enable or facilitate the access of patients with anti-HCV positive (pre-operation evaluation, dental procedures, or blood bank) to infectious diseases or gastroenterology departments.

b. A direct referral chain can be established between PWID centers and infectious diseases or gastroenterology departments, or relevant specialist physicians can be assigned to PWID centers at certain times.

5. Facilitating accession to qualified physicians and medication

a. Family physicians or internists should have an active role in HCV diagnosis, treatment, and follow-up processes.

b. The follow-up of patients infected with HCV should be conducted in a centralized system.

6. Simplifying the accession to medication

a. Effective anti-viral regimens should be prescribed unrestrictedly by all infectious diseases or gastroenterology specialists in all hospitals in all provinces.

b. Biopsy and fibrosis stage assessment, which is essential for using direct-acting anti-viral therapy in patients who have not received treatment before, should be removed.

c. Patients in PWID centers should be treated by all physicians occupied in the centers regardless of specialty on-site or infectious disease and gastroenterology specialists may be assigned to these institutions on certain days.

d. Every patient, including immigrants, should have access to direct-acting anti-viral agents.

e. Patients should be able to receive all their treatments at the proper timing without delay.

f. Physicians should be able to make their selection of direct-acting anti-viral agents to give optimal treatment to their patients.

7. Optimizing evaluation and monitoring

A. A centralized system designed to monitor HCV-infected patients should be implemented.

B. Models that predict the benefits and treatment costs of HCV treatment and elimination should be developed.

Micro-elimination programs in some patient populations, achieving rapid success, and sharing it in appropriate environments will lay the groundwork for raising awareness about the issue. Subpopulations having priority for micro-elimination are listed below.

1. Patients are currently followed in the health system under the following categories

- a. Advanced liver disease,
- b. Advanced chronic kidney disease,
- c. Haematological diseases (haemophilia, thalassemia, etc.) that require blood product usage,
- d. History of transplantation and those receiving immunosuppressive treatment,
- e. Patients who have already been found to be anti-HCV positive.

2. Demographic or individual characteristics accompanied by high risk

- a. Born before 1970,
- b. Living/living in areas known to have a high prevalence of HCV,
- c. Using intravenous drugs,
- d. Prison inmates.

Elimination of Hepatitis B Virus

A participatory project was carried out with opinion leaders and relevant stakeholders to develop and facilitate the implementation of the Hepatitis B Elimination Roadmap in the direction defined by the Ministry of Health "Turkish Viral Hepatitis Prevention and Control Program". The main purpose of the study was to stop the transmission of hepatitis B in Turkey in the short term, prevent the progression of the disease, improve the quality of life, and ensure its elimination in the long term. After evaluation of the current status in 2020, the "National Hepatitis B Elimination Roadmap" (15) was created in cooperation with VHSD and TASL.

The project process consisted of five stages:

1. Review of current hepatitis B strategies and plans,
2. Conducting preliminary interviews,
3. Conducting workshops,
4. Preparation of the Hepatitis B Elimination Roadmap within the scope of the National Hepatitis Elimination Program,
5. Evaluation of National Hepatitis B Elimination Roadmap projects.

2. Current Situation in 2022

Turkish Viral Hepatitis Prevention and Control Program was implemented by the Turkish Ministry of Health, General Directorate of Public Health, Department of Infectious Diseases, and Early Warning covering the years 2018-2023.

In the evaluation of the Viral Hepatitis Prevention and Control Program of Turkey conducted by the Ministry of Health in 2021. The reported achievement rate was reported as 42%. Also, officially declared, a great part of activities (44%) were ongoing and the remaining 14% were waiting for started (Figure 3). The 14% parts, which have not yet started, mostly

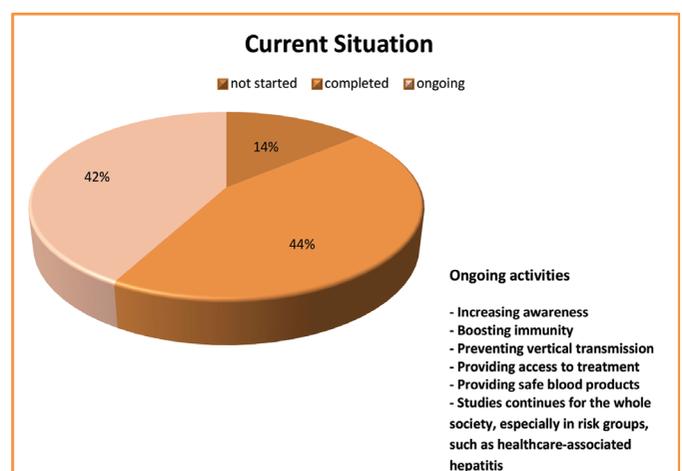


Figure 3. Turkish Viral Hepatitis Prevention and Control Program (2019-2023), evaluation in 2021

require the contribution of other ministries, this was the reason for the delay.

Training and raising awareness seemed to have priority in the implementation process. In this context, completed activities were reported as listed below

- The Viral Hepatitis Educator Guide and educational slide sets were prepared and shared by the Ministry of Health in 2019.
- Before the pandemic, 104 family physicians were trained in Konya and Niğde. Also, the training of the family physician was carried out in Çorum, in the late phase of the pandemic.
- In the southeast region of Turkey, training sessions were completed online.
- Meetings were organized in various provinces to raise public awareness of hepatitis among the public, and posters were posted on billboards.

Additionally, The National Haemovigilance Guide for safe blood transfusion was updated in 2020.

The Viral Hepatitis Prevention and Control Program by Ministry of Health was re-evaluated in the scope of Hepatitis C Elimination Roadmap Recommendations and Hepatitis B Elimination Roadmap Recommendations one year later, on June 28th, 2022. Being aware of the fact that six months are left until 2023, completed and ongoing activities were revised under the guidance of the government's improvements and gained experience. The recommendations were summarized as listed below.

1. Generally, the program should be implemented in the field prevention should be prioritized, and the progress of the program should be shared with reports at regular intervals. Stakeholders must motivate each other for the success of the program.
2. Viral hepatitis awareness and screening should first be started by healthcare associate professionals working with doctors and nurses. Screening and training of personnel working in hospitals should be obligated.
3. From June 2022, it is planned to organize face-to-face training in big cities until the end of 2022. For instance, İstanbul Provincial Health Directorate Public Health Department will organize a training program dedicated to physicians having the intention to collaborate in İstanbul in cooperation. A series of face-to-face training sessions will be organized with the participation of 50-100 family physicians. Increasing HBV and HCV awareness and screening rate of risky groups will be put as goals of these sessions. The family medicine or family medicine specialty associations should be identified as stakeholders and their support and participation should be requested at the organization stage.
4. Alternative methods for adult education such as Flipped Classroom could be put into practice with the collaboration of educational sciences.
5. Evaluation of training sessions performed in the province of Niğde revealed that learning efficiency was about 70% considering pre-test and post-test scores. The reflection of knowledge in practice should be the most important parameter to be monitored at certain periods.
6. The pre-test-post-test success performance can be considered a reference to gain the right to free of charge

participation in the training meetings organized by the relevant associations operating in the field of hepatitis.

7. There are a significant number of individuals who have been exposed to hepatitis viruses in Turkey. Positive individuals should be obligated to take a place in a periodic in follow-up process beyond verbally informed. This task can be handled by disease card or special information integrated in national health information system.

8. According to the Centers for Disease Control, absolute screening of adults is recommended in regions with a prevalence of more than 0.1%. The frequency of HCV in Turkey is 0.3-1.0% (1,2). For this reason, anti-HCV and HBsAg should be checked and documented in everyone over the age of 18 and younger ones in risk categories. The avoidance of repeated tests would create a resource for precise diagnosis (HCV-RNA polymerase chain reaction confirmation) and effective treatment.

9. Accurate and reliable surveillance data should be collected and handled by the Ministry of Health and used in national health policymaking.

10. Intuition-based hepatitis B and C screening data collecting activities should be centralized and confirmed carrier status could be transmitted to relevant professionals and institutions. Electronic prevention practices developed during the coronavirus disease-2019 (COVID-19) pandemic would be a model for a hepatitis-specific e-disease management system.

11. An electronic identity card specific to the prevention of communicable disease could be designed in close collaboration between the General Directorate of Health Information Systems of the Ministry of Health and the Turkish Ministry of Health General Directorate of Public Health, Communicable Diseases and Early Warning Department. The proposed digital could be tested in pilot projects before it is rolled out across the country.

Hepatitis C Virus Specific Recommendations

1. Prisons and PWID centers should be prioritized in HCV screening.
2. In actual state, HCV treatment can be given in 60 hospital pharmacies at 44 provinces/in Turkey. An arrangement is required to get available HCV treatment in every province.
3. Micro-elimination projects can be launched in the provinces of Konya and Niğde where family physicians' training is completed.
4. Rapid testing, shifting away from centralized management and focusing on local practices, and simplified treatment regimens are needed to increase access to treatment for people at risk.

Hepatitis B Virus Specific Recommendations

1. The HBV vaccination rate is an actual performance measure for family physicians in HBV vaccination is outstanding. The actual rate of three doses of HBV vaccination in infants is 98%. The infrastructure of this success should also be applied to the screening of HBV. It is necessary to create a performance measurement policy with a central approach. Encouraging family

reduction in regional the prevalence of hepatitis in their region can be rewarded by encouraging family physicians.

2. Keeping in the mind an annual pregnancy rate of one million, HBsAg screening during pregnancy is the most accessible target in this scope.

3. The widely shared misunderstanding of “noting is needed for a carrier” among many community members and health professionals should be changed. The concept of “being a carrier of HBV does not mean that you do not have the disease” would be getting a community education subject focused especially on hepatitis B carriers. Awareness among society and family physicians about surrogacy should be increased. The perception of “if the patient is a carrier, nothing is needed” should be changed by regular training.

4. Improving access to treatment: In HBV-infected patients with certain characteristics, treatment should be started without liver biopsy.

Discussion

Viral hepatitis seems to continue to be a major public health problem in the coming decades. Despite global health insurance coverage and successful infant vaccination programs, reaching WHO's goals for the elimination of viral hepatitis in 2030 is challenged by several factors.

Concerning the existing policy changes aligned with the GHSS, unpredictable geopolitical states, and uncertain economic conditions weighed especially COVID-19 hinder the purpose of improvement in the process.

Besides the changing demography due to unregulated migration, widely existing awareness might be overcome by digitalization transformation. Gained experience in controlling infectious diseases during pandemics might be an advantage for defining and raising the efficiency of anti-viral treatment. Integrating the viral status of individuals in their electronic health identity would decline the transmission rate and raise the rates of early access to treatment.

Decentralizing the drug supplying system, reorganizing of patient referral system for providing accession to qualified specialists, and integrating family physicians into the disease management process would increase treatment attendance and resulting treatment success rates.

The treatment protocols and relevant reimbursement rules should be modified in favor of early treatment taking into account non-invasive novel diagnostic technologies (16). In this respect, it should be encouraged to develop new economic assessment models considering cost-effectiveness and economic burden in the long term.

Conclusion

Turkey is one of the candidates having a possibility of reaching goals defined by WHO. In addition to the existing healthcare workforce and infrastructure, considering great achievements in health information systems, it can be hoped major drawbacks could be overcome. But this seems to be possible by defining problems and rational solutions with close collaboration among different stakeholders.

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Ethics

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Authorship Contributions

Surgical and Medical Practices: U.S.A., N.B., R.G., F.G., R.I., S.K., İ.K., F.T., T.Y., Concept: U.S.A., N.B., R.G., F.G., R.I., S.K., İ.K., F.T., T.Y., Design: U.S.A., N.B., R.G., F.G., R.I., S.K., İ.K., F.T., T.Y., Data Collection or Processing: U.S.A., N.B., R.G., F.G., R.I., S.K., İ.K., F.T., T.Y., Analysis or Interpretation: U.S.A., N.B., R.G., F.G., R.I., S.K., İ.K., F.T., T.Y., Literature Search: U.S.A., N.B., R.G., F.G., R.I., S.K., İ.K., F.T., T.Y., Writing: U.S.A., N.B., R.G., F.G., R.I., S.K., İ.K., F.T., T.Y.

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