National Hepatitis C Elimination Program Progress Report

Georgia, 2018-2019

MINISTRY OF INTERNALLY DISPLACED PERSONS FROM THE OCCUPIED TERRITORIES, LABOUR, HEALTH AND SOCIAL AFFAIRS OF GEORGIA

NCDC
NATIONAL CENTER FOR DISEASE CONTROL AND PUBLIC HEALTH

DEPARTMENT OF HEALTH & HUMAN SERVICES USA
CDC

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LIST OF ABBREVIATIONS

AMR	Antimicrobial resistance
DAA	Direct-acting antivirals
EASL	European Association for the Study of the Liver
ELPA	European Liver Patients Association
EQA	External quality assessment
FIND	Foundation for Innovative New Diagnostics
GFATM	Global Fund to Fight AIDS, Tuberculosis, and Malaria
GHRN	Georgian Harm Reduction Network
HAI	Hospital acquired infection
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HCVcAg	Hepatitis C virus core antigen
HCW	Healthcare workers
HIV	Human immunodeficiency virus
HR	Harm reduction
HRU	Health Research Union
IBSS	Integrated Bio-Behavioral Surveillance Survey
ICU	Intensive care unit
IDACIRC	Infectious Diseases, AIDS and Clinical Immunology Research Center
IPC	Infection prevention and control
MoIDPLHSA	Ministry of Internally Displaced Persons from the Occupied Territories Labour, Health, and Social Affairs
NAT	Nucleic acid testing
NCDC	Georgia's National Center for Disease Control and Public Health
NSP	Needle and syringe program
OST	Opioid substitution treatment

PCR	Polymerase chain reaction
PHC	Primary healthcare centers
PPS	Point prevalence survey
PT	Proficiency testing
PWID	Persons who inject drugs
RAMA	Regulation Agency for Medical Activities
RDT	Rapid diagnostic test
RIQAS	Randox International Quality Assessment Scheme
SMS	Short message service
SOPs	Standard operating procedures
SSA	Social Service Agency
SVR	Sustained virologic response
TTI	Transfusion transmissible infections
UHP	Universal healthcare program
U.S. CDC	United States Centers for Disease Control and Prevention

INTRODUCTION

Since 2015, Georgia has been working towards the country-wide elimination of hepatitis C virus (HCV) infection, defined as a 90% reduction in HCV prevalence. Georgia's elimination program stands out for its comprehensive approach, with strategies in place to not only identify those infected with HCV and link them to care and treatment services, but also to improve access to quality diagnostics, safeguard the nation's blood supply, and reduce infection with blood borne pathogens among persons who inject drugs (PWID) and in healthcare settings.

This report highlights the impact of various policy changes and initiatives occurring during 2018-2019 aimed at improving outcomes across the continuum of hepatitis C care. This report supplements the findings in the *National Hepatitis C Virus Elimination Progress Report, 2015–2017*[1] and *National Hepatitis C Virus Elimination Progress Report, January 1, 2017-June 30, 2018*[2] and includes the following:

- Highlights of accomplishments and key findings
- Challenges remaining to the achievement of the hepatitis C elimination goals
- Tables containing monitoring and evaluation data on key performance indicators for the reporting period
- Technical Advisory Group (TAG) recommendations
- Appendices (1-4)

A major hallmark in 2018 and 2019 for the Georgia program is the decision to integrate screening, care and treatment services in primary healthcare centers and harm-reduction centers throughout the country. Several factors contributed to Georgia's leadership in hepatitis C elimination, including high levels of political commitment, allocation of substantial resources, and the program's comprehensive nature. The great success achieved by the program thus far has led to Georgia being named the world's first European Association for the Study of the Liver (EASL)-International Liver Foundation Center of Excellence in HCV Elimination.[3]

The information contained in this current progress report mirrors the following six elimination strategies presented in the larger *Strategic Plan for the Elimination of Hepatitis C Virus in Georgia, 2016–2020*[4].

1. Improve Advocacy, Awareness, Education, and Partnerships for HCV-Associated Resource Mobilization
2. Prevent HCV Transmission through Harm Reduction, Blood Safety, and Infection Prevention and Control
3. Identify and Link to Care Persons Infected with HCV
4. Improve HCV Laboratory Diagnostics
5. Provide Comprehensive HCV Care and Treatment
6. Improve HCV Surveillance

[1]Available from: https://www.moh.gov.ge/uploads/files/2019/Failebi/25.04.2019-1.pdf
[2] Available from: https://www.moh.gov.ge/uploads/files/2019/Failebi/25.04.2019-2.pdf
[3] Available from: https://doi.org/10.1016/j.jhep.2019.06.026 & https://centre-of-excellence.easl-ilf.org/
[4]Available from: https://www.moh.gov.ge/uploads/files/2017/akordeoni/failebi/Georgia_HCV_Elimination_Strategy_2016-2020.pdf

STRATEGY-SPECIFIC PROGRESS MADE TOWARDS HCV ELIMINATION

Strategy 1. Improve Advocacy, Awareness, Education, and Partnerships for HCV-Associated Resource Mobilization

The government of Georgia has supported communication campaigns to raise awareness of the importance of early HCV diagnosis and to ensure that all Georgians have the opportunity to be tested and receive highly effective treatment, for free. With the contribution of numerous stakeholders working across a range of settings, a variety of activities were undertaken to increase both professional and public understanding of hepatitis C to help find patients who are undiagnosed and untreated.

Key Accomplishments and Findings

- Implementation of public communication campaigns:
    - ”Time to test, Time to treat and Time to cure,” “Stop C,” and “Future without C” were the primary communication campaign slogans during June-December 2018.
    - A campaign in 2019 (May-December) conveyed targeted messages towards those with no screening tests for hepatitis C as well as HCV-infected persons who did not engage in treatment. The messages included “You too get involved,” “You too get cured,” “Invisible C - just because you can't see it, doesn't mean it doesn’t exist,” and "HCV Kills - Causes cancer; Causes cirrhosis”.
    - Various printed communication materials were developed and promotional products designed: 8,000 posters, 38,000 booklets and 65,000 leaflets in Georgian, Azerbaijani and Armenian languages; 10,000 car window decals, 15 adhesive banners for Public Service Halls, 8 billboards across Georgia, 100 caps and logo bags and 400 t-shirts.
- During 2018-2019, social media websites (c.moh.gov.ge and https://www.ncdc.ge/) and TV media were used to provide real-time information about the elimination program to the general population, high-risk subgroups, patients, healthcare professionals, and international partners.
    - Overall, 172 HCV-related Facebook blog posts, 24 banners, 16 video blogs, over 15 live streaming videos of campaign activities, as well as HCV providers’ live chats on Facebook responding to questions were created.
    - More than 200 TV reports and ten TV shows with invited guests (hepatitis experts, ministry and NCDC leadership), six radio shows and articles, three video clips for TV campaigns, and one animated video for social media have been produced.
- Similar to what was done in 2017, a mobile communication strategy that involved using brief text messages (SMS—short message service) was again implemented in 2018 (August and November) and in 2019 (July and December) targeting the general population (approximately 1.8 million people).

- During the World Hepatitis Day 2018 and 2019 campaigns, a number of communication activities were conducted throughout the country. These included:
    - "STOP C" high level meeting and press conference held by the government of Georgia, Ministry, NCDC and partner organizations;
    - Meeting between NCDC and the governors of Shida Kartli and Kvemo Kartli regions to boost the visibility of the hepatitis C elimination program and contribute to increasing treatment engagement;
    - Joint communication activities were conducted by the state attorney, governor of the Kakheti administration and NCDC at Telavi State Museum conference hall;
    - Hepatitis C screening activities at Public Service Halls in Tbilisi and other cities in the region along with SMS messages inviting people for hepatitis C screening and treatment where necessary;
    - Hepatitis C elimination program workshops for primary health care workers in Batumi and Adjara region;
    - Public discussions at Batumi Shota Rustaveli State University, Telavi City Hall and Zugdidi referral hospital carried out jointly by Hepatitis C Cured Patient Association and NCDC in collaboration with HCV service providers and public health centers;
    - More than 150 students from local universities were trained to volunteer for hepatitis C screening awareness activities at Public Service Halls operated at twelve sites throughout Georgia.
- Three Facebook surveys among 15,000 respondents revealed that most respondents had moderate knowledge about how people become infected with hepatitis C and how to prevent transmission. Over 20% of surveyed persons were not aware that direct-acting antiviral (DAA) treatment is available for persons on opioid substitution therapy.
- In December 2018, Hepatitis C Cured Patient Association, in partnership with Georgian Corporate Sports Federation, organized a marathon at the lake Lisi. Volunteers included university students, health officials and other casual visitors. Free hepatitis C testing was performed at the site. Charitable donations were transferred to HCV-infected patients in need.
- In December 2018, Hepatitis C Cured Patient Association became a member of the World Hepatitis Alliance.
- Since June 2019, Hepatitis C Cured Patients Association has been a member of the European Liver Patients Association (ELPA). During December 1-5, 2019 Hepatitis C Cured Patients Association, together with other ELPA members from 24 countries, attended the multi-stakeholder meeting and training held in Barcelona, Spain, where participants had the opportunity to share inspiring research projects for 2020 and beyond.
- During June-July 2019, a qualitative survey (six focus-group discussions among the general population and four in-depth interviews with healthcare workers [HCWs]), was undertaken in Tbilisi, Kutaisi and Batumi to assess the barriers to HCV treatment access. Low level of information about the elimination program, lack of motivation, other concurrent priorities, as well as mistrust of people on HCWs were the main barriers to lower treatment uptake.
- A study of barriers and facilitators to enrollment in Georgia's hepatitis C elimination program among PWID revealed a lack of information on the elimination program, perceived high cost of care, lack of treatment sites, and younger age to be significant barriers to treatment engagement.

Strategy 2. Prevent HCV Transmission through Harm Reduction, Blood Safety, and Infection Prevention and Control

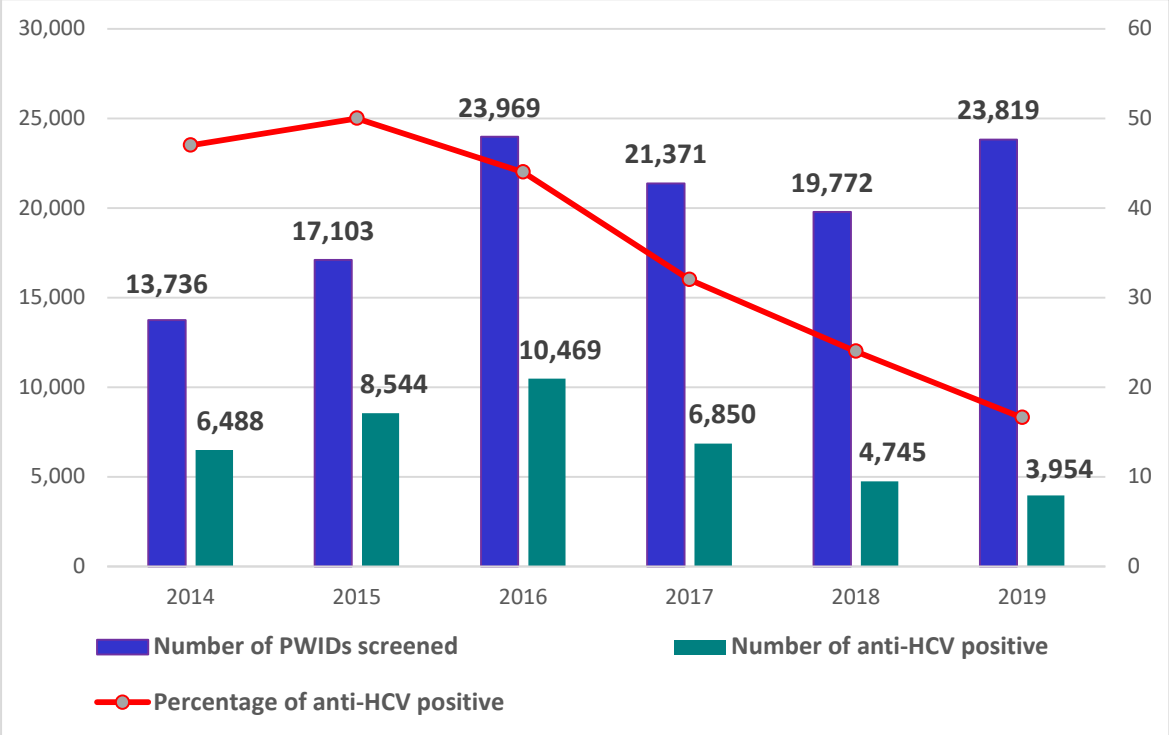
Preventing new HCV infections is crucial to achieving elimination goals. Although increased awareness of the risks associated with hepatitis C transmission can support prevention efforts, improvement is needed in other areas, including greater integration of HCV services at harm reduction sites, continued provision of services and monitoring of coverage provided at needle and syringe programs (NSP) and opioid substitution treatment (OST) programs, and more robust blood bank and infection-prevention control practices.

Harm Reduction

Key Accomplishments and Findings

- Harm reduction (HR) services have been expanded considerably in both scope and scale in Georgia through adding new service points, mobile laboratory services (9 in total), and peer-driven activities carried out by more than 88 HR workers.
- Since 2017, upon full transition of Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM)-supported OST programs to state-based funding, which abolished co-payment requirements for program beneficiaries, the number of PWID enrolled in OST increased from 5,228 in 2017 to 9,552 in 2019. As of December 31, 2019, out of 8,426 PWID who received HCV antibody (anti-HCV) screening at OST sites, 7,189 (85.3%) were positive, and of those tested for viremia, 84.3% (n=5,224/6,198) had active hepatitis C infection. Of those infected, 4,364 (83.5%) had initiated treatment, and 96.6% (n=2,617/2,709) of those tested for sustained virologic response (SVR) achieved cure.
- HCV screening efforts among PWID, both at NSP sites (14) and mobile van/laboratories (9), substantially increased the total number of PWID aware of their HCV infection status, from 13,736 in 2014 (baseline) to 23,819 in 2019 (Georgian Harm Reduction Network [GHRN] data). The proportion of PWID testing positive for anti-HCV declined from 32.0% in 2017 to 16.6% in 2019. (Figure 2.1).
- As of December 31, 2019, based on available data from the national HCV screening and treatment databases, of 16,590 registered beneficiaries of the HR program, 4,479 (27.0%) were anti-HCV positive, and of those 75.4% (n=3,377) received viremia testing; 84.4% (n=2,850) were positive. Of those with active HCV infection, 2,123 (74.5%) initiated treatment, and 98.6% (n=1,255/1,273) of those assessed for SVR were cured of their HCV infection.

Figure 2.1 Number of persons who inject drugs (PWID) screened for hepatitis C, and number and percent tested positive in Georgia, 2014–2019, Georgian Harm Reduction Network



- The Foundation for Innovative New Diagnostics (FIND) in Geneva, Switzerland, together with Georgia NCDC piloted the Hepatitis C Elimination through Access to Diagnostics (HEAD Start) study in 2017. A primary aim of the study was to determine the impact of point-of-care hepatitis C viremia testing on the care cascade among PWID. Preliminary results of this collaborative study demonstrated that collecting blood from anti-HCV positive PWID for HCV viremia testing at HR centers improved access to such testing.
    - Overall, 1,958 persons were evaluated for study eligibility. From May 2018 through October 2019, of persons having blood drawn at HR centers with testing either done on site (Group 1; n=621) or sent to Lugar Center for centralized HCV core antigen (HCVcAg) testing (Group 2; n=486), 100% completed HCV viremia testing. In contrast, only 77.5% (n=438/565) of persons referred to service providers for their blood draw and HCV viremia testing (Group 3) completed such testing. The majority (98.0%; n=345/352) of HCV-infected persons from Group 3 have initiated treatment, followed by 77.4% (n=401/518) in Group 1 and 70.9% (n=273/385) in Group 2.
- During January-October 2019, with FIND technical and financial support in partnership with GHRN, a total of 293 beneficiaries of four HR sites (in Tbilisi, Zugdidi, Kutaisi and Batumi) have been tested for HCV RNA after they have been treated and cured from chronic HCV infection. Of these, 17 persons had possible reinfection with an overall re-infection incidence rate of 2.5 per 100 person-years.
- Other projects focusing on PWID conducted during 2018-2019 include:

    - Implementation of hepatitis C treatment in four HR centers - 3 NSP sites and 1 OST program. (For more details, see Strategy 5: Provide Comprehensive HCV Care and Treatment)
    - Evaluation of integrated hepatitis C treatment program within Georgia's HR centers.
    - A study of barriers and facilitators to enrollment in Georgia's hepatitis C elimination program among PWID. (For more details, see Strategy 1: Improve Advocacy, Awareness, Education, and Partnerships for HCV-Associated Resource Mobilization)
- In 2019, a survey on risk-taking behaviors among 987 beneficiaries of NSP revealed that out of 375 persons treated for hepatitis C within the elimination program, 66.4% (n=249) reported injecting drugs during treatment. In addition, of 339 PWID who completed treatment, 32.7% (n=111) resumed risky behavior after treatment.

Blood Safety

Key Accomplishments and Findings

- A total of 185,477 blood donations (91,020 donations in 2018 and 94,457 in 2019) were collected at 22 blood banks. Voluntary, non-remunerated blood donations comprised 27.5% (n=25,064) and 32.7% (n=30,876) of total donations in respective years.
- In 2018, 51,289 donors (1.4% of the population of Georgia) were recorded in the national donor database, 66.8% (n=34,283) of whom were male. The majority were repeat donors (64.0%; n=32,807).
- In 2019, there were 55,779 blood donors. The proportion of first-time donors slightly decreased from 36.0% (n=18,482) in 2018 to 32.7% (n=30,928) in 2019.
- Anti-HCV positive prevalence among the donor population decreased from 1.4% in 2017 to 1.1% in 2018 and 0.8% in 2019.
- In 2019 the highest anti-HCV positive prevalence was observed in middle-aged donors: 1.2% among those aged 40–49 and 1.4% among those aged 50–59 years. This was also the case in 2018, when the prevalence in these age groups was 1.8% and 1.9%, respectively.
- Anti-HCV positive prevalence was higher among first-time donors (2.4% in 2018 and 1.2% in 2019) than repeat donors (0.3% in 2018 and 0.2% in 2019).
- The highest anti-HCV positive prevalence was observed in relative/replacement donors, followed by unpaid volunteer donors, and paid donors in both 2018: 2.2% (n=217/9,916) vs. 0.8% (170/20,055) vs. 0.7% (152/21,055) respectively, and 2019: 1.6% (129/8,293) vs. 0.7% (196/26,347) vs. 0.4% (82/20,266).
- Of blood donors previously tested anti-HCV negative, 33 screened positive in 2018 and 22 seroconverted in 2019.
- From 2015 through 2019, of 2,506 donors who screened positive for HCV antibody and received viremia testing, 69.6% (n=1,745) were diagnosed with active infection, and of those 71.9% (n=1,254) initiated treatment.

- From January through December 2018, a total of 2,983 blood aliquots randomly selected from blood banks participating in the State Safe Blood Program[5] were submitted to the Lugar Center for retrospective serologic testing for HCV, HIV, hepatitis B virus (HBV) and syphilis. Of these, 36 samples were rejected due to spilled content and 2,947 samples were retested by Lugar Center. Overall, 35 (1.2%) of these samples were found to have discrepant transfusion transmitted infection (TTI) antibody testing results from the blood banks: 1 false positive and 4 false negatives for HCV, 2 false positives and 7 false negatives for HBV, and 1 false positive and 20 false negatives for syphilis.
- All 15 blood banks in 2018 and all 16 blood banks in 2019 participating in the state program were involved in the Proficiency Testing (PT) program for TTI conducted by two internationally accredited laboratories (European Society for External Quality Assessment and Randox International Quality Assessment Scheme). Inconsistencies were found in 4 blood banks in 2018 (1 false negative for HIV, 1 false negative and 2 false positives for syphilis) and 4 blood banks in 2019 (1 false positive for HIV, 1 false positive for HCV, and 3 false positives for syphilis).
- During January - December 2019, as part of routine external quality-control testing, a total of 1,501 blood samples were retested for HCV, HIV, HBV and syphilis, which showed the following discrepancies: 5 false negatives and 2 false positives for syphilis, and 6 false negatives for hepatitis B.
- In June 2019, two multiplex nucleic acid testing (NAT) machines were purchased with the financial support of the GFATM. Four laboratory specialists were trained in the operation of the multiplex NAT machine systems.
- The pilot project of centralized NAT testing of donations from selected Tbilisi blood banks will be launched within the State Blood Safety Program in January 2020.
- In July 2019, a Twinning project on "Strengthening Blood Safety System in Georgia," intended to approximate national blood safety regulations with European Union (EU) directives, was approved by the European Commission. The Twinning project envisages a comprehensive reformation of the blood transfusion system in Georgia, including upgrade of national blood safety legislation in accordance with European regulations; establishment of both a regulatory body at central level (National Competent Authority) and national reference laboratory; blood transfusion system reorganization; introduction of effective quality mechanisms and a haemovigilance system; NAT implementation through development of testing standards; support transition to unpaid voluntary donations, and capacity building at administrative and service provider institutions.
    - In October 2019, Lithuania and Netherlands were accepted as EU partner countries to Georgia in this joint Twinning project where the Lithuania National Blood Center, and the Central Project Management Agency of Netherlands will be the implementing organizations. The launch of the Twinning project is planned for early 2020.
- During 2018-2019, voluntary blood donation communication and recruitment campaigns were conducted. These included:
    - More than 9,300 motivational SMS messages sent to blood donors;

[5] Georgia launched its State Safe Blood Program in 1997, which aims to ensure the safety of blood and blood components through high-quality testing of donors' blood for HCV, HBV, HIV and syphilis, availability and equal accessibility to blood products.

- Over 200 posts, 32 infographics, 7 video blogs and 10 personal stories of blood donors posted on the Facebook page "I am Donor"; https://www.facebook.com/gaxdidonori/
- 16 TV programs, 14 radio visits, 19 educational articles in print and online media, and onscreen ads at the cinema were utilized to promote regular unpaid blood donation;
- World Blood Donor Day celebrations and recognition ceremonies for blood donors took place on June 14;
- 8 banners in Tbilisi, 200 posters, 150 certificates, 300 t-shirts, 300 badges, 38,000 booklets, 400 blood donor awareness rubber bracelets, 2,000 cards and 200 calendars were distributed among the donor population;
- One TV clip and video history was prepared and broadcasted.

Infection Prevention and Control

The Ministry of Internally Displaced Persons from the Occupied Territories Labour, Health, and Social Affairs (MoIDPLHSA) issued a Decree №01-5/6[6] on February 7, 2018 to establish the Infection Prevention and Control (IPC) System assessment framework for hospitals enrolled in the Universal Healthcare Program (UHP) in Georgia. Based on the above-mentioned decree, a national IPC assessment team was established within MoIDPLHSA to periodically assess inpatient facilities in the country. The IPC team is comprised of representatives from MoIDPLHSA, NCDC and State Regulation Agency for Medical Activities (RAMA).

A structured observational checklist is used to assess various IPC requirements in hospitals by the team, which includes environmental control; water, sanitation and hygiene; waste management; IPC system organization; sterilization and disinfection; safe injection practices; nosocomial infection control; and antimicrobial stewardship.

MoIDPLHSA and NCDC team members conduct initial monitoring visits of hospitals. The first visit is conducted to assess the aforementioned checklist of IPC requirements; any compliance issues are identified, and recommendations are given to bring the hospital into compliance. A follow-up visit is scheduled for non-compliant hospitals to verify the implementation of recommendations. If hospitals are still not in compliance, written recommendations are given once more and a list of these hospitals is sent to a RAMA representative for final inspection. Non-compliant hospitals at the end of this process are suspended from the UHP and sent to court, where they could be fined.

Inpatient facilities have a mandatory IPC assessment requirement before they can be licensed, while dental clinics are assessed only during their practice based on selective criteria.[7]

Key Accomplishments and Findings

- From January 2018 through December 2019, an assessment team visited 54 hospitals in Tbilisi, Kutaisi, Batumi, Telavi, Zugdidi, Marneuli and Rustavi for the first round of monitoring and

[6] https://matsne.gov.ge/ka/document/view/4049939?publication=0

[7] a) concerns for healthcare quality and patient safety b) medical facility changed the address c) non-compliances identified during preceding years d) reports on healthcare quality improvement efforts are not available etc. https://matsne.gov.ge/ka/document/view/1507093?publication=0

evaluation. Of those, 48 (89.0%) hospitals had poor compliance with national IPC system requirements and needed a follow-up assessment.
    - 92.6% (50/54) of hospitals had their own SOPs/IPC guidelines;
    - Safe injection practices were observed in 16.7% (9/54) of inpatient facilities.
    - 85.2% (46/54) of healthcare facilities received IPC training on the topics of safe handling of sharps and safe injection practices;
    - 96.3% (52/54) of inpatient facilities appointed an IPC focal point, and 92.6% (50/54) had an active IPC committee;
    - 29.6% (16/54) of hospitals reported full compliance with national legislation requirements on sterilization and disinfection;
- During 2018-2019, RAMA representatives visited a total of 44 hospitals. Of these, 43.2% (n=19) were suspended from the UHP. Fines were imposed on 17 hospitals due to substandard infection control practices and one hospital received a verbal warning.
- In October 2018, the national Coordination Council of IPC and Antimicrobial Resistance (AMR) renewed its efforts and commitments to coordinate IPC interventions across Georgia and to implement the national AMR strategy.
- An IPC national strategy and action plan are being developed and are expected to be finalized by the end of 2020 with technical assistance from United States Centers for Disease Control and Prevention (U.S. CDC).
- A comprehensive set of national IPC guidelines was developed in October 2019 by the IPC guidelines technical working group in collaboration with U.S. CDC, MoIDPLHSA and NCDC, WHO, and the Infection Control Africa Network.
    - Core components of IPC are covered in 18 chapters of the developed IPC guidelines. The topics range from the basics (e.g. standard and transmission-based precautions, hand hygiene, safe injection practices, and waste management) to IPC guidelines for intensive care units, blood banks and blood transfusions. A list of resources was included at the end of each chapter. An expansion of the IPC guidelines is planned, which will include additional modules on hemodialysis, dental procedures and other settings with risk of exposure to blood-borne pathogens.
- In 2019, the Georgian Dental Association updated the national guideline on “Infection Prevention and Control in Dentistry” and developed the guideline for “Waste Management in Dentistry”.
- IPC training courses are conducted by Tbilisi State Medical University, University of Georgia, Caucasus University, Georgian Institute of Public Affairs and several professional associations.
- During 2018-2019, on-the-job training on IPC policies was provided to 150 epidemiologists and physicians and approximately 1,200 staff members from non-medical facilities (e.g., beauty salons, tattoo salons, and other facilities performing cosmetic procedures or providing non-traditional healthcare services). The training was conducted by the Georgian Association of Epidemiologists, infection control specialists, and the epidemiology department of Tbilisi State Medical University.
- Since the launch of the hepatitis C elimination program, more than 4,000 dentists, dental nurses and staff responsible for decontamination procedures were trained in IPC by the Georgian Dental Association.

- As of December 31, 2019, over 1,700 dental clinics throughout the country were officially registered in the MoIDPLHSA database (http://cloud.moh.gov.ge), including 238 new dental clinics that opened their practice during 2018-2019. Of 130 dental clinics monitored by RAMA for infection control measures in 2018-2019, non-compliance was observed in 63.1% (n=82) compared to 53.9% (420/778) of dental clinics visited during 2015-2017.
- In 2018, MoIDPLHSA, in collaboration with U.S. CDC and ICAP (the International Center for AIDS Care and Treatment Programs) at Columbia University's Mailman School of Public Health conducted interviews and observations at 41 randomly-selected hospitals throughout Georgia to evaluate the performance of IPC systems and WHO core components of IPC.[8]
    - 78.0% (32/41) of facilities reported having IPC guidelines in place and only 43.9% (18/41) of clinics had SOPs outlining the steps for how to implement the IPC guidelines;
    - 80.5% (33/41) of facilities had conducted an internal IPC audit within the past 6 months; only 60.6% (20/33) of these facilities documented the results;
    - 82.9% (34/41) of facilities did not have any monitoring/audit plan;
    - 19.5% (8/41) of facilities always used the IPC monitoring results to guide and improve their IPC SOPs;
    - 75.6% (31/41) of facilities reported doing surveillance for healthcare associated infections (HAI), although 32.3% (10/31) of them used standardized case-definitions and data collection methods.
- During 2018-2019, a total of nine training courses on the Point Prevalence Survey (PPS) of antimicrobial use, HAI and AMR were conducted for hospital and public health center epidemiologists. The courses demonstrated the PPS methodology, survey design and critical elements of data collection.
- In 2018, PPS was conducted in 14 intensive care units (ICUs) from 10 hospitals. Nosocomial infection was identified in 28.6% (34/119) of ICU patients, of whom 64.7% had nosocomial pneumonia (n=22). In 2019, a similar survey carried out in 19 ICUs from 14 hospitals revealed 34.3% (82/239) of ICU patients had nosocomial infection, of whom 51.2% had nosocomial pneumonia (n=42).
- Overall, 907 nosocomial infections were registered in the Electronic Integrated Disease Surveillance System by hospitals during 2018-2019.
- As of December 2019, eight hospitals were participating in the HAI surveillance state program.
- "Technical regulation on IPC sanitary norms for aesthetic and cosmetic procedures at facilities of public importance"[9] was published in 2019.
- From January 2018 to August 2019, a total of 2,229 non-medical facilities were examined by NCDC and regional public health centers for IPC compliance in non-healthcare settings. Of these, non-compliance was observed in 33.2% (n=740) of facilities. Sanctions were imposed on 2.6% (n=57) of non-medical facilities.

[8] https://www.who.int/gpsc/ipc-components-guidelines/en/ *WHO eight core components constitute of: IPC programmes; IPC guidelines; IPC education and training; HAI Surveillance ; multimodal strategies; monitoring audit of IPC practices and feedback; workload and staffing and bed occupancy; built environment, materials and equipment for IPC at the facility level.*

[9] https://www.moh.gov.ge/uploads/files/oldMoh/01_GEO/jann_sistema/higienuri-Norm/mtavrob-dadgen/5.pdf

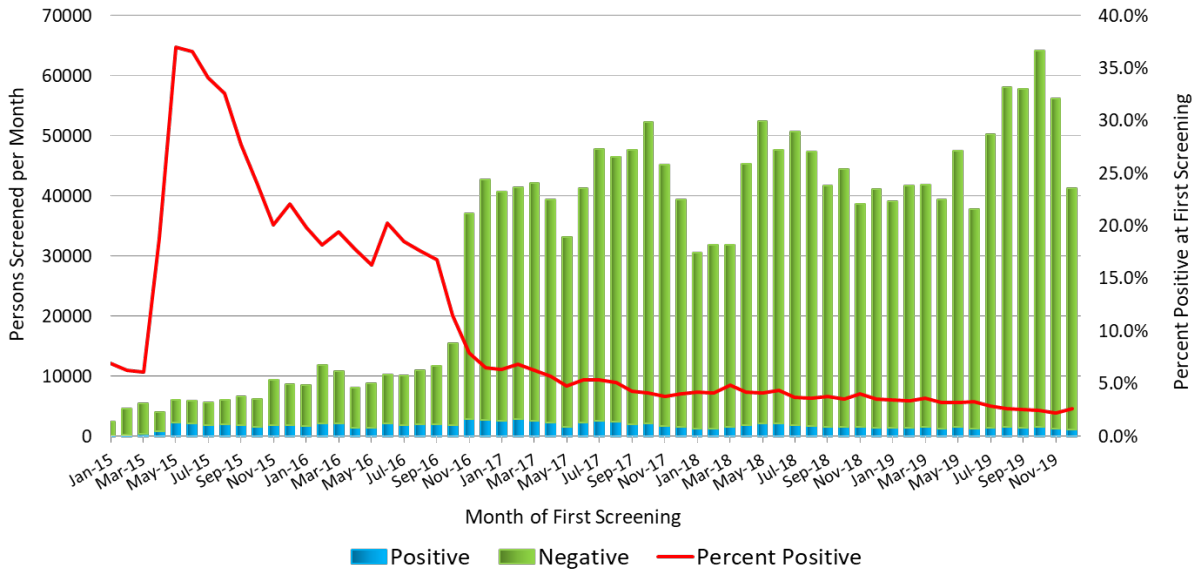
Strategy 3. Identify and Link to Care Persons Infected with HCV

To achieve the 2020 target of diagnosing 90% of HCV-infected persons, the government of Georgia has prioritized resources and commissioned services to increase uptake of screening, testing and diagnosis for HCV, and to improve linkage to care for those diagnosed with HCV infection but not yet in treatment.

Key Accomplishments and Findings

- As of December 31, 2019, more than 1.9 million adults (67% of the adult population) have been screened with HCV rapid diagnostic tests (RDT) at over 1,200 settings across the country.
- The majority of adults received their most recent HCV testing during outpatient services (41.6%; n=687,866) and inpatient hospitalization (32.5%; n=536,273); other groups receiving HCV screening included blood donors (10.2%; n=168,296), and pregnant women (2.8%; n=46,348).
- Of all persons screened, 128,799 (6.7%) had a positive anti-HCV result. The percentage of anti-HCV positive persons has gradually decreased from 37.0% at the launch of program in May 2015 to 2.6% in December 2019 (Figure 3.1).

Figure 3.1 Number of persons screened for hepatitis C per month, and number and percent tested positive in Georgia, 2015–2019

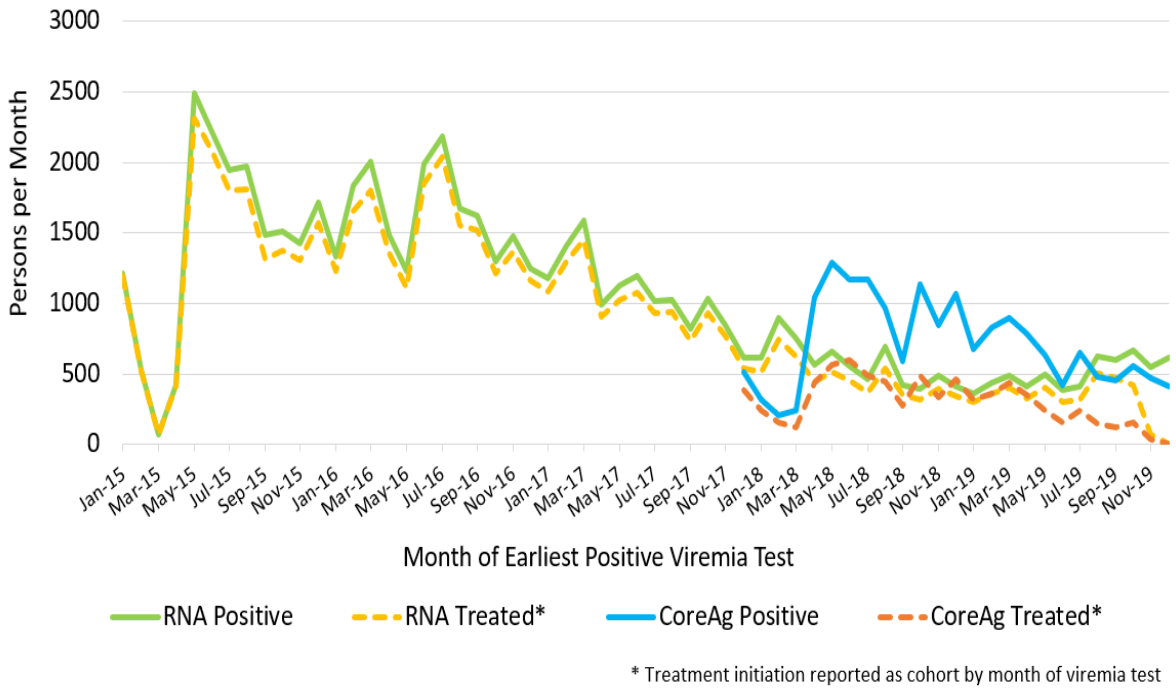


- Males aged 40-49 years had the highest overall rate of anti-HCV positivity (25.3%).
- On October 9, 2018, NCDC initiated free HCV antibody screening services at the designated areas in Public Service Halls operating under the Ministry of Justice. Over one year, a total of 69,316 adults were screened for HCV antibody at Public Service Halls in 12 cities across Georgia. The screening tests were evenly distributed by sex and were more common among younger age groups (24% 18-29 years; 24% 30-39 years; 20% 49-59 years; 17% 50-59 years; 15% >60 years). Of those screened, 2.8% (n=1,944) tested HCV antibody positive, 61.8% (n=1,202) of those

received viremia testing and of those, 82.5% (n=992) were diagnosed with active HCV infection. Among persons with active infection, 66.3% (n=658) had initiated HCV treatment.

- From January 2015 through December 2019, a total of 211,941 children under 12 years of age were screened and 0.3% were HCV antibody positive. Anti-HCV positivity prevalence was highest among those aged 0-2 years old (0.5%), (including passive maternal antibodies).
- An integrated TB/HIV/HCV screening program at primary healthcare centers (PHC), piloted in Samegrelo-Zemo Svaneti region in April 2018 with financial support from GFATM, was expanded to every region across the country except Samtskhe-Javakheti and Shida Kartli. As of December 31, 2019, a total of 384,879 persons have been screened (84% of the targeted adult population), with 1.1% (n=4,308) of those tested positive.
- Despite a wide landscape and improved geographical accessibility of viremia testing, more than 23,000 documented anti-HCV positive persons had not yet received viremia testing and were not linked to HCV care as of December 31, 2019. Of those not linked to care, 29.9% had their most recent screening test done in hospitals and 26.2% in outpatient settings. However, out of 6,666 hospitalized patients who tested anti-HCV positive and did not have viremia testing, 63% (n=4,180) were tested before reflex HCVcAg testing was launched, covering all hospitals in the country, in March 2018.
- The implementation of reflex HCVcAg testing in March 2018 increased the rate of identification of viremic individuals, though it did not increase the rate of infected persons initiating treatment (Figure 3.2).

Figure 3.2 Hepatitis C virus RNA or HCV core antigen diagnostic testing and treatment initiation by test method and month of diagnosis, January 2015-December 2019



- A variety of strategies to improve linkage to viremia testing and treatment initiation have been implemented:
    - **Active follow-up of screened anti-HCV positives:** During September - November 2018, NCDC in coordination with public health centers piloted a follow-up study of anti-HCV positive individuals who failed to receive viremia testing. A total of 772 of 1,280 (60.3%) persons were reached in 32 municipalities across Georgia. Of those, 336 (43.5%) were tested for viremia and 205 (61.0%) were positive. Only 26 (12.7%) persons were linked to HCV treatment.
    - **Reflex RNA testing:** From November 6, 2018[10], in parallel with the HCVcAg testing for hospitalized patients at the Lugar Center, six HCV service providers started performing viremia tests at their clinics for selected hospitals in Tbilisi. The proportion of anti-HCV positive inpatients who received viremia tests at HCV provider sites was slightly less (80.8%) when compared to those who had a reflex HCVcAg testing performed at the centralized laboratory in Lugar Center (82.5%) over the same length of time. Among those who tested positive for viremic infection at these sites, the rate of treatment initiation was slightly higher for those tested at HCV provider sites (52.5%) compared to Lugar Center (49.5%).
    - **Active follow-up of viremic persons:** From November 2018 to March 2019, Social Service Agency (SSA) staff successfully reached and conducted telephone interviews with 10,194 HCV-infected persons who were not yet enrolled in treatment using a standardized questionnaire. As of September 10, 2019, these efforts by SSA staff resulted in 14.3% (n=1,453) of patients initiating treatment.
    - **Active follow-up of viremic persons by HCV providers:** Based on the Ministry of Health decree №01-1287/ო[11] dated November 6th, 2018, which is related to interventions to increase case-finding and linkage to care within the national hepatitis C elimination program, a total of 10 HCV provider clinics across the country agreed to contact HCV-infected persons who were not engaged in treatment to invite them for treatment at their clinic. Data on approximately 29,400 persons diagnosed with HCV were released to those 10 HCV providers by SSA. As of September 10, 2019, these efforts resulted in 8,725 (29.7%) patients engaging in treatment.

[10] https://matsne.gov.ge/ka/document/view/4310537
[11] http://ssa.gov.ge/files//01_GEO/KANONMDEBLOBA/Saagentos-Aqtebi/504.pdf

Strategy 4. Improve HCV Laboratory Diagnostics

Georgia continues to use a mixed public-private model for the provision of HCV diagnostic and monitoring tests in accordance with the National Testing Algorithm (Appendix 2). In 2017, in collaboration with U.S. CDC, Lugar Center produced a national HCV PT panel for viral load and genotyping based on College of American Pathologists PT program model. Although the rate of diagnosing chronic HCV has improved over the last 4 years from 26.9% in 2015 to 61.1% in 2019, Georgia has not yet met the HCV diagnosis target of 90% for 2020.

Key Accomplishments and Findings

- As of December 31, 2019, more than 500 laboratory service providers were registered in the MoIDPLHSA database[12].
- Primary detection of HCV infection in Georgia relies on voluntary testing for anti-HCV, which, if positive, should be followed by viremia testing. In 2019, the government purchased a total of 600,000 HCV RDT kits from two manufactures (Healgen and Acro Biotech Inc.) as part of the hepatitis C elimination program. The performance of these RDT kits were assessed at the Lugar Center, and showed 100% sensitivity and specificity.
- The landscape of hepatitis C screening methods, including existing and approved assays to diagnose active HCV infection, has been broadened since the launch of hepatitis C elimination efforts (Table 1).

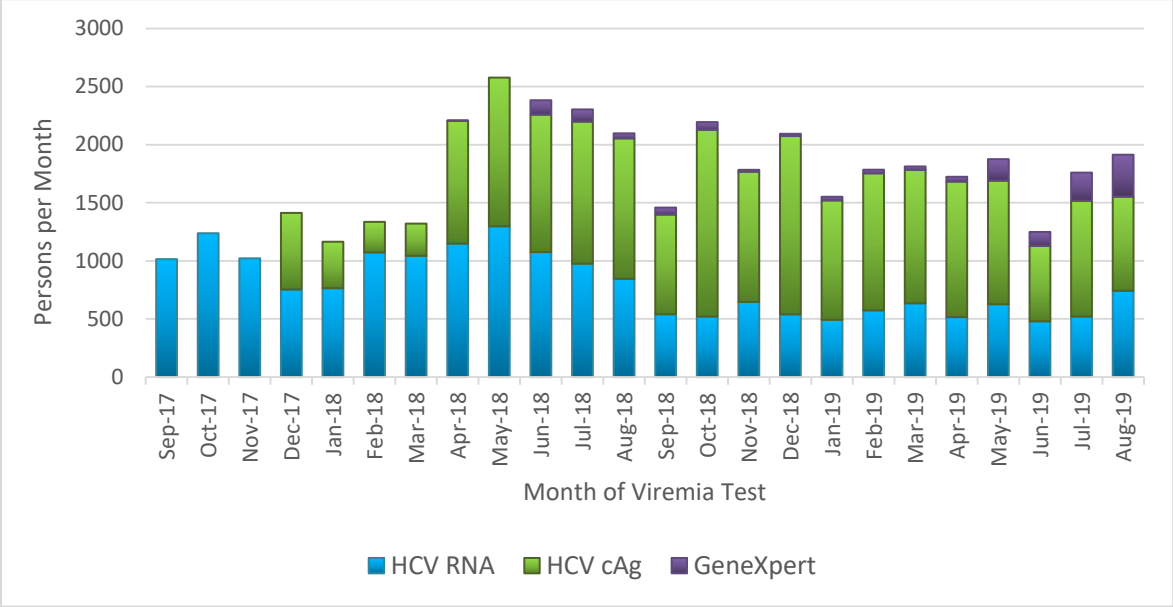
Table 1. Hepatitis C screening methods and diagnostic tests used in the HCV elimination program, December 2019

Methods	Facility/Population
Rapid diagnostic test (government procurement)	Outpatient clinics, NCDC lab network, general population, pregnant women, harm reduction centers
Rapid diagnostic test (from various vendors)	Hospitals (inpatients)
Laboratory based serology methods (ELISA; CLIA; CMIA)	Blood banks (blood donors)
Quantitative HCV RNA • All platforms • GeneXpert®	HCV treatment provider sites (n=16) Lugar Center for Public Health Research, NCDC NCDC laboratories (n=8) Harm Reduction centers (n=4)
Qualitative HCV RNA	HCV treatment provider sites (n=14)
HCV core antigen	Lugar Center for Public Health Research, NCDC

[12] http://cloud.moh.gov.ge

- In December 2017, HCVcAg testing was introduced to increase access to free-of-charge HCV viremia testing. Since March 2018, centralized HCVcAg testing by national reference laboratory, Lugar Center has been expanded to test anti-HCV positive persons screened at various settings:
    - HCV specialized and decentralized provider sites (n=15)
    - NCDC regional labs (n=2)
    - Georgian harm reduction network sites (n=13)
    - Hospitals, excluding day-patient care units (n=340)
    - Blood banks (n=22)
    - Antenatal clinics (n=326)
- During May-December 2019, the FIND-supported integration of HCV RNA testing on existing GeneXpert machines in Georgia resulted in a total of 3,511 HCV viremia tests using GeneXpert being performed at eight NCDC labs. Of these, 76.3% (n=2,680) were positive and 39.2% (n=1,050) initiated treatment.
- The efforts to improve access to free-of-charge HCV viremia testing increased the uptake of HCV diagnostic tests within the hepatitis C elimination program (Figure 4.1).

Figure 4.1 Number of persons with HCV viremia testing per month by test methods, Georgia, September 2017 through August 2019



- The cost for diagnostic evaluation of HCV-infected patients (excluding screening and viremia testing) as well as monitoring tests during the treatment course was recognized as a deterrent to active scale up of testing and treatment services. To address this barrier the government of Georgia took following measures:
    - HCV genotyping for individuals with active infection was provided free-of-charge from September 1, 2018 through the end of 2019, after which HCV genotyping was no longer required, by ministerial decree.
    - On August 1, 2019, all diagnostics for pretreatment assessment as well as monitoring during treatment became free-of-charge (Appendix 2).

- Since 2017, overall 17 laboratories (including the national reference laboratory) have been enrolled in the National External Quality Assurance (EQA) Program. During 2018-2019 HCV PT panels were distributed five times (twice in 2018 and three times in 2019) to each lab. In 2018, an HCV qualitative assay was added to the EQA Program in addition to HCV viral load and genotyping (Appendix 1). For each PT specimen, the mean and standard deviation (SD) of quantitative viral load results were calculated from all laboratories, including Lugar Center Reference Laboratory. The assessment of EQA results was based on the following criteria: +/-1SD is regarded "Excellent"; +/-2SD is regarded as "Good" and +/-3SD is regarded as "Acceptable".
    - A total of 16 labs in 2018 and 15 labs in 2019 participated in at least one of the scheduled PT rounds and performed HCV RNA viral load and genotyping tests. Of them, 13 laboratories performed qualitative HCV RNA tests.
    - The cumulative 2018 EQA Program results for quantitative HCV RNA viral load were "excellent" in 78.1% of all PT specimens, "good" in 8.1%, and "acceptable" in 1.9%. According to 2019 EQA Program results, the results for quantitative HCV RNA viral load were "excellent" in 74.7%, "good" in 21.1%, and "acceptable" in 4.1%. In most cases, the problems identified were related to improper use of quantitative HCV PCR calibrators, or non-compliance to the manufacturer's recommendations on PCR platform-reagent combinations.
    - In 2018, all laboratories accurately detected prevalent genotypes. Only 31.5% of laboratories (5/16) correctly interpreted an unusual genotype (1b/2). In 2019, nine laboratories reported incomplete genotype results and one laboratory reported a false genotype result.
    - Six laboratories reported false negative results for the qualitative interpretation of HCV RNA specimen during 2019 EQA PT rounds. No false positive results were reported by any laboratories.
- The first National EQA Program Workshop was held on April 19-21, 2019 in Borjomi, Georgia. The workshop emphasized the important role of the national reference laboratory in quality assurance of the National EQA Program. The discussion topics included EQA program report evaluation; quality assurance of pre- and post-analytical stages; monitoring activities of EQA Panel preparation (labeling, packaging, cold chain, shipment, etc.); data management systems; and future steps to improve EQA Program effectiveness.

Strategy 5. Provide Comprehensive HCV Care and Treatment

To achieve its elimination goal, the country of Georgia has set forth the 2020 target of treating 95% of people with chronic HCV infection and curing 95% of persons treated of their HCV infection. Launched in April 2015, the initial phase of the hepatitis C elimination program prioritized antiviral therapy for populations at highest risk for HCV-associated morbidity and mortality: infected persons with advanced liver disease, defined as F3 or F4 by METAVIR fibrosis score and/or FIB-4 score >3.25, severe extrahepatic manifestations, and co-infection with HIV. In June 2016, eligibility criteria expanded, allowing all HCV-infected adult persons to enroll in the program regardless of liver-disease severity. Curative antiviral therapy was provided free of charge through a partnership with Gilead Sciences. At the start of the program, all participants received sofosbuvir (SOF)-based antiviral treatment regimens, in combination with ribavirin alone or with pegylated interferon and ribavirin. Beginning in March 2016, the majority of patients began receiving sofosbuvir/ledipasvir (SOF/LED)-based regimens.

Key Accomplishments and Findings

- The number of treatment centers has increased since the launch of the elimination program, from four centers in April 2015 to 40 centers by December 31, 2019. Three HR sites, one OST site and eight PHCs started providing HCV care and treatment during 2018, with three more PHC sites joining the program during 2019 as an effort to increase the decentralization of HCV care and treatment services.
- Since August 1, 2018, HCV-infected patients' cases have been reviewed electronically in real-time by the treatment inclusion committee members, reducing delays to treatment initiation. The median number of days between committee revision and treatment initiation was 28 (interquartile range [IQR]: 21-38) during February-July 2018 compared to 9 days (IQR: 5-16) after the implementation of electronic committee review (August 2018 - January 2019).
- From December 2018, Velpatasvir/Sofosbuvir (Epclusa) medicine became available for patients with HCV genotypes 2 and 3.
- On August 1, 2019, treatment guidelines were updated within the hepatitis C elimination program and clinical monitoring and laboratory assessment was simplified upon TAG recommendations (Appendix 2).
- The national screening registry and HCV treatment database allow for clinical monitoring and program evaluation across the care cascade. As of December 31, 2019, a total of 64,537 HCV-infected persons were enrolled in the treatment program, which represents 50.3% of national target of treating 95% of diagnosed persons by 2020.
- Since peaking in 2016, treatment uptake gradually declined to approximately 1,000 patients per month and remained stable during 2019.
- SVR rates reached 98.7% (42,194/42,734) among patients eligible and tested for SVR, including retreatments; the SVR rate calculated using an "intent to treat" analysis (which took into account persons who discontinued treatment and those who completed treatment but did not receive SVR testing) was 73.6%.
- A total of 1,552 persons were retreated, with 94.2% (729/774) of those tested achieving SVR.
- In 2019, Georgia's comprehensive hepatitis C elimination program was recognized as the first European Association for the Study of Liver-international Liver Foundation (EILF) Center of Excellence in Viral Hepatitis Elimination.

- Since the launch of decentralization of HCV care and treatment among PHCs in August 2018, a total of 11 PHCs throughout the country have been providing HCV care services. At the initial phase of decentralization efforts by the government, only HCV treatment-naïve patients with no or mild fibrosis (FIB-4 score <1.45) were treated using simplified diagnostics and a treatment monitoring approach. Treatment eligibility criteria were later expanded to those with FIB-4 score between 1.45 and 3.25, while persons with cirrhosis were referred to specialized clinics.
- Overall, 557 patients received DAA treatment at PHC facilities by the end of 2019 and 94.6% (122/129) achieved SVR.
- MoIDPLHSA has begun improving access for PWID by allowing 3 HR centers and 1 OST site to provide HCV care and treatment onsite.
- As of December 31, 2019, a total of 801 HCV antibody positive PWID received HCV RNA or HCVcAg testing to determine active HCV infection after decentralizing the HCV care and treatment in HR sites; 672 persons (83.9%) had active HCV infection and 519 were tested for FIB-4 score on site. Overall, 269 persons initiated treatment and 10 persons discontinued treatment. Among 123 persons tested for SVR, 121 (98.4%) have been successfully cured.

Strategy 6. Improve HCV Surveillance

Key Accomplishments and Findings

- Four infectious disease hospitals were selected[13] in Tbilisi, Imereti, Samegrelo and Adjara regions as sentinel sites for HCV and HBV biomarker testing and collection of epidemiological information. NCDC revised the case definitions for acute and chronic hepatitis C and B and developed surveillance reporting forms. The sentinel sites are now mandated to fill the reporting forms and register hepatitis C and B confirmed cases in an Excel database (Governmental decree dated December 31st, 2019)[14].
- From July through December 2018, within the research project (for more details, see Research and Science section) a total of 222 cases with acute viral hepatitis and 40 cases of jaundice were studied using the medical charts from 24 medical facilities in 9 regions of Georgia. Study findings demonstrated that clinical diagnoses do not correspond to case definitions in the national epidemiological surveillance. Of 61 acute HCV cases diagnosed by clinical signs and symptoms in combination with anti-HCV results, 50.8% (n=31) were not laboratory confirmed.
- From November 2018 through January 2019, a total of 119 medical charts of liver cancer cases from multiple hospital types and regions were studied. The largest proportion (42.0%; n=50) were categorized as unspecified liver cancer, followed by 28.6% (n=34) cases with hepatocellular carcinoma (HCC). Nearly 50% of all HCC cases were reported to have chronic HCV infection. Symptoms and risk factors for most HCC patients were not properly described in the medical charts. Overall, 37 out of 119 patients (31.1%) were found to have hepatitis C screening results after data was linked with the national screening registry and of those, 75.7% (n=28) were anti-HCV positive.
- Based on the governmental decree dated December 31, 2019, state programs, including the Epidemiologic Surveillance Program and municipal public health centers should ensure tracking and linkage of anti-HCV positive persons to care who have not yet received HCV viremia testing[11].

[13] the high volume of beneficiaries with viral hepatitis infection, geographical accessibility and being an HCV care provider

[14] https://matsne.gov.ge/ka/document/view/4762618

STRATEGY-SPECIFIC CHALLENGES TO HCV ELIMINATION

Improving Awareness:

- Limited scope of communication campaigns due to limited resources
- Low quality and effectiveness of campaigns due to:
    - Barriers to contract professional public relations companies due to complex bidding process
    - Professional public relations companies not interested in the project due to low budget allocation for health promotion and awareness activities by the government
- Inadequate involvement of primary healthcare workers in HCV awareness activities due to lack of information, low motivation, and poor interpersonal communication skills

Preventing Transmission:

Harm Reduction:

- Lack of trust regarding perceived confidentiality and anonymity among PWID entered into the national screening registry
- Inconsistencies in data between the HR program and the national screening registry
- Existing drug addiction-related stigma, particularly of female drug users, hinders access to HR services and HCV care
- Low awareness of the hepatitis C elimination program among PWID
- Lack of educational programs in HR sites to address misconceptions about the treatment program

Blood Safety:

- Lack of a supervisory body at the central level
- Existence of profit-based and unregulated blood banks
- The predominant practice of paying donors, which compromises blood safety practices
- Lack of standardization of clinical guidelines and deficient testing algorithms for donated blood in some blood banks
- Suboptimal donor selection and laboratory screening practices
- Reliance on semi-automated and rapid-test platforms for testing blood donations
- Lack of effective quality assurance and control systems
- Suboptimal national regulations and non-compliance with European standards

Infection Prevention and Control:

- Need for a national IPC strategy and action plan - only partially noted in national Antimicrobial Resistance Strategy and Hepatitis C Elimination Program Strategy documents
- Absence of IPC monitoring in facilities with ambulatory care
- Absence of mandatory pre-licensing IPC system assessment for new dental clinics
- Scarce data on HAI limits the opportunity for effective and timely IPC interventions

- Low engagement and involvement of professional medical associations to educate medical personnel about IPC
- Lack of standardized curriculums in IPC
- Lack of IPC measures in beauty salons, including inefficient and inadequate inspection processes

Identifying Infected Persons and Linking Them to Care:

- Steadily declining rates of anti-HCV positivity among the screened population
- Suboptimal numbers of anti-HCV positive persons receiving viremia testing
- Hepatitis C screening and testing for viremia are often conducted at different sites
- Insufficient counselling of patients diagnosed by HCVcAg
- Suboptimal rates of linkage to care among persons with HCV infection confirmed by reflex HCVcAg testing

Improving Laboratory Diagnostics:

- Lack of a quality assurance system for HCV rapid tests
- No national system for licensing laboratory professionals
- Absence of uniform national standard operating procedures (SOPs) for the country's HCV diagnostic laboratories
- Lack of standardized comprehensive training programs for laboratory personnel on quality and biosafety standards and practices
- Lack of HCV viremia testing sites in the regions

Providing Care and Treatment:

- Lack of EASL or American Association for the Study of Liver Diseases recommended regimens to guide therapy for patients who require retreatment after failing to achieve SVR with their initial DAA course
- Limited treatment options for patients with end-stage kidney disease, including hemodialysis
- Limited provider capacity and scarcity of treatment centers, especially PHCs in some rural and geographically disparate areas
- Need for futher simplification of treatment algorithms and patient management
- Need for increased training for PHC doctors and HR staff to improve their knowledge and skills in HCV management
- HCC surveillance among cirrhotic patients with SVR not yet incorporated into the hepatitis C elimination program

Improving Surveillance:

- Issues of timeliness, accuracy, and completeness of data collection associated with current HCV surveillance system
- Failure of current system to adequately capture and promptly identify seroconversion cases of HCV infection among populations at risk (e.g., PWID, persons receiving dialysis, repeat blood donors)
- Lack of an HCC surveillance system among cirrhotic patients treated within the hepatitis C elimination program

Monitoring & Evaluation: Advocacy, Awareness and Education, and Partnerships

Objective	Indicator name	Measurement	Data Source	Value/Result (2019)	Value/Result (2018)	Value/Result (2017)	Value/Result (2015-2016)
1.1. Educate the public and high-risk groups about viral hepatitis and the importance of testing	1. Levels of awareness among the general public regarding a) HCV transmission b) HCV prevention c) Testing and diagnosis d) Treatment	**High Awareness** All or most participants aware **Medium Awareness** Some participants aware **Low Awareness** Few or no participants aware	* KAP survey 2016 ** Small scale Facebook survey *** Qualitative survey	*** a) n/a b) n/a c) Low d) Low	** a) Medium b) Medium c) Medium d) Low	** a) High b) Medium c) High d) Medium	* a) High b) Medium c) High d) Medium
	2. Levels of awareness among PWID regarding a) HCV transmission b) HCV prevention c) testing and diagnosis d) treatment	**High Awareness** All or most participants aware **Medium Awareness** Some participants aware **Low Awareness** Few or no participants aware	* KAP survey 2016 ** Integrated Bio-Behavioral Surveillance Survey (IBSS) 2017 *** Qualitative study (GHRN)	*** a) n/a b) n/a c) Low d) Low	Data not available	** a) Medium b) Low c) Medium d) Medium	* a) High b) Medium c) High d) Medium
1.2 Reduce community-level stigma and discrimination associated with HCV infection	3. Level of perceived HCV-related stigma and discrimination experienced among HCV patients in healthcare and other settings (e.g., work, housing, school, corrections)			Data not available	Data not available	Data not available	Data not available

Monitoring & Evaluation: Harm Reduction

Objective	Indicator name	Measurement	Data source	Value/Result (2019)	Value/Result (2018)	Value/Result (2017)	Value/Result (2015-2016)
2A. Decrease HCV incidence among PWID by promoting harm reduction	1. Number and percentage of PWID reached with preventive counseling (Defined Package of Services) * The beneficiary is considered reached if received at least two services from the list of basic package (condom, consultation, information materials, syringe/needle) and one of them has to be syringe/needle	**Numerator** Number of PWID reached with preventive counseling	Database of PWID receiving HIV counseling and testing (HCT); GHRN	**68.2%** **(N=35,811)**	**56.9%** **(N=29,891)**	**51.9%** **(N=27,250)**	**61.0%** **(N=30,330)**
		Denominator Estimated number of PWID	Population size estimation (PSE) of PWID in Georgia	**(N=52,500)** *PSE 2017*	**(N=52,500)** *PSE 2017*	**(N=52,500)** *PSE 2017*	**(N=49,700)** *PSE 2014*
	2. Number and percentage of PWID enrolled in OST	**Numerator** Number of PWID enrolled in OST	Social Service Agency	**58.7%** **(N= 9,552)**	**59.0%** **(N= 9,606)**	**45.4%** **(N=7,381)**	**20.2%** **(N=4,435)**
		Denominator Estimated number of opioid user PWID	IBSS 2017 **31% of estimated PWID	**(N=16,275)**** *IBSS 2017*	**(N=16,275)**** *IBSS 2017*	**(N=16,275)**** *IBSS 2017*	**(N=22,000)**** *IBSS 2014*

Objective	Indicator name	Measurement	Data source	Value/Result (2019)	Value/Result (2018)	Value/Result (2017)	Value/Result (2015-2016)
	3. Number and percentage of PWID screened for HCV infection at: a. NSP sites and Outreach b. OST service centers c. Mobile ambulatories	**Numerator** Number of PWID screened for HCV infection	a) Harm reduction program records b c) National HCV screening registry	**a. 23.0%** **b. 51.8%** **c. 27.2%** **a. N= 12,065** **b. N=8.426**** **c. N= 14,259**	**a. 20.4%** **b. 47.1%** **c. 18.4%** **a. N= 10,691** **b. N=7,660**** **c. N= 9,659**	**a. 22.6%** **b. n/a** **c. 18.6%** **a. N= 11,885** **b. N=n/a** **c. N= 9,745**	**a. 48.2%** **b. n/a** **c. 20.7%** **a. N= 23,969** **b. N=n/a** **c. N= 10,304**
		Denominator Estimated number of current PWID	*PSE **IBSS	**(N=52,500)*** **(N=16,275)****	**(N=52,500)*** **(N=16,275)****	**(N=52,500)***	**(N=49,700)***
	4. Number and percentage of PWID with presence of anti-HCV antibodies	**Numerator** Number of PWID with anti-HCV positivity	∗Harm reduction program records	**16.6%*** **(N=3,945)∗** **27.0%**** **(N= 4,479)∗∗**	**22.8%*** **(N= 4,574)∗** **30.8%**** **(N= 3,411)∗∗**	**32.1%*** **(N= 6,850)∗** **36.8%**** **(N= 1,941)∗**	**43.6%*** **(N= 10,469)∗** **N/A**
		Denominator Number of PWID tested for HCV infection	∗∗National HCV screening registry	**(N= 23,819)∗** **(N=16,590)∗∗**	**(N= 20,067)∗** **(N=11,085)∗∗**	**(N= 21,371)∗** **(N=5,280)∗∗**	**(N= 23,969)∗**

Objective	Indicator name	Measurement	Data source	Value/Result (2019)	Value/Result (2018)	Value/Result (2017)	Value/Result (2015-2016)
	5. Number and percentage of PWID testing positive on rapid tests who undergo HCV viremia testing	**Numerator** Number of PWID tested for HCV RNA or HCV core antigen testing	Elimination C	**75.4%** **(N=3,377)**	**64%** **(N=2,187)**	**50.5%** **(N=981)**	Data not available
		Denominator Number of PWID with anti-HCV positive results	National HCV screening registry	**(N= 4,479)**	**(N= 3,411)**	**(N=1,941)**	
	6. Number and percentage of PWID diagnosed with active HCV infection	**Numerator** Number of PWID diagnosed with active HCV infection based on virologic biomarker testing	Elimination C	**84.4%** **(N=2,850)**	**90.0%** **(N=1,968)**	**87.7%** **(N=861)**	Data not available
		Denominator Number of PWID who were tested for HCV RNA or HCV core antigen testing	National HCV screening registry	**(N=3,377)**	**(N=2,187)**	**(N=981)**	
	7. HCV prevalence among PWID by IBBS study		IBBS	**N/A**	**N/A**	**63.2%** *Value is pooled estimate from IBBS 2017. Actual numerator unknown.*	**66.2%** *Value is pooled estimate from IBBS 2014. Actual numerator unknown.*

Objective	Indicator name	Measurement	Data source	Value/Result (2019)	Value/Result (2018)	Value/Result (2017)	Value/Result (2015-2016)
	8. Number and percentage of PWID with active HCV infection who started HCV treatment	**Numerator** Number of PWID started HCV treatment	Elimination C	**74.5%** **(N= 2,123)**	**68.3%** **(N= 1,346)**	**75.6%** **(N= 651)**	Data not available
		Denominator Number of PWID with diagnosed HCV infection		**(N=2,850)**	**(N=1,968)**	**(N= 861)**	
	9. Number and percentage of PWID treated in the program who completed treatment	**Numerator** Number of PWID completed antiviral treatment	Elimination C	**89.5%** **(N= 1,900)**	**82.6%** **(N= 1,112)**	**78.5%** **(N= 511)**	Data not available
		Denominator Number of PWID initiated HCV treatment		**(N= 2,123)**	**(N= 1,346)**	**(N= 651)**	
	10. Number and percentage of PWID completing treatment who achieved sustained virologic response (SVR)	**Numerator** Number of PWID who achieved SVR	Elimination C	**98.6%** **(N=1,255)**	**97.0%** **(N=619)**	**95.8%** **(N=282)**	Data not available
		Denominator Number of PWID assessed for SVR 12-24 weeks after the end of treatment		**(N=1,273)**	**(N=638)**	**(N=294)**	

Objective	Indicator name	Measurement	Data source	Value/Result (2019)	Value/Result (2018)	Value/Result (2017)	Value/Result (2015-2016)
	11. Percentage of PWID reporting use of sterile injecting equipment the last time they injected	**Numerator** Number of PWID reporting use of sterile injecting equipment the last time they injected **Denominator** Estimated number of PWID	IBBS	**N/A**	**N/A**	**91.6%** *Value is estimate from IBBS 2017. Actual numerator unknown* **(N=52,500)**	**80.4%** *Value is estimate from IBBS 2014. Actual numerator unknown* **(N=49,700)**

Monitoring & Evaluation: Blood Safety

Objective	Indicator name	Measurement	Data source	Value/Result (2019)	Value/Result (2018)	Value/Result (2017)	Value/Result (2015-2016)
2B.a Prevent healthcare-related transmission of viral hepatitis by improving blood safety	1. Number and percentage of all blood banks participating and operating in the Unified Blood Donor Electronic Database (Donor Database)	**Numerator** Number of blood banks participating and operating in the Donor Database	Donor Database	**100.0%** **(N=22)**	**100.0%** **(N=22)**	**95.5%** **(N=21)**	**90.0%** **(N=18)**
		Denominator Total number of blood banks holding state license in blood production service	State Regulation Agency for Medical Activities	**(N=22)**	**(N=22)**	**(N=22)**	**(N=20)**
	2. Lead agency is established at central level to oversee and coordinate blood service in the country	Appropriate legislative act	MoIDPLHSA	Not established	Not established	Not established	Not established
	3. Licensing regulations for blood banks are established, approved, and published	Appropriate legislative act	Legislative Department of MoIDPLHSA	Not established	Not established	Not established	Not established
	4. Number and percentage of voluntary donations among all blood donations	**Numerator** Number of voluntary donations	Donor Database	**32.7%** **(N=30,876)**	**27.5%** **(N=25,064)**	**23.1%** **(N=20,283)**	**30.5%** **(N=26,379)**
		Denominator Total number of blood donations		**(N=94,457)**	**(N=91,020)**	**(N=87,881)**	**(N=86,608)**

Objective	Indicator name	Measurement	Data source	Value/Result (2019)	Value/Result (2018)	Value/Result (2017)	Value/Result (2015-2016)
	5. Proportion of anti-HCV reactive persons among blood donors	**Numerator** Number of blood donors with anti-HCV positive results	Donor Database	**0.8%** **(N=419)**	**1.1%** **(N=541)**	**1.4%** **(N=727)**	**1.8%** **(N=912)**
		Denominator Total number of unique blood donors		**(N=55,779)**	**(N=51,289)**	**(N=51,799)**	**(N=51,731)**
	6. Proportion of blood donors tested for HCV by NAT and/or other sensitive tests	**Numerator** Number of blood donors tested for viremia after a positive serologic test	Donor Database Elimination C STOP-C databases National HCV screening registry	**62.3%** **(N=2,506)**	**60.7%** **(N=2,226)**	**41.7%** **(N=1,193)**	Data not available
		Denominator Number of seroreactive blood donors		**(N=4,025)** *Donors screened 2015-2019*	**(N=3,665)** *Donors screened 2015-2018*	**(N=2,860)** *Donors screened 2015-2017*	
	7. Proportion of blood donors diagnosed with chronic HCV infection	**Numerator** Number of blood donors tested positive by HCV viremia testing (Core Ag, PCR)	Elimination C STOP-C databases National HCV screening registry	**69.6%** **(N=1,745)**	**71.2%** **(N=1,584)**	**75.8%** **(N=904)**	Data not available
		Denominator Total number of unique blood donors tested for viremic HCV infection		**(N=2,506)**	**(N=2,226)**	**(N=1,193)**	

Objective	Indicator name	Measurement	Data source	Value/Result (2019)	Value/Result (2018)	Value/Result (2017)	Value/Result (2015-2016)
	8. Degree of the continuity of care (Percentage of HCV confirmed blood donors enrolled in the HCV treatment program)	**Numerator** Total number of HCV viremic donors enrolled in the treatment program **Denominator** Total number of donors with active HCV infection	Elimination C STOP-C databases National HCV screening registry *Data since the launch of the program in 2015*	**71.9%** **(N=1,254)** **(N=1,745)**	**75.2%** **(N=1,191)** **(N=1,584)**	**79.9%** **(N=722)** **(N=904)**	Data not available

Monitoring & Evaluation: Infection Prevention and Control

Objectives	Indicator name	Measurement	Data source	Value/Result (2019)	Value/Result (2018)	Value/Result (2017)	Value/Result (2015-2016)
2C.a Prevent healthcare-associated transmission of viral hepatitis by improving infection control in healthcare facilities	1. National guidelines on IPC	**Scale indicator:** 0 = not started; 1 = under development; 2 = draft complete /developed; 3 = published.	Published guidelines	**2**	**2**	**2**	**1**
	2. Number of medical universities and nursing colleges with IPC curriculum introduced into training program		Survey conducted by MoIDPLHSA/ NCDC Ministry of Education	**4**	**2**	**2**	**1**
	3. Percentage of healthcare facilities in compliance with national IPC guidelines	**Numerator** Number of health-care facilities compliant with national guidelines	Survey conducted by MoIDPLHSA / NCDC	**11.0%*** **(N=6)**	**11.0%*** **(N=6)**	**18.2%** **(N=12)**	**26.3%** **(N=5)**
		Denominator Number of health-care facilities surveyed		**(N=54)**	**(N=54)**	**(N= 66)**	**(N=19)**
	4. Percentage of healthcare facilities with an appointed IPC focal person	**Numerator:** Number of health-care facilities with appointed IPC focal person	Survey conducted by MoIDPLHSA / NCDC	**96.3%*** **(N=52)**	**96.3%*** **(N=52)**	**100.0%** **(N=66)**	**100.0%** **(N=19)**

Objectives	Indicator name	Measurement	Data source	Value/Result (2019)	Value/Result (2018)	Value/Result (2017)	Value/Result (2015-2016)
		Denominator: Number of health-care facilities surveyed		**(N= 54)**	**(N= 54)**	**(N= 66)**	**(N= 19)**
	5. Percentage of healthcare facilities with functional IPC committees	**Numerator:** Number of health-care facilities with active IPC committees	Survey conducted by MoIDPLHSA / NCDC	**92.6%*** **(N=50)**	**92.6%*** **(N=50)**	**100.0%** **(N=66)**	**73.7%** **(N=14)**
		Denominator: Number of health-care facilities surveyed		**(N= 54)**	**(N= 54)**	**(N= 66)**	**(N= 19)**
	6. Percentage of healthcare facilities displaying materials on IPC awareness	**Numerator** Number of health-care facilities displaying IPC-awareness materials	Survey conducted by MoIDPLHSA / NCDC	**72.2%*** **(N=39)**	**72.2%*** **(N=39)**	**90.9%** **(N=60)**	**42.1%** **(N=8)**
		Denominator Number of health-care facilities surveyed		**(N= 54)**	**(N= 54)**	**(N= 66)**	**(N= 19)**
2C.b Prevent HCV transmission in non-traditional healthcare and	1. Percentage of non-medical facilities where SOPs are available	N**umerator** Number of non-medical facilities where SOPs are available	Survey conducted by NCDC and regional public health	**75.4%** **(N=3,377)**	**89.0%** **(N=733)**	**100.0%** **(N=416)**	*Data not available Survey planned for 2017*

Objectives	Indicator name	Measurement	Data source	Value/Result (2019)	Value/Result (2018)	Value/Result (2017)	Value/Result (2015-2016)
other community settings		**Denominator** Total number of surveyed non-medical facilities	centers	**(N= 1,405)**	**(N= 824)**	**(N= 416)**	
	2. Number of non-medical facility staff trained in IPC		NCDC and regional public health centers	**1,200**	**824**	**1,500**	**50**

Monitoring & Evaluation: Identifying Infected Persons and Linking Them to Care

Objective	Indicator name	Measurement	Data source	Value/Result** (2019)	Value/Result (2018)	Value/Result (2017)	Value/Result (2015-2016)
3.1 Expand HCV testing to better reach high-risk populations	1. Number of persons tested for hepatitis C antibody 1) All locations* 2) Prisoners 3) People living with HIV/AIDS 4) Pregnant women at ANC clinics 5) TB patients 6) Hemodialysis patients 7) Inpatients 8) PWID		National HCV screening registry State Healthcare Program	1) **965,422** 2) **2,628** 3) **4,011** 4) **34,004** 5) **1,994** 6) **N/A** 7) **307,626** 8) **6,157**	1) **702,061** 2) **2,020** 3) **3,599** 4) **42,218** 5) **2,693** 6) **2,679** 7) **287,978** 8) **5,905**	1) **744,983** 2) **4,127** 3) **1,220** 4) **43,097** 5) **414** 6) **1,912** 7) **378,762** 8) **5,280**	1) **472,890***** 2) **14,053***** 3) **1,790** 4) **53,852***** 5) **N/A** 6) **N/A** 7) **48,506** 8) **44,410*****
	2.Proportion of persons screened anti-HCV positive 1) All locations 2) Prisoners 3) People living with HIV/AIDS 4) Pregnant women at ANC clinics 5) TB patients 6) Hemodialysis patients 7) Inpatients 8) PWID	**Numerator** Number of persons with HCV seropositivity **Denominator** Number of persons screened for Hepatitis C	National HCV screening registry	1) **2.2%** (21,421) 2) **12.3%** (324) 3) **36.0%** (1,442) 4) **0.5%** (182) 5) **16.6%** (331) 6) **N/A** 7) **21.5%** (6,609) 8) **18.6%** (1,144)	1) **3.5%** (24,988) 2) **23.5%** (474) 3) **39.5%** (1,420) 4) **1.1%** (481) 5) **19.7%** (532) 6) **23.8%** (637) 7) **3.0%** (8,740) 8) **24.9%** (1,471)	1) **5.0%** (37,351) 2) **12.6%** (521) 3) **30.6%** (1,220) 4) **0.6%** (243) 5) **18.1%** (75) 6) **16.7%** (320) 7) **3.8%** (14,521) 8) **36.8%** (1,941)	1) **11.0%** (52,018) 2) **37.4%** (5,255) 3) **24.9%** (446) 4) **0.4%** (2015) 5) **N/A** 6) **N/A** 7) **4.9%** (2,353) 8) **45.0%** (19,984)

Objective	Indicator name	Measurement	Data source	Value/Result** (2019)	Value/Result (2018)	Value/Result (2017)	Value/Result (2015-2016)
	3. Number and percentage of children born to HCV-positive women screened for hepatitis C	**Numerator** Number of children born to HCV-infected mothers and screened for hepatitis C		Data not available	Data not available	Data not available	Data not available
		Denominator Total number of children born to HCV-positive women during the reporting period					
* Includes outpatients, blood banks, NCDC, Public Service Halls, et al. in addition to those listed in the table ** Individual year data are not mutually exclusive *** Unique persons screened for 2015-2016 are unavailable – number of screening tests performed are presented							

Monitoring & Evaluation: Laboratory Diagnostics

Objective	Indicator name	Measurement	Data source	Value/Result (2019)	Value/Result (2018)	Value/Result (2017)	Value/Result (2015-2016)
4.1 Improve laboratory detection of HCV infection	1. Number of HCV viremia testing sites (laboratories and point of care diagnostic sites)* enrolled in the national hepatitis C EQA program		NCDC Lugar Center * includes the national reference laboratory	**N=17**	**N=17**	**N=16**	**N=0**
	2. Proportion of HCV viremia testing sites that participated on **all** EQA challenges per year	**Numerator** Number of laboratories performing HCV viremia testing that participated on **all** EQA challenges per year	NCDC Lugar Center * includes the national reference laboratory	**76.5%** **(N=13)**	**88.2%** **(N=15)**	**75.0%** **(N=12)**	**(N=0)**
		Denominator* Total number of laboratories performing HCV viremia testing enrolled in national EQA		**(N=17)**	**(N=17)**	**(N=16)**	
	3. Quality Management System (QMS) standards for certification are defined, approved, and published		Published QMS standards	Ongoing	Ongoing	Ongoing	Not done yet

Objective	Indicator name	Measurement	Data source	Value/Result (2019)	Value/Result (2018)	Value/Result (2017)	Value/Result (2015-2016)
	4. Proportion of labs providing HCV lab services certified according to national laboratory quality management system (QMS) standards	**Numerator** Number of laboratories performing HCV lab services that are certified according to national QMS standards	MoIDPLHSA Not applicable until national laboratory QMS standards are approved	**N/A**	**N/A**	**N/A**	**N/A**
		Denominator Total number of laboratories performing hepatitis C laboratory services					

Monitoring & Evaluation: Care and Treatment

Objective	Indicator name	Measurement	Data Source	Value/Result (2019)	Value/Result (2018)	Value/Result (2017)	Value/Result (2015-2016)
5.1. Promote universal access to HCV care and treatment	1. Proportion of anti-HCV positive persons assessed for viremic HCV infection	**Numerator** Number of HCV antibody positive persons tested for viremic HCV infection	Elimination C STOP-C databases National HCV screening registry *Data since the launch of the program in 2015*	**80.4%** **(N=100,844)**	**74.6%** **(N=78,611)**	**63.0%** **(N=51,205)**	**65.5%** **(N=38,113)**
		Denominator Number of people with a presence of anti-HCV antibodies (treatment eligible Age ≥ 12)		**(N=124,312)**	**(N=105,393)**	**(N=81,242)**	**(N=58,223)**
	2. Proportion of persons diagnosed with chronic HCV infection	**Numerator** Number of persons diagnosed with chronic HCV infection based on virologic biomarker testing	Elimination C STOP-C databases National HCV screening registry *Data since the launch of the program in 2015*	**81.8%** **(N=82,486)**	**85.2%** **(N=67,001)**	**91.0%** **(N=46,573)**	**95.3%** **(N=36,322)**
		Denominator Number of persons tested for viremia after a positive serological result ◊ Target of identifying **90%** of persons infected with HCV infection: **N=135,000**	National sero-prevalence survey conducted in **2015**	**(N=100,844)** **◊61.1%**	**(N=78,611)** **◊49.6%**	**(N=51,205)** **◊34.5%**	**(N=38,113)** **◊26.9%**

Objective	Indicator name	Measurement	Data Source	Value/Result (2019)	Value/Result (2018)	Value/Result (2017)	Value/Result (2015-2016)
	3. Proportion of persons with chronic HCV infection who initiated antiviral therapy	**Numerator** Number of persons diagnosed with chronic HCV infection who initiated antiviral therapy	Elimination C STOP-C databases National HCV screening registry *Data since the launch of the program in 2015*	**78.2%** **(N=64,537)**	**78.5%** **(N=52,594)**	**91.0%** **(N=42,391)**	**76.0%** **(N=27,595)**
		Denominator Number of persons diagnosed with chronic HCV infection ◊Target of treating **95%** of persons with chronic HCV infection: **N=128,250**	 National sero-prevalence survey conducted in 2015	**(N=82,486)** **◊50.3%**	**(N=67,001)** **◊41.0%**	**(N=46,573)** **◊33.0%**	**(N=36,322)** **◊21.5%**
	4. Proportion of patients engaged in antiviral therapy who have completed treatment	**Numerator** Number of patients with chronic HCV infection who have completed treatment	Elimination C STOP-C databases *Data since the launch of the program in 2015*	**92.2%** **(N=59,485)**	**93.0%** **(N=48,928)**	**89.5%** **(N=37,948)**	**71.7%** **(N=19,778)**
		Denominator Number of patients diagnosed with chronic HCV infection who initiated treatment		**(N=64,537)**	**(N=52,594)**	**(N=42,391)**	**(N=27,595)**

Objective	Indicator name	Measurement	Data Source	Value/Result (2019)	Value/Result (2018)	Value/Result (2017)	Value/Result (2015-2016)
	5. Proportion of patients achieving SVR to HCV therapy	**Numerator** Number of patients who completed treatment and achieved SVR (undetectable viral load 12-24 weeks after the end of treatment)	Elimination C STOP-C databases *Data since the launch of the program in 2015*	**98.7%** (Per-protocol) **73.6%** (Intention-to-treat) **(N=42,194)**	**98.3%** (Per-protocol) **73.9%** (Intention-to-treat) **(N=34,493)**	**98.2%** (Per-protocol) **75.7%** (Intention-to-treat) **(N=26,692)**	**84.1%** (Per-protocol) **(N=26,692)**
		Denominator Number of patients who completed antiviral therapy and were assessed for SVR 12-24 weeks post treatment ◊ Target of curing 95% of persons treated for their HCV infection: **N=121,838**	 National sero-prevalence survey conducted in **2015**	**(N=42,734)** **◊34.6%**	**(N=35,106)** **◊28.3%**	**(N=27,181)** **◊21.9%**	**(N=27,181)** **◊21.9%**
	6. Number of physicians providing HCV services OR provider/resident ratio	**Numerator** Number of physicians providing HCV services:	MoIDPLHSA	**5.1 per 100,000 residents** **N=155**	**5.1 per 100,000 residents** **N=155**	**4.6 per 100,000 residents** **N=139**	**4.6 per 100,000 residents** **N=139**
		Denominator Estimated resident population: **3,010,200**					

Objective	Indicator name	Measurement	Data Source	Value/Result (2019)	Value/Result (2018)	Value/Result (2017)	Value/Result (2015-2016)
	7. Number of a) Primary Healthcare Centers b) Harm Reduction Sites providing HCV care and treatment		MoIDPLHSA	**a) 7** **b) 4**	**a) 7** **b) 4**	**0**	**0**

Monitoring & Evaluation: Surveillance

Objective	Indicator name	Measurement	Data source	Value/Result (2019)	Value/Result (2018)	Value/Result (2017)	Value/Result (2015-2016)
6.1 Estimate the national burden of chronic viral hepatitis C	1. The incidence of HCV infection	**Numerator** Total number of new infections with HCV, defined as anti-HCV positive, per year **Denominator** Total population minus people living with hepatitis C	Prospective cohort study of the reinfection rate among treated and cured PWID*	Data not Available	Data not available	**1.2 per year*** **2/169 person-years of follow-up**	**1.4 per year*** **2/138.9 person-years of follow-up**
	2. Number of deaths attributable to HCV-associated cirrhosis or hepatocellular carcinoma (HCC)	Number of deaths from HCC and cirrhosis attributable to HCV infection	Death Registry/Cancer registry HCC (ICD-10 code C22.0) Cirrhosis (ICD-10 codes K74.3, K74.4, K74.5, K74.6)	Data not Available	Data not available	Data not available	Data not available

Research and science

Progress and Outcomes

- In 2017-2019 the Scientific Committee (SC) continued program support by reviewing and approving research proposals focused on hepatitis C-related topics. The committee, representing a diverse group of interests such as policy makers, clinicians, and researchers was established in August 2016. Besides its primary purpose (review and approval of submitted proposals), the committee performed the following tasks:
  - Assisted the researchers in:
    - ✓ Securing funding
    - ✓ Obtaining IRB approvals
    - ✓ Study implementation
    - ✓ Data analysis and manuscript writing
  - Coordinated its activities with the MoIDPLHSA, Program Clinical Committee, and international organizations to increase overall efficiency of the supported research programs.
  - Served as a platform for the invited speakers to disseminate international research findings.
- As of December 31, 2019, the committee reviewed a total of 63 research proposals, of which 55 were approved. Approved proposals represent different types of research such as:
  - Description of both immediate and long-term clinical outcomes of DAA treatment in both general and special populations
    - ✓ **Assessment of the national hepatitis C elimination program: treatment outcomes and associated factors**
      Objective: evaluation of treatment outcomes of the elimination program.
      PI: Dr. Tengiz Tsertsvadze, Infectious Diseases AIDS and Clinical Immunology Research Center (IDACIRC)/Clinic Hepa
    - ✓ **Long-term health outcome among HCV patients with advanced liver fibrosis treated through HCV elimination program in Georgia**
      Objective: evaluation of long-term treatment outcomes (changes in liver fibrosis level, five-year risk of decompensated liver cirrhosis, five-year risk of hepatocellular carcinoma, survival, and changes in quality of life) among patients with advanced liver fibrosis treated with DAAs after achieving SVR.
      PI: Dr. Maia Butsashvili, Health Research Union (HRU)/Clinic Neolab
    - ✓ **Epidemiology of HBV infection among HCV patients treated with Direct Acting Antivirals (DAAs)**
      Objective: Description of HBV infection epidemiology and evaluation of DAA treatment outcomes among HBV/HCV co-infected patients treated as part of the program.
      PI: Dr. George Kamkamidze, Health Research Union (HRU)/Clinic Neolab
    - ✓ **Comparing engagement in HCV care and treatment outcomes between HIV negative and HIV positive persons within the national hepatitis C elimination program**
      Objective: Description of the care cascade and evaluation of DAA treatment outcomes among HIV/HCV co-infected patients treated as part of the program.
      PI: Dr. Tengiz Tsertsvadze, IDACIRC/Clinic Hepa
    - ✓ **Epidemiology of tuberculosis and hepatitis C co-infection in the country of Georgia**
      Objective: Description of tuberculosis (TB) epidemiology and evaluation of DAA treatment outcomes among TB/HCV co-infected patients treated as part of the program.
      PI: Dr. Davit Baliashvili, Emory University

- ✓ **Eliminating HCV infection in prison settings in Georgia**
  Objective: Evaluation of engagement in the HCV care continuum in prison settings of Georgia
  PI: Dr. Tengiz Tsertsvadze, IDACIRC/Clinic Hepa

- Evaluation of novel treatment and diagnostics delivery models at both specialized and non-specialized (such as primary healthcare and harm reduction) HCV care settings
  - ✓ **Integrating HCV screening and simplified treatment services in primary healthcare** Objective: Implementation and evaluation of integrated simplified diagnostic and monitoring algorithms coupled with hepatitis C treatment ("one stop shop") in primary healthcare settings. This project served as decentralization pilot project and preceded national roll-out of HCV care decentralization into primary healthcare setting.
    PI: Dr. Tengiz Tsertsvadze, IDACIRC/Clinic Hepa
  - ✓ **Feasibility, acceptability, effectiveness and cost-effectiveness of a decentralized and a centralized model of HCV viremia testing for confirmation and cure versus standard of care among harm reduction site attendees in Georgia**
    Objective: Determination of the feasibility, acceptability, effectiveness and cost effectiveness of HCV viremia testing at a harm reduction setting using point-of-service (decentralized) HCV RNA testing or off-site (centralized) HCVcAg testing versus referral to an HCV treatment center (standard of care) among PWID in Georgia.
    PI: Dr. Irma Khonelidze, NCDC (collaboration with FIND)
  - ✓ **Implementing HCV treatment in harm reduction centers in Georgia**
    Objective: Implementation and evaluation of integrated simplified diagnostic and monitoring algorithms coupled with HCV treatment in harm reduction setting.
    PI: Dr. Maia Butsashvili, HRU/Clinic Neolab
  - ✓ **Simplification of pretreatment diagnostic evaluation and on-treatment monitoring procedures within HCV Elimination Project**
    Objective: Implementation and evaluation of integrated simplified diagnostic and monitoring algorithms at the selected specialized HCV care centers.
    PI: Dr. Jaba Zarkua, Clinic Mrcheveli

- Evaluation of access to care and novel screening models to improve case finding and linkage to care
  - ✓ **Increase the number of patients who register in the HCV treatment program through assessing the barriers and facilitators to enrollment in the program**
    Objective: Assessment of the barriers and facilitators of linkage to care and treatment services among anti-HCV positive persons who did not or did register in treatment program
    PI: Dr. Maia Tsereteli, NCDC
  - ✓ **Study of barriers to enrollment into HCV elimination program among PWID**
    Objective: Assessment of the barriers and facilitators of linkage to care and treatment services among anti-HCV positive PWID who did not or did register in the treatment program
    PI: Dr. Maia Butsashvili, HRU/Clinic Neolab
  - ✓ **Evaluation of pilot activities to improve HCV screening and linkage to care in Georgia**
    Objective: Evaluation of 3 small-scale interventions to identify effective approach to increase HCV testing coverage and linkage to care using i) door to door screening, ii) patient navigators at tertiary hospitals, and iii) screening at the workplace.
    PI: Dr. Maia Butsashvili, HRU/Clinic Neolab

- Acute/chronic hepatitis C and the sequelae surveillance
  - ✓ **Descriptive, retrospective study on the prevalence of acute viral hepatitis in Georgia**
    Objective: Evaluation of diagnostic algorithms used in patients hospitalized with the diagnosis of acute viral hepatitis (HAV, HBV, HCV, and HEV) and jaundice.
    PI: Dr. Ketevan Galdavadze, NCDC
  - ✓ **Establishing Georgian PWID cohort study to estimate incidence of HCV infection**
    Objective: Estimation of point prevalence and incidence of HCV infection by following up the seronegative PWID to detect seroconversion cases. Validation of hepatitis C Recent Infection Testing Algorithm (RITA) assay.
    PI: Dr. Tengiz Tsertsvadze, IDACIRC/Clinic Hepa
  - ✓ **Identification and characterization of HCV-attributable hepatocellular carcinoma among persons with hepatobiliary cancer diagnoses in Georgia: 2015-2016.**
    Objective: Estimation of HCV-attributable hepatocellular carcinoma using cancer registry, E-health, and *GeoStat* mortality databases.
    PI: Drs. Geoff Beckett, CDC and Ana Aslanikashvili, NCDC
  - ✓ **The impact on mortality of a national hepatitis C elimination program, Georgia, 2015-2019**
    Objective: Evaluation of the impact of DAA treatment to all hepatitis C virus (HCV) infected persons on all-cause mortality as part of the elimination program.
    PI: Dr. Lia Gvinjilia, TEPHINET

- Evaluation of novel diagnostic assays
  - ✓ **Xpert HCV VL performance evaluation**
    Objective: Evaluation of the Xpert HCV VL Assay in resource-limited settings using operators with minimal laboratory experience
    PI: Dr. Maia Alkhazashvili, NCDC/Lugar Center (collaboration with FIND)
  - ✓ **Evaluation of the diagnostic performance of the Xpert® Fingerstick HCV Viral Load (VL) Assay**
    Objective: Evaluation of the sensitivity, specificity and quantitation of the Xpert® Fingerstick HCV VL assay for the detection of HCV in capillary and venous whole blood. Comparison of the sensitivity, specificity and quantitation of the Xpert® Fingerstick HCV VL assay in capillary and venous whole blood to that of CE IVD Xpert® HCV VL test in plasma.
    PI: Dr. Maia Alkhazashvili, NCDC/ Lugar Center (collaboration with FIND)
  - ✓ **Evaluation study of Rapid Diagnostic Tests (RDTs) detecting antibodies against hepatitis C virus**
    Objective: Evaluation of sensitivity and specificity of anti-HCV RDTs in archived plasma samples, collected from HCV-infected and HCV-uninfected individuals either co-infected or not co-infected with HIV, measured against the composite reference standard composed of two Enzyme Immunoassays (EIAs) and a Line Immunoassay (LIA)
    PI: Dr. Maia Alkhazashvili, NCDC/ Lugar Center (collaboration with FIND)
  - ✓ **Evaluation of (i) dry blood spots (DBS) for HCV RNA testing, and (ii) the Genedrive® HCV ID Kit in Georgia**
    Objective: Evaluation of the performance, as measured by sensitivity and specificity, of three laboratory-based assays for detection of HCV RNA assays using capillary blood collected on DBS. Additionally, Genedrive® HCV ID kit for the detection of HCV is being evaluated to study the sensitivity, specificity, negative predictive value, and positive predictive value of the kit.
    PI: Dr. Maia Alkhazashvili, NCDC/ Lugar Center (collaboration with FIND)

- ✓ **Evaluation of the diagnostic performance of HCVcAg as test of cure in for hepatitis C among PWID in Georgia**
  Objective: Evaluation of the performance of HCVcAg assay in confirming sustained virological response at SVR12. Sensitivity and specificity of HCVcAg assay at SVR12 is measured against reference test (Abbott RealTi*me* HCV VL assay).
  PI: Dr. Nazirbola Chitadze, NCDC/ Lugar Center (collaboration with FIND)

- Capacity building for molecular research
  - ✓ **Characterization of HCV recently infected and re-infected cohort among people who inject drugs (PWID) at selected harm reduction sites in Georgia using GHOST technology**
    Objective: Analyze and visualize transmission patterns of HCV infection among those PWID who test positive for HCV recent infection and reinfection at selected harm reduction sites located in Tbilisi and Zugdidi
    PI: Drs. Maia Tsereteli (NCDC) and Adam Kotorashvili, NCDC/Lugar Center
- Establishment of the biobank for future studies
  - ✓ **Establishment of the system for archiving samples collected within the Hepatitis C Elimination Program in Georgia**
    Objective: Establishment of the biobank of samples collected as part of the HCV research projects and elimination program.
    PI: Dr. Nazibrola Chitadze, NCDC
- Modeling and cost-effectiveness studies
  - ✓ **Estimation of the cost benefits of the HCV treatment program in Georgia**
    Objective: Estimation of the cost benefits of the HCV treatment program in Georgia
    PI: Dr. Josephine Walker, University of Bristol
  - ✓ **Learning lessons from Georgia - Using economic modelling to determine optimum screening and linkage-to-treatment strategies for achieving high treatment coverage in Eastern Europe and Central Asia**
    Objective: Analysis of different strategies to improve screening and linkage to care for HCV treatment in Georgia will be conducted. Additionally, cost minimization analysis to determine the optimal screening and linkage to care strategies for eliminating HCV in Georgia will be conducted. The model findings for Georgia will be generalized to other countries in region to project the most cost-effective strategies for improving screening and linkage to care for HCV treatment.
    PI: Dr. Josephine Walker, University of Bristol

- During the reporting period research findings were presented via oral and poster presentations at various international scientific forums such as European Association for the Study of the Liver, American Association for the Study of Liver Diseases, and World Hepatitis Summit (please see Appendix 3: Scientific Meeting Presentations of the Hepatitis C Elimination Program).

Challenges

- Securing funding for long-term research projects or new projects addressing emerging research questions is challenging due to limited number of funders in the field of hepatitis research.

3rd Hepatitis Technical Advisory Group (TAG) Recommendations for the Georgia Hepatitis C Elimination Program

On November 30 and December 1, 2017, the Georgian Ministry of Labour, Health, and Social Affairs (MoLHSA), together with experts from the U.S. Centers for Disease Control and Prevention's (CDC) Division of Viral Hepatitis (DVH), the World Health Organization (WHO), and other international partners, convened Georgia's third external Hepatitis C Technical Advisory Group (TAG) meeting. A total of nine experts in the field of viral hepatitis prevention and control served as TAG members. The two-day meeting began with opening remarks from the Minister of MoLHSA followed by remarks from the US Ambassador to Georgia, the director of the European regional office of WHO, the Vice-President of Gilead Sciences, and the director of the CDC country office. The program review began with representatives of the Georgia National Centers for Disease Control and Public Health (NCDC), and CDC providing TAG members reported the progress of the HCV Elimination Program since its launch in April 2015. The TAG then explored progress of the HCV elimination program in five areas- HCV diagnostics; HCV testing and linkage to care; HCV care and treatment; community resource mobilization; preventing transmission among persons who inject drugs; infection control and blood safety; and monitoring progress toward elimination goals. Sessions to explore these topics included presentations from Georgian public health officials, academicians and clinicians. For each session, a TAG member led a discussion with other TAG members, representatives of MoLHSA and NCDC and members of the audience. Following a time for deliberation, the TAG presented draft recommendations for review and comment.

First and foremost, the TAG expressed admiration for the remarkable progress in all aspects of the Hepatitis C Elimination Program since the last TAG meeting. The TAG appreciates the sustained commitment of the Georgian government to improve the Program, the commitment of Georgian staff working on the Program and the efforts of staff to implement or revise activities in response to the recommendations of the 2016 TAG. The TAG also appreciates the open and transparent presentation of data; the quality of evaluation data and the frank discussions of Program strengths and challenges.
Based on the presented information and discussions, the TAG developed seven sets of recommendations to resolve key challenges for the Program and assist the country of Georgia in successful achievement of country goals for HCV elimination.

Recommendations:

1. **Leadership**: A new leader at the national level is needed, under the direction of the MoLHSA Director, to guide program activities, coordinate the work of implementing partners, and manage emerging issues in a timely and transparent manner. The leader must be seen as the official accountable for the Program. To be meet this responsibility, the leader must have sufficient staff to manage and coordinate all aspects of the program.
2. **Finances**: The national goals for HCV elimination are ambitious. Achievement of these goals by 2020 will require a substantial and immediate expansion of the program staff and budget to remove bottlenecks to testing and treatment scale up. In 2018, program leaders should develop a budget plan to support activities needed to reach the 2020 elimination goals; the budget plancan be based on the data from available health models projecting the annual number of successful HCV treatments necessary to achieve national elimination targets. The current Program practices requiring citizens to pay either full or in part to receive testing, care and other services must be abolished. The current requirements for citizen payment to receive HCV testing, care and treatment services are disincentives for participation in the program and present a formidable barrier to achievement of elimination goals.
3. **Scale up of testing and treatment services**: To meet elimination goals, a rapid scale up is needed in all components of HCV testing, linkage to care and treatment.

a. The number of sites providing Program services should include all hospitals, all prisons, all needle and syringe programs, all medication assisted treatment centers and all TB and HIV treatment sites. To decrease barriers to linkage to care, HCV testing and treatment services should be available together in all sites participating in the Program.
b. Evaluations of testing and treatment programs are encouraged. However, the scale up of program activities should not be delayed pending completion of feasibility studies. Rather, existing evaluation studies can continue in parallel with a scale up of program activities. As evaluation studies are completed, the data can be used on an ongoing basis to improve program performance.
c. To reach HCV elimination goals, the number of providers in primary care or medical specialties other than infectious diseases, gastroenterology and hematology trained to test and treat HCV must rapidly increase. This will require training of physicians, pharmacists and other mid-level providers to deliver these services. At a minimum, by the 2018 TAG, every sub-national area should have at least an HCV test and treat site in a primary care setting, a hospital setting, and a medication assisted treatment settings, and if present, a prison setting. Training of providers can occur via ECHO and other modalities.
d. Referral relationships should be formalized and strengthened between the current major HCV treatment sites and primary care, corrections, and other non-tertiary care providers integrating HCV testing and treatment services in clinical settings. For these providers, the major HCV treatment sites can provide mentors and educators to guide HCV testing and treatment; ECHO provides a platform to strengthened educational and training relationships. Also referral pathways should be developed to ensure providers can promptly refer the most complex patients to tertiary care specialists.

4. **Improvements in the HCV test and cure cascade:** The TAG is concerned regarding the large numbers of persons who have been screening positive for anti-HCV, but not been confirmed viremia nor entered into care. The process to monitor laboratory quality should continue including validation of sensitivity and specificity of both first line HCV antibody tests as well as virus detection tests. The HCV testing and treatment programs should prioritize services that help persons positive on anti-HCV testing receive HCV RNA or HCV core antigen testing and appropriate treatment services. Financial barriers to undergo testing and treatment should be removed. The integration of testing and treatment within the same facilities should improve care linkages as can the expansion of testing and treatment services in non-tertiary care settings described previously. The TAG also recommends large mass media campaign to increase public awareness of the program and motivate members of key populations to seek testing. Patients and key opinion leaders can be influential role models.
5. **Scale up harm reduction and drug treatment services:** The TAG recognizes the plans and progress made in increasing the availability of these services. These efforts must continue resulting in large increases in persons receiving these services. The program should monitor data on ongoing basis to track progress in implementation of these services. As treatment scales up, harm reduction services funding should not be compromised. Indeed, resources should be made available to fully integrate HCV testing and treatment with harm reduction and drug treatment services. Models of care (e.g., peer support) that help PWID complete the HCV testing and cure cascade of services must be implemented and evaluated. To eliminate financial disincentives, harm reduction and drug treatment services should be made available at no cost to clients. Sources of stigmatization and other barriers to persons who inject drugs receiving these services should be identified and addressed. To improve client trust in the program, unique identifiers for PWID should be used in syringe service and opioid substitution therapy centers.

6. **Continue improvements in blood safety:** The national efforts to improve blood safety are laudable. Recruitment of first time donors with low risk for HCV infection (e.g., HCV seronegative females) to become repeat donors should be encouraged. TAG supports continued development of systems for hemovigilance in blood banks and hospitals, and provider training to reduce the number of unnecessary transfusions. Blood banks should have systems in place to ensure blood donors with serologic evidence of HCV infection are linked to care and treatment. The addition of HCV PCR or core antigen testing can reduce the number of HCV contaminated blood donations missed by laboratory testing in blood banks.
7. **Continue improvements in infection control:** The TAG recognizes the complexity of efforts to institute a culture of patient safety comprised to improve infection prevention and control (IPC) in a national health system. To assist this effort, TAG recommends the creation of a central multidisciplinary authority accountable for implementation of national and healthcare level IPC programs in Georgia. The central authority should develop a national plan for infection control to guide implementation of infection control policies and practices at the facility level. The central authority can adapt or develop evidence-based national IPC guidelines for the purpose of reducing healthcare-associated infections. In addition, the central authority should support the education and training of the health workforce as one of its core functions by adopting an IPC training curriculum including basic and advanced IPC standards and providing the training to all HCWs by December 2020. TAG encourages a communication strategy to promote behavior change of healthcare providers and non-traditional healthcare providers to ensure safety of practices. To monitor progress of IPC implementation, the TAG recommends establishing a system for monitoring, evaluating, and reporting key IPC indicators

4th Hepatitis C Technical Advisory Group (TAG) Recommendations for the Georgia Hepatitis C Elimination Program

4th Hepatitis C Technical Advisory Group Recommendations

On November 29-30, 2018, the Georgian Ministry of Internally Displaced Persons from the Occupied Territories, Labour, Health and Social Affairs (MoIDPLHSA), together with experts from the U.S. Centers for Disease Control and Prevention's (CDC) Division of Viral Hepatitis (DVH), the World Health Organization (WHO), and other international partners, convened Georgia's fourth external Hepatitis C Technical Advisory Group (TAG) meeting. A total of eleven experts in the field of viral hepatitis prevention and control served as TAG members. The two-day meeting began with opening remarks from the Minister of MoIDPLHSA. These were followed by remarks from the US Ambassador to Georgia, the Director of the CDC country office, the Vice-President of Gilead Sciences, and the Georgia office of WHO. The program began with introduction of the TAG members and review of last year's recommendations followed by an overview of the progress of the HCV Elimination Program since its launch in April 2015, including the activities on decentralization and integration of HCV services in primary healthcare centers, hospitals and harm reduction settings in Georgia. The TAG then explored progress of the HCV elimination program on topics including: HCV surveillance; HCV testing and linkage to care; HCV care and treatment; community engagement through advocacy and resource mobilization; preventing transmission among persons who inject drugs; blood safety; infection control in healthcare and community settings; and HCV diagnostics. Sessions to explore these topics included presentations from Georgian public health officials, academicians and clinicians. For each session, two TAG members led a discussion with other TAG members, representatives of MoIDPLHSA, the Georgian National Centers for Disease Control and Public Health (NCDC), and members of the audience. Following a time for deliberation, the TAG presented draft recommendations for review and comment.

First and foremost, the TAG expresses admiration for the remarkable progress in all aspects of the Hepatitis C Elimination Program since the last TAG meeting. The TAG appreciates the sustained commitment of the Georgian government to improve the Program, the commitment of Georgian staff and clinical partners working on the Program and the efforts to implement or revise activities in response to the recommendations of the 2017 TAG. The TAG also appreciates the open and transparent presentation of data. The quality of evaluation data and the discussions of Program strengths and challenges facilitated the work of the TAG. Based on the presented information and discussions, the TAG developed the following recommendations to resolve key challenges for the Program and assist the country of Georgia in successful achievement of country goals for HCV elimination. Overall, a considerable upscale of annual HCV treatment numbers are needed for next two to three years to achieve 2020 elimination target.

The TAG Committee included:

Dr. Paul Weidle (co-chair), U.S. Centers for Disease Control and Prevention

Dr. Margaret Hellard (co-chair), Burnet Institute, Australia

Dr. Evan Bloch, The Johns Hopkins University, USA

Dr. Carlos del Rio, Emory University, USA

Dr. Maha Talaat, World Health Organization, Egypt

Dr. Anders Widell, Lund University, Sweden

Dr. Tatjana Reic, European Liver Patients Association, Belgium

Dr. Antons Mozalevslais, World Health Organization, Denmark

Dr. Jorge Mera, Cherokee Nation Health Services, USA

Dr. Sharon Hutchison, Glasgow Caledonian University, UK

Dr. Graham Foster, Queen Marys, University of London, UK

Section 1: Improve HCV Surveillance and Program Effectiveness

- Establish surveillance for acute/incident HCV infections if resources and costs permit. This can be accomplished by various strategies and settings including: a) utilizing existing screening systems to identify serconversions and conducting investigations; b) establishing sentinel sites (e.g. infectious disease hospitals); and c) enhancing surveillance at select settings serving at risk populations (e.g. persons who inject drugs (PWID), prisoners).
- Establish surveillance for reinfection (e.g. RNA testing every 6 months) among high-risk populations (e.g. PWID) and ensure linkage to care and treatment.
- Monitor the prison population for HCV prevalence and incident HCV infections.
- Link prison screening and treatment data systems to the national screening and treatment databases.
- Establish enhanced surveillance activities (e.g. collection of risk factor data) among "young" persons (< 18 years old) who screen positive.
- Consider situations from above list where use of molecular epidemiology may be appropriate (e.g. surveillance or outbreak investigations).

Section 2: Identify and Link to Care Persons Infected with HCV

- Continue current extensive testing and screening efforts; A formal recommendation such as: "all persons age 18 and older should be screened for HCV prior to 2020" should be considered and if accepted disseminated widely to the public and providers.
- Ensure quality screening and linkage to care efforts among high-risk populations (e.g. prisoners, war veterans, PWID) and high prevalence age/sex cohorts (e.g. men aged 30 – 60 years).
- Employ respondent-driven sampling (e.g. snowballing) and other novel strategies, such as "bring in a friend/family/high-risk contact for screening", to identify, test, and link HCV-infected persons to care.
- Expand screening and linkage to care efforts into additional healthcare settings such as at dentist offices, pharmacies, and additional primary healthcare centers.
- As there currently are > 20,000 persons who have been identified with HCV infection (HCV-Ab+ or RNA/HCV core Ag+) and have not been linked to confirmatory testing and/or care, there is an urgent need to ensure linkage to care for each diagnostic environment including: hospitals, prisons, blood donation centers, community screening, harm reduction centers, and others. Utilize evidence-based interventions and best practices.

Section 3: Provide HCV Care and Treatment

- To facilitate access to treatment, remove unnecessary barriers preventing same-site testing and treatment, such as centralized approval process for treatment, and camera recording of patients taking the first dose of medication for each bottle dispensed.
- Introduce pangenotypic DAA regimens as soon as feasible; this will eliminate the need for genotype testing, simplifying the workup and reducing costs.
- Minimize "on-treatment monitoring" utilizing best practices from WHO, EASL, and AASLD guidelines and expert opinion.
- Expand patient eligibility for treatment at primary healthcare centers, harm reduction sites and other non-specialist sites to include all HCV infected patients except when decompensated cirrhosis or other serious co-morbidities are present. Ensure expert consultation is available for all providers (e.g. via ECHO, phone hotline) providing care and treatment.
- Patients with compensated cirrhosis (FIB-4 score > 2) and/or platelets < 150,000, following completion of treatment at primary healthcare sites, harm reduction sites, and other sites, should be referred to a specialist for post-treatment cirrhosis evaluation and care.
- New data on safety of sofosbuvir based regimens (sof-ledipasvir and sof-velpatasvir) and renal impairment suggests that these drugs should be included as a treatment option for patients with chronic kidney disease (CKD) stage 1,2,3 (2108 AASLD-IDSA Hepatitis C Guidance. *Clin Infec Dis* 2018;67:2477-92) and can be prescribed by non-specialists. Patients with eGFR < 30 ml/min (CKD stage 4 or stage 5) should be under the care of a specialist for treatment of their HCV infection.
- Incorporate hepatocellular carcinoma surveillance (e.g. regular ultrasound for cirrhotic patients) of cirrhotic patients, following sustained virologic response, as part of the Elimination Program.
- Expand the list of providers, such as primary healthcare providers, narcologists, TB specialists, etc., that are eligible to treat HCV infected patients.
- Introduce non-specialist (i.e. primary healthcare centers and harm-reduction sites) treatment sites in a deliberate and phased approach to ensure high quality of care and treatment services.
- Remove financial barriers for diagnosis and care and treatment for persons who are at-risk for re-infection (e.g. PWID) following cure.
- Ensure high quality monitoring and evaluation of decentralized care and treatment.
- Consider expanding the program to include screening and treatment of hepatitis B virus (HBV) infection.

Section 4: Promote Advocacy, Awareness, Education, and Partnerships for HCV-associated Resource Mobilization

- Expand current public awareness campaigns to ensure the public are aware of and understand: a) the risk factors for HCV transmission; b) the importance of screening for HCV infection and the meaning of screening positive for HCV-Ab; c) that hepatitis C testing and treatment is available at low-cost or no-cost.
- Provide regular education/awareness of hepatitis C treatment to the community – including "myth" busting around misinformation.
- Provide education and awareness for health professionals (including clinicians at primary healthcare centers, pharmacists, dentists, others) to increase their knowledge and awareness about hepatitis C.
- Ensure incorporation of messages to reduce stigma and misinformation in all campaigns.
- Facilitate PWID access to screening, care and treatment services. Engage with law enforcement to jointly develop strategies to improve access to services for this population.

Section 5: Prevent HCV Transmission: Harm Reduction

- Ensure harm reduction funding is maintained, and expanded where needed, in the context of decreasing support from Global Fund. Continue support to ensure level of harm reduction (including needle-syringe programs and opioid substitution treatment) coverage is sufficient to reduce hepatitis C transmission among PWID.
- Implement HBV vaccination of PWID and other at-risk populations.
- Treatment for HCV should be offered at the same site where persons are receiving harm reduction services such as needle-syringe programs and opioid substitution treatment ("one-stop shop" principle).
- Expand pool of persons who are allowed to treat HCV infection among PWID to include narcologists.

Section 6: Prevent HCV Transmission: Blood Safety
(items are listed by chronology of suggested implementation)

2019

- Mandate participation of ALL blood collection sites in Blood safety program.
  - Continue to develop regulatory oversight such as licensing and accreditation of blood transfusion facilities.
- Conduct a situational analysis including:
  - Comprehensive assessment of ALL blood banks,
  - Simplification of reporting and collation of databases/datasets.
- Laboratory Testing
  - Assess and ensure high quality testing at all sites including standard testing algorithms, and implementation of repeat and confirmatory testing.
  - Evaluate merits of nucleic acid testing (NAT) for HCV:
    - Conduct comprehensive survey of blood bank practices, including parallel HCV Ab and NAT,
    - Conduct pilot testing to inform NAT strategy implementation in blood banks; if implemented, NAT should be centralized.

2019 - 2021

- Modify blood donor selection and recruitment
  - Phased transition to all-voluntary donor pool; establish targets with incentives for blood banks that meet target.
  - Establish a national blood donor deferral database.
- Quality assurance
  - Develop standardization and standard operating procedures at blood banks.
  - Mandate proficiency testing and utilize the results from the commercial proficiency testing program (Randox) that the majority of blood banks participate in to identify and follow up poor performing labs.
    - Simplify external quality assurance system (EQAS) program at Lugar center if appropriate (i.e. HCV confirmatory testing).
  - Implement external quality assessments every 2-3 years.
- Post-transfusion surveillance
  - Establish a "look-back" surveillance system with the capacity to investigate suspected window-phase or occult infections among blood donors (i.e. seroconverters from negative to positive for HCV and possibly HBV and HIV). Should include the capacity to trace components and prior donations up to 12 months beyond last negative donation. This would require development of additional storage capacity and an information system.
  - Adopt framework for reporting surveillance findings (e.g. The National Healthcare Safety Network (NHSN) Hemovigilance criteria).

Section 7: Prevent HCV Transmission: Infection Control in Healthcare, Non-traditional Healthcare, and Community Settings

- Organizational Structure of Infection Prevention and Control (IPC) program
  - The Ministry of Health should develop a national IPC plan to achieve implementation of IPC standards in all healthcare facilities by December 2020 (including clear objectives, functions, activities and timeline for implementation).
  - Expand the national IPC team within the MOH to include a multidisciplinary team (microbiologists, epidemiologists, and nursing professionals).
  - There should be established a functioning IPC program (e.g. facility IPC team) in all acute healthcare facilities. It is recommended globally that a minimum ratio of one full-time nurse or doctor per 100-150 beds should be appointed with clear IPC roles and responsibilities.
  - Assign one IPC focal person (e.g. a nurse) in each primary healthcare unit or center to ensure implementation of IPC practices.
- Complete National IPC Guidelines
  - Develop a National IPC Guidelines dissemination plan to reach all healthcare sectors.
  - Develop tools to support implementation of National IPC Guidelines.
  - Additional IPC modules should be added to the National IPC Guidelines that address dentistry, hemodialysis, and other settings with risk of exposure to blood-borne pathogens.
  - Ensure adequate resources to ensure guideline dissemination and implementation.
- Training and education on IPC
  - The national IPC group should support and ensure:
    - IPC training and capacity building of hospital and facility level IPC teams,
    - Hospital IPC teams ensure regular and ongoing IPC training of all healthcare workers involved in healthcare delivery,
    - New employment IPC training be required.
- Monitoring/audit of IPC practices and feedback
  - The national IPC group should review and agree on a defined list of standardized IPC indicators and tools focusing on process IPC indicators.
  - Implement regular auditing of IPC practices of healthcare facilities by the national IPC team and development of an annual report for feedback and improvements by healthcare facilities.
  - Healthcare facilities should select specific process indicators for auditing and feedback to healthcare staff and senior management.
  - Use evidence-based approaches when implementing IPC programs.
- Non-traditional and community healthcare:
  - Conduct a comprehensive assessment of community health practices that might contribute to unsafe health provision and transmission of HCV (population based research studies).

Section 8: Improve HCV Laboratory Diagnostics

- Ensure that rapid tests used for screening are of high quality, and consistent with WHO Testing Guidelines.
- Perform local validation of rapid tests supervised at the Lugar Center, NCDC in field conditions.
- Ensure quality training and monitoring at community-based testing sites so that testing meets WHO Testing Guidelines.
- Conduct proficiency testing, including clinical chemistry and blood cell counts, at all levels and establish mechanism for corrective action of non-conforming testing sites.
- Mandate laboratories participating in the elimination program participate in an external quality assurance program to address the trend of labs opting out of participation in the program.
- Investigate discordant test results patients to identify and rectify the causes.
- Continue support for archiving of key blood samples for future research and public health applications (e.g. outbreak investigations).
- Utilize optimal and cost-effective confirmatory testing strategies (e.g. conventional RNA/NAT, HCV Core antigen, and GenXpert) that may vary depending on setting.

5th Hepatitis C Technical Advisory Group (TAG) Recommendations for the Georgia Hepatitis C Elimination Program

On November 19-20, 2019, the Georgian Ministry of Internally Displaced Persons from the Occupied Territories, Labour, Health and Social Affairs (MoIDPLHSA), together with experts from the U.S. Centers for Disease Control and Prevention's (CDC) Division of Viral Hepatitis (DVH), the World Health Organization (WHO), and other international partners, convened Georgia's fifth external Hepatitis C Technical Advisory Group (TAG) meeting. A total of twelve experts in the field of viral hepatitis prevention and control served as TAG members. The two-day meeting was opened with remarks from the First Deputy Minister of MoIDPLHSA, the US Embassy Charge d'Affaires, the Director of CDC's DVH, a representative from Gilead Sciences, and the Head of the WHO Georgia office. The program began with introduction of the TAG members and review of last year's recommendations followed by an overview of the progress of the HCV Elimination Program since its launch in April 2015, including the activities on decentralization and integration of HCV services in primary healthcare centers, hospitals and harm reduction settings in Georgia. The TAG then explored progress of the HCV elimination program on topics including: promote advocacy, awareness, education, and partnerships for HCV-associated resource mobilization; prevent HCV transmission: harm reduction, blood safety, and infection control; identify and link to care persons infected with HCV; improve HCV laboratory diagnostics; provide HCV care and treatment; and improve HCV surveillance. Sessions to explore these topics included presentations from Georgian public health officials and clinicians. For each session, two TAG members moderated, and specific discussants were invited on stage to lead the discussion and answer questions. On the final day, following a time for deliberation, the TAG presented draft recommendations for review and comment.

First and foremost, the TAG would like to congratulate Georgia on the remarkable progress in all aspects of the Hepatitis C Elimination Program since the last TAG meeting. The TAG appreciates the sustained commitment of the Georgian government to improve the Program, the commitment of Georgian staff and clinical partners working on the Program, and the efforts to implement or revise activities in response to the recommendations of the 2018 TAG. The TAG also appreciates the open and transparent presentation of data. The quality of evaluation data and the discussions of Program strengths and challenges facilitated the work of the TAG. Based on the presented information and discussions, the TAG developed the following recommendations to resolve key challenges for the Program and assist the country of Georgia in successful achievement of country goals for HCV elimination.

The TAG Members included:

Dr. Carolyn Wester (co-chair), U.S. Centers for Disease Control and Prevention
Dr. Margaret Hellard (co-chair), Burnet Institute, Australia
Dr. Evan Bloch, The Johns Hopkins University, USA Dr.
Carlos del Rio, Emory University, USA
Dr. Graham Foster, Queen Marys, University of London, UK
Dr. Sharon Hutchison, Glasgow Caledonian University, UK
Dr. Jeffrey Lazarus, Barcelona Institute for Global Health, Spain
Dr. Jorge Mera, Cherokee Nation Health Services, USA
Dr. Antons Mozalevskis, World Health Organization, Denmark
Dr. Priti Patel, U.S. Centers for Disease Control and Prevention
Dr. Tatjana Reic, European Liver Patients Association, Belgium
Dr. Anders Widell, Lund University, Sweden

Overarching Considerations:

- Recommend developing an updated 2021–2025 National Strategic Plan for the Elimination of Hepatitis C Virus in Georgia
    - Should be integrated into Georgia's Universal Health Care response
    - Consider including HBV

Section 1: Promote Advocacy, Awareness, Education, and Partnerships for HCV-associated Resource Mobilization

- Prioritize increased engagement of HCV cured patients to assist with increasing broader community awareness about hepatitis C and hepatitis C cure:
    - Create paid opportunities for individuals with lived hepatitis experience to participate in the elimination program (e.g. patient navigators, media campaigns)
- Involve peers in all aspects of HCV elimination, including those cured of HCV, key populations such as people who inject drugs (PWID), and from both liver patient associations and related associations, such as haemophilia
- Continue to explore ways to minimize the impact of the criminal justice system on harm reduction efforts:
    - Modify laws regarding the carrying of injecting paraphernalia for drug users and syringe service providers, including safe disposal of syringes
- Continue dialogue with other stakeholders (Ministry of Justice, Police, Government) about the public health approaches in drug policies
- Initiate campaigns to reach marginalized populations, including ethnic minorities, immigrants, and internally displaced persons including the use of outreach workers/peers.

Section 2: Prevent HCV Transmission: Harm Reduction

- Ensure HCV testing, care, and treatment services are available at all harm reduction sites.
    - Ensure that all necessary HCV diagnostics are accessible at all harm reduction sites.
    - Eliminate delays in government approval for implementation of HCV services
    - Allow opioid substitution treatment (OST) physicians and narcologists to provide HCV services
        - Ensure adequate supervision, training, and support for OST physicians and harm reduction physicians providing HCV testing, care, and treatment services [e.g. utilizing the ECHO model (Extension of Community Healthcare Outcomes)]
    - Improve synergies with harm reduction and existing HCV testing, diagnostics, and treatment services
- Ensure all harm reduction related mobile van services have the capacity to provide needle and syringe services, OST, and hepatitis C testing, diagnostics, and treatment for remote areas
- Eliminate regulatory barriers (e.g. cameras, on-site doctor, physical space requirements, safes) to facilitate rapid integration of HCV services into harm reduction
- Pilot integration of HCV services and primary healthcare services into harm reduction sites consistent with Universal Health Coverage
- Develop a strategy to ensure that harm reduction funding is maintained going forward

Section 3: Prevent HCV Transmission: Blood Safety

- Mandate participation of all blood collection sites in Georgia's State Safe Blood Program
- Perform phased implementation of NAT testing with a view to testing of all donor specimens for the major transfusion transmitted viruses (i.e. HIV, HCV and HBV)
    - Maintain a trial period with limited implementation (e.g. restrict to limited numbers of centers) to evaluate workflow; identify challenges, particularly with respect to turn around time, logistical considerations (e.g. transportation of samples) and the impact on regional blood supply (i.e. shortages in blood products); and evaluate the costs of implementation as well as measures to improve efficiency of testing (e.g. pooling)
- Implement standardization and quality assurance of serological testing and algorithms within Georgia State Program
- Assess feasibility of centralized testing for all blood screening
- Develop an accreditation framework:
    - State Safe Blood Program evaluation of blood services to determine adherence to standard practice
- Develop a look-back system including sample archiving to identify recipients of blood products from positive donors and ensure positive donors are linked to care
- Continue efforts to increase proportion of voluntary blood donors

Section 4: Prevent HCV Transmission: Infection Control in Healthcare, Non-traditional Healthcare, and Community Settings

- Utilize epidemiologic and molecular data on acute cases to determine contribution of healthcare to new HCV cases:
    - Conduct a special study of cases without recognized risk factors to identify healthcare exposures and healthcare-related outbreaks
    - Investigate clusters of healthcare transmission to identify risk factors and prevent additional cases
    - Determine the relative contributions of different healthcare settings to new HCV infections, including nontraditional healthcare
- Complete the national infection prevention and control (IPC) guidance
    - Develop a dissemination plan and implementation guidance with standard protocols
    - Dedicate resources to support implementation of the national guidance
- Strengthen IPC training and engagement of clinical staff in healthcare settings; perform ongoing IPC quality assessments in healthcare settings with risk of bloodborne pathogen transmission
- Consider a pilot study to assess critical infection control practices (e.g. injection safety, instrument sterilization) in select healthcare setting considered high-risk (e.g. dental and endoscopy) to inform prevention needs
- Implement and assess routine monitoring for HCV in special populations (e.g. CDC recommends maintenance hemodialysis patients be screened upon outpatient dialysis initiation and every 6 months thereafter for susceptible patients)

Section 5: Identify and Link to Care Persons Infected with HCV

- Integration of testing for HCV with:
    - Primary care screening for non-communicable diseases (NCDs)
    - HIV and TB
- Assess testing uptake and proportion positive
- Assess the role of migration and internally displaced populations contributing to the lost to follow-up tested HCV-positive (labor migrants to the European Union, Turkey, Russia, and other locations) and consider tailored campaigns (e.g. inform Georgian citizens leaving the country to work/returning from abroad about the HCV elimination program)
- Focus testing efforts towards high-yield populations using evidence-based approaches:
    - Geographically (e.g. Tbilisi)
    - High burden settings (e.g. emergency departments and correctional facilities)
    - Men age 30 and above with special attention to war veterans
    - Persons with a history of incarceration
    - Limit pediatric HCV testing to exposed infants (eliminate routine testing for hospitalized children <12 years of age)
    - Explore the feasibility of innovative strategies for testing:
        - PWID (e.g. respondent-driven sampling, bring in a friend/family/household/high-risk contact for screening)
        - Expanding community-based testing among populations with limited access to healthcare services
        - Targeted outreach efforts (e.g. lost to follow-up following positive anti-HCV screening)
- Improving linkage to care:
    - Increase number of people tested and treated by community providers (harm reduction and primary health care) so that a substantial proportion of treatment is delivered where client is tested
    - Eliminate barriers to care (e.g. cameras, taxation of commodities, regulations that prohibit specialized providers such as narcologists, dentists, pharmacists)
    - Explore role of patient incentives for linkage
    - Explore the role of provider incentives for linkage and treatment
    - Implement peer navigator strategies where appropriate (e.g. high-volume screening locations)
    - Additional strategies to be considered:
        - Treatment services should be available where testing is conducted
        - Provide training for primary care physician and harm reduction physicians in counseling patients with HCV to increase linkage to care
        - Minimize turnaround time and notification to patients of viremia testing results
        - Pilot innovative test and treat strategies (e.g. allow patients to change providers once treatment is initiated if necessary)
        - Navigation of released prisoners from screening, viremia testing, treatment initiation, and treatment completion should be initiated

Section 6: Improve HCV Laboratory Diagnostics

- Continue quality controls and proficiency monitoring and make these standard operating procedures
- Use the quality data generated on 13 rapid diagnostic tests at Lugar to select those with the highest sensitivity and specificity for procurement for the HCV elimination program
- Continue to study the utility of dried blood spot (DBS) for inclusion in the HCV elimination program
- Continue support for archiving of key blood samples for future use (outbreak investigations, DAA resistance appearance, and research)
- Explore cost-effective approaches for confirming core antigen negative results (e.g. pool testing)
- Develop and implement strategies for expanded and shared use of GeneXpert machines in the HCV elimination program

Section 7: Provide HCV Care and Treatment

- To facilitate access to treatment, remove unnecessary barriers preventing "one-window" testing and treatment, such as centralized approval process for treatment, and camera recording of patients taking the first dose of medication for each bottle dispensed
- Introduce pangenotypic DAA regimens as soon as feasible; this will eliminate the need for genotype testing, simplifying the workup and patient care pathway, and reducing costs
- Implement the use of both branded and licensed generic versions of medications for treatment of hepatitis C and hepatitis B in Georgia.
- Minimize on-treatment monitoring utilizing best practices from WHO, EASL, and AASLD guidelines (see attached)
- Expand patient eligibility for treatment at primary healthcare centers, harm reduction sites and other non-specialist sites to include all HCV infected patients except when decompensated cirrhosis or other serious co-morbidities are present. Ensure expert consultation is available for all providers (e.g. via ECHO, phone hotline, academic detailing) providing care and treatment
    - Patients with possible compensated cirrhosis (FIB-4 score > 3.25; platelets < 150,000 mm3; APRI >2.0; or fibroscan stiffness >12.5 kPa) following completion of treatment at primary healthcare sites, harm reduction sites, and other sites, should be referred to a specialist for post-treatment cirrhosis evaluation and care
- Following confirmation of viremia, treatment should be initiated immediately, prior to staging or other testing
- SOF/VEL should be used for end-stage renal disease HCV infected patients (FDA approved and AASLD recommended)
    - Consider HCV micro-elimination within dialysis patient population
- Expand the list of providers, such as primary healthcare providers, narcologists, TB specialists, etc., that are eligible to treat HCV infected patients so that patients are treated

where diagnosed

- Implement micro-elimination of HCV in the prison population:
    - Eliminate barriers to treatment (e.g. minimum sentence requirement, care navigators)
- Engage key stakeholders (e.g. hospital administrators, mayors, prison wardens, nephrologists, hematologists, etc.) to implement targeted micro-elimination efforts
- Re-testing (including RNA testing for those previously treated) in high risk groups should be implemented on a regular basis and documented
- Re-testing and re-treatment for potential reinfection should be encouraged in key populations and made free of charge for all patients
- Consider incorporating comprehensive care and treatment of NCDs for HCV patients engaged in treatment

<u>Section 8: Improve HCV Surveillance</u>

- Develop, implement, and strengthen surveillance for acute/incident HCV infections:
    - Include sentinel sites with high volume emergency departments; persons with suspected hepatitis should be tested for acute hepatitis A, B, and C
    - Identify and investigate new HCV infections among repeat blood donors and blood donors who test antiHCV-/NAT positive
    - Establish surveillance for acute infections and re-infections at select settings serving at-risk populations (e.g. persons who inject drugs (PWID), prisoners, dialysis patients, and persons who receive blood products)
        - Perform screening with NAT in immunocompromised persons
- Utilize GHOST (Global Hepatitis Outbreak Surveillance Technology) program to detect and intervene on transmission networks
- Assess HCV cascade of care by region and key populations
- Establish hepatocellular carcinoma (HCC) surveillance among cirrhotic patients treated in the program:
    - HCC treatment should be linked to the elimination program
    - If resources are limited, consider identifying a high-risk cohort for prioritized screening

Appendix 1.

Hepatitis C Virus Diagnostic Methods and Genotyping Test Kits

PCR Equipment	HCV RNA VL kits	HCV Qualitative kits	Genotyping kits
Abbott m2000rt	Abbott RealTime HCV kit	HCV Real Time TmQual (Sacache) ref# TVI-100 FRT	**Abbott** RealTime HCV genotype II kit
COBAS Taqman 48 ROCHE	Cobas TaqMan HCV Quantitative Test V2.0, Roche	Bosphore HCV Detection kit V1, Anatolia Geneworks	**Siemens** Versant HCV Genotype 2.0 LIPA
Applied-Biosystems Quant Studio Dx	RoboGene® HCV RNA Quantification Kit 3.0 Germany	HCV RT. Qual. Sacace Biotechnologies	**Sacace Biotechnologies** RTA HCV Genotyping qRCR kit
COBAS 6800 ROCHE	HCV Real TM Quant Dx V1, Sacace Biotechnologies	RT-GEPATOGEN-C Quant PCR Amplif Kit, DNA Technology	**DNA Technology** RT-GEPATOGEN-C Genotype RNA Ampli Kit
Applied-Biosystems Quant Studio 5 RT PCR	Bosphore HCV Quantitation Kit, Anatolia Geneworks	RTA HCV Qualitative Real Time PCR Kit	**Roche** Cobas, HCV Genotyping
Applied-Biosystems 7500 RT PCR	HCV Real TM Quant Dx V1, Sacace Biotechnologies		**Bosphore,** HCV Genotyping kit v1
Thermo fisher Scientific Quant Studio 5 Real-Time PCR System	HCV Real-Time PCR Kit, Human Diagnostic		**NLM, ITALY** HCV Gen-C 2.0
RotorGene 6000 Qiagen	RT-GEPATOGEN-C Quant PCR Amplification Kit, DNA Technology		
DTlite DNA-Technology	Gene Prof Hepatitic ,,C" virus		
Applied Biosystems 7500 FastDx	Robogene HCV RNA Quantification kit 3.0 (Analytikjena)		

Simplified HCV Diagnostic Algorithm for

Specialized HCV Care Providers

Hepatitis C Elimination Program in Georgia (since April 1, 2017)

Clinical assessment
HCV RNA quantification or HCVcAg
HCV genotyping
Complete blood count
ALT, AST, creatinine, bilirubin, albumin, INR, alkaline phosphatase, G-GT, glucose
HBsAg, anti-HBc total
FIB-4 for liver fibrosis assessment*
Abdominal ultrasound

**** Patients with FIB-4 score between the lower and upper cut-off values (1.45-3.25) undergo liver elastography to assess fibrosis stage***

Simplified HCV Treatment Monitoring Algorithm for Specialized HCV Care Providers

Hepatitis C Elimination Program in Georgia (since August 2, 2019)

Measurements	Treatment Duration *(in weeks)*						After treatment completion (weeks)
	4	8	12	16	20	24	12 or 24
Clinical assessment	X	X	X			X	X
HCV RNA Quantitative							X
Complete blood count	X	X*	X			X	
ALT	X	X	X	X**	X**	X	
AST							
Creatinine			X	X*	X*	X	
Bilirubin			X			X	

* *for ribavirin-containing regimens*

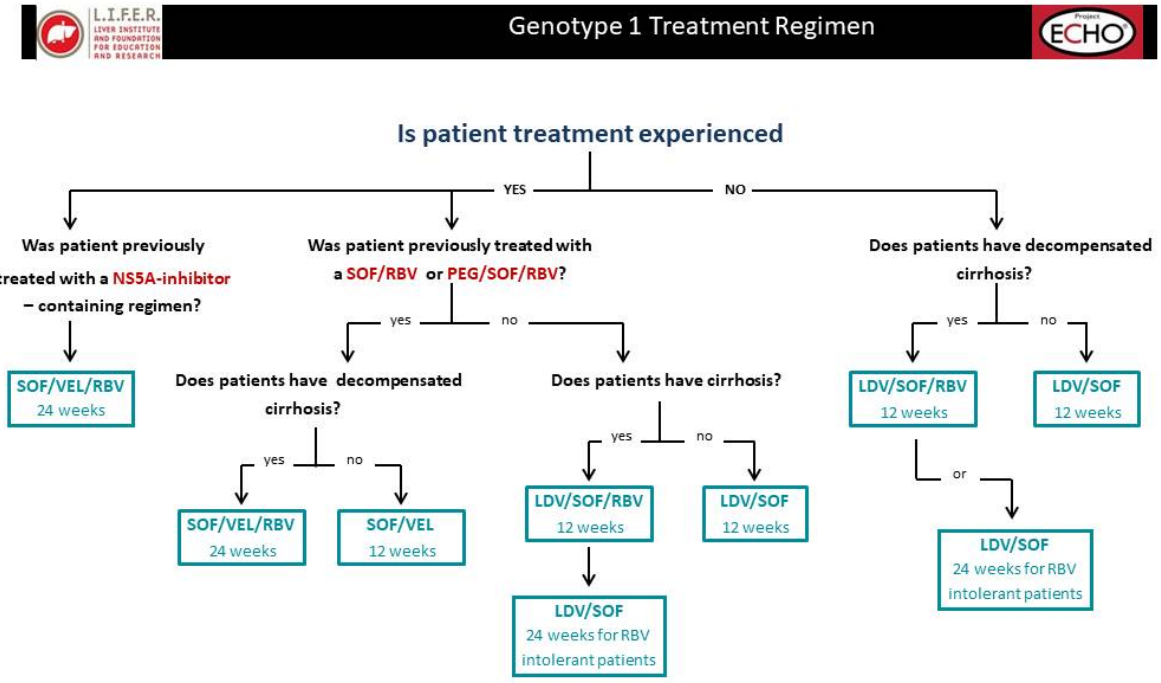
** *for ribavirin-free regimens*

Appendix 2.

Hepatitis C Elimination Program in Georgia

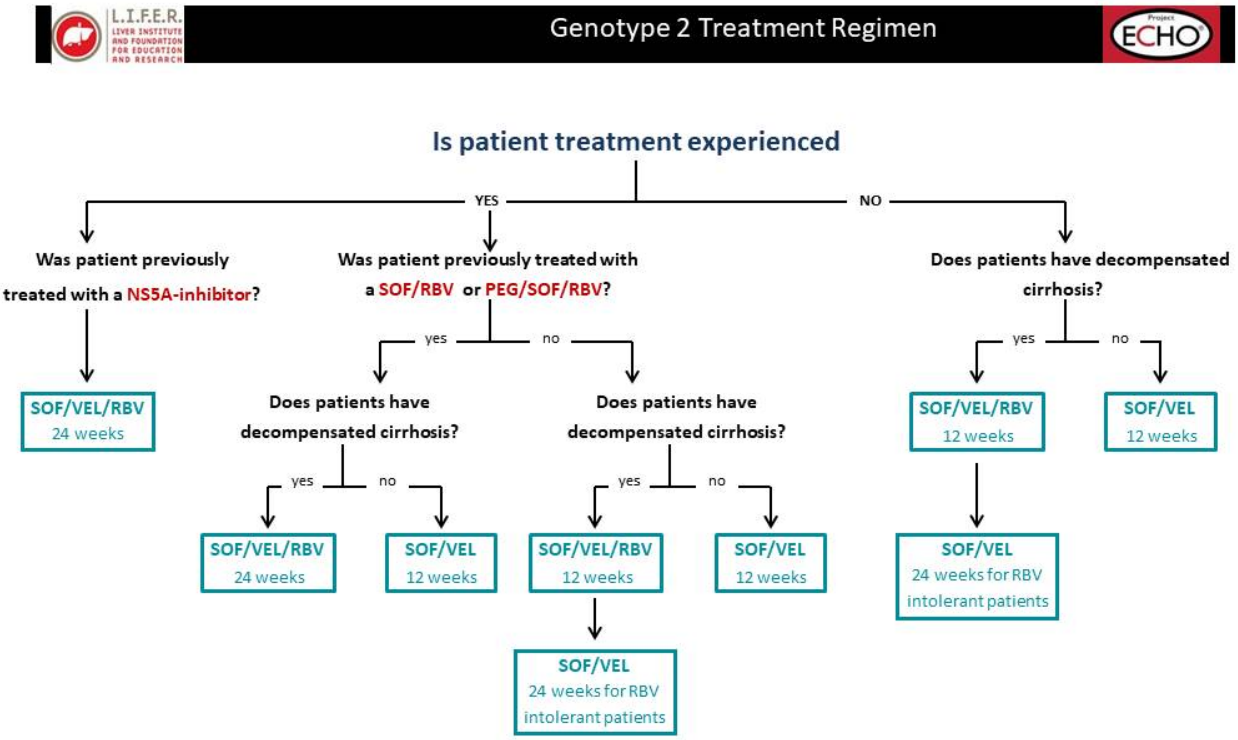
HCV Treatment Decision Trees (2018-2019)

Patients Infected with HCV Genotype 1



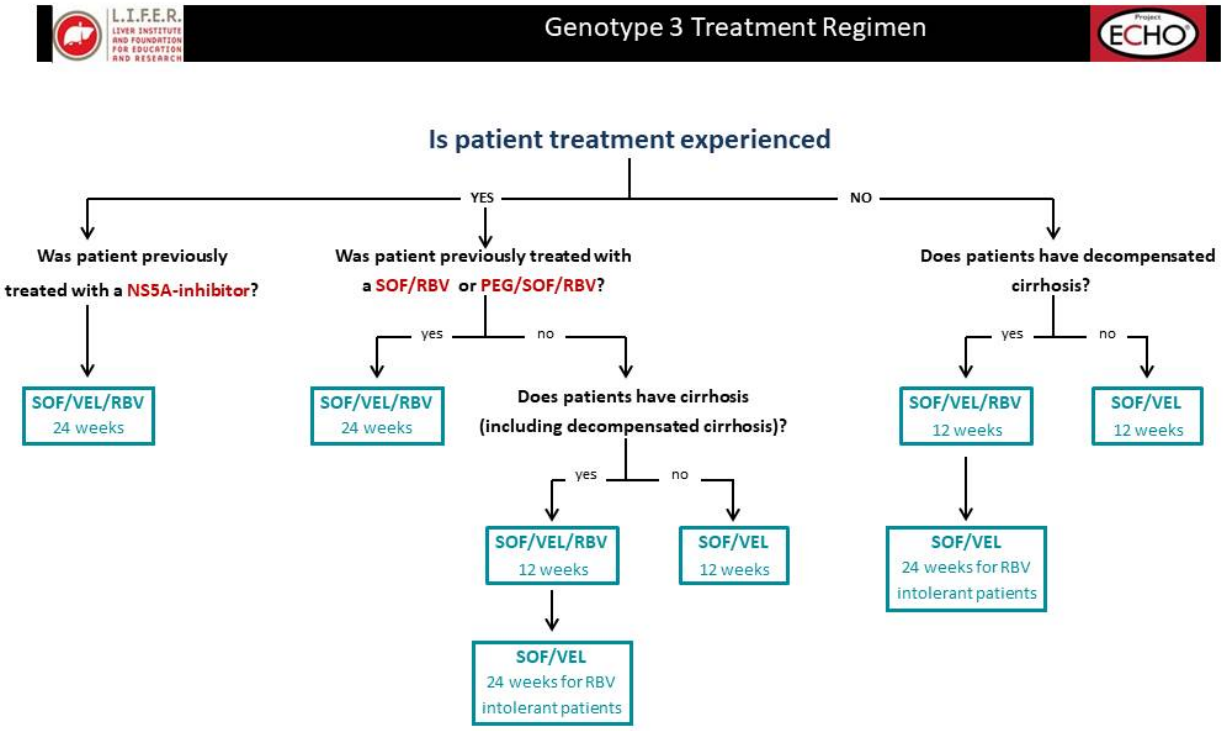
NOTE: All decompensated cirrhotic patients should receive 600mg RBV
All others should receive weight-based ribavirin (RBV) dosage: Patients with weight <75kg receive 1000mg RBV daily and ≥75Kg receive 1200mg RBV daily.

Patients Infected with HCV Genotype 2



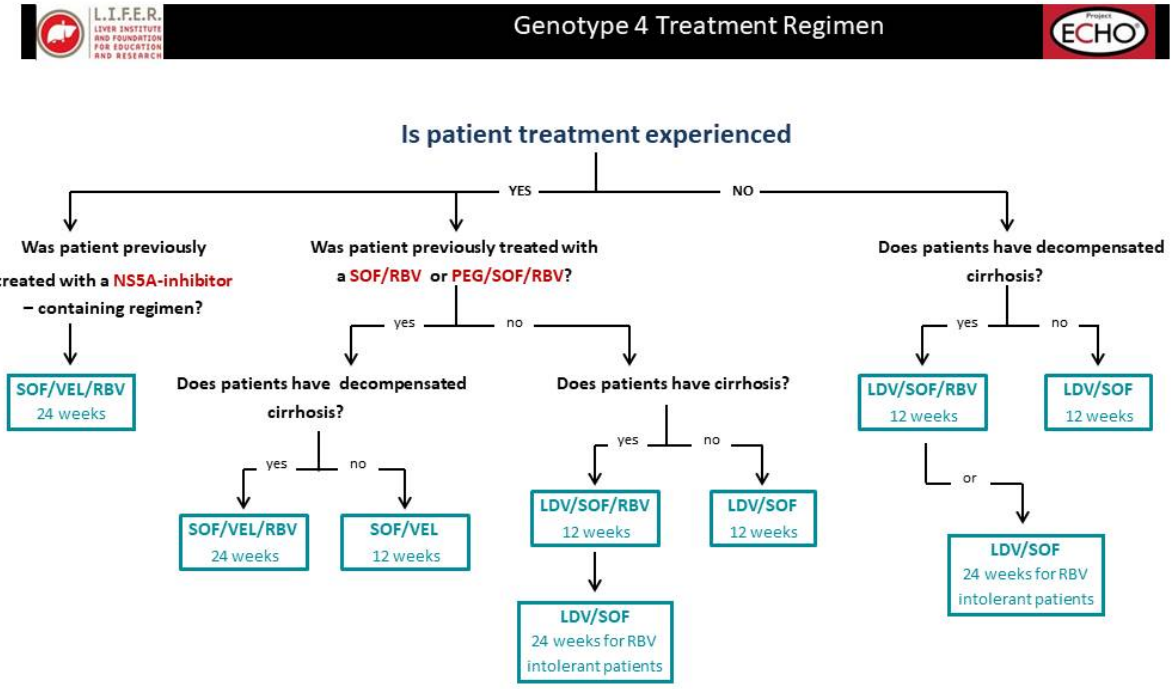
NOTE: All decompensated cirrhotic patients should receive 600mg RBV
All others should receive weight-based ribavirin (RBV) dosage: Patients with weight <75kg receive 1000mg RBV daily and ≥75Kg receive 1200mg RBV daily.

Patients Infected with HCV Genotype 3



NOTE: All decompensated cirrhotic patients should receive 600mg RBV
All others should receive weight-based ribavirin (RBV) dosage: Patients with weight <75kg receive 1000mg RBV daily and ≥75Kg receive 1200mg RBV daily.

Patients Infected with HCV Genotype 4



NOTE: All decompensated cirrhotic patients should receive 600mg RBV
All others should receive weight-based ribavirin (RBV) dosage: Patients with weight <75kg receive 1000mg RBV daily and ≥75Kg receive 1200mg RBV daily.

Appendix 3.

Scientific Meeting Presentations of the Hepatitis C Elimination Program

Abstracts

1. **Hepatitis C screening among the population of Georgia within the national elimination program**

Abstract Presented at EASL, 2019; Vienna, Austria.

Authors:

David Sergeenko,[1] Maia Lagvilava,[1] Ana Aslanikashvili,[2] Maia Tsereteli,[2] Davit Baliashvili,[3] Vladimer Getia,[2] Alexander Turdziladze,[2] Irma Khonelidze,[2] Maia Alkhazashvili,[2] Ekaterine Adamia,[1] Paata Imnadze,[2] Amiran Gamkrelidze[2]

1 Ministry of Internally Displaced People from Occupied Territories, Labour, Health and Social Affairs, Tbilisi, Georgia

2 National Center for Disease Control and Public Health, Tbilisi, Georgia

3 Emory University, Rollins School of Public Health, Department of Epidemiology, Atlanta, United States

Background and Aims: Georgia is high hepatitis C (HCV) prevalence country. According to the latest nationwide seroprevalence study conducted in 2015, 7.7% of the population is anti-HCV antibody positive and 5.4% has chronic hepatitis C infection. Since the launch of the National HCV Elimination Program in 2015, the country of Georgia has stepped up its efforts to achieve the goals of the National HCV Strategy and identify 90% of the HCV infected population by 2020. Therefore, screening campaigns became massive and rigorous in the country, with the active involvement from public and private organizations. Over 800 sites provide HCV screening across the country free-of-charge, following the National HCV Screening Protocol approved by the Ministry of Health. Full coverage is achieved among blood donors, pregnant women, hospitalized patients and military recruits.

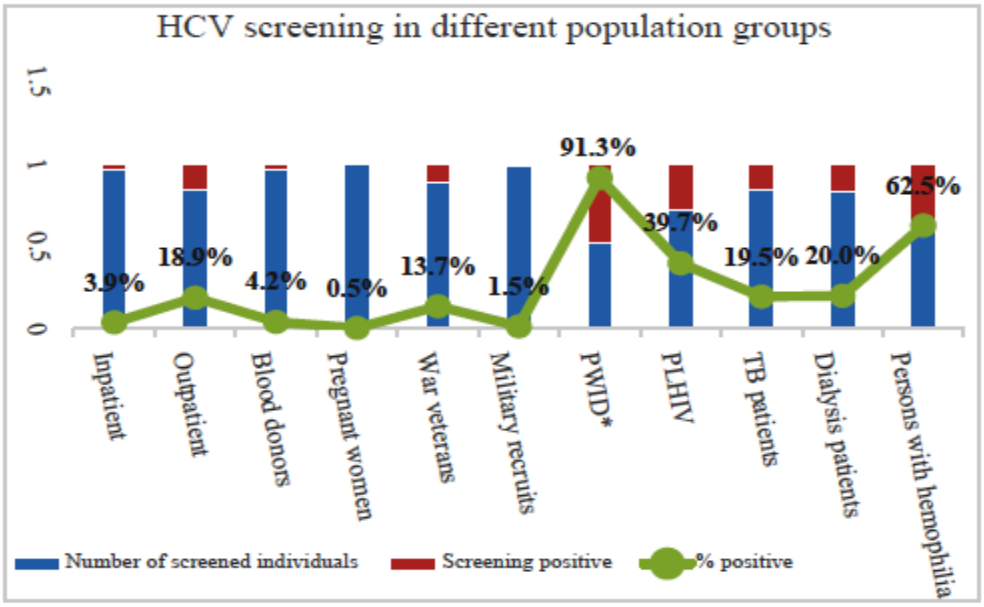
Methods: This analysis was prepared based on the data from the unified electronic HCV screening database, which is being used by all screening provider sites. The database is administered by the National Center for Disease Control and Public Health and it captures information of each HCV screening performed in the country. We looked at the numbers of screened individuals by different

populations, as well as positivity rates among them

Results: Since the launch of the Elimination Program in April 2015 through April 2018, more than 1.2 million individuals have been screened on HCV, with the overall positivity rate-9%. Positivity rates vary through the population groups, with the lowest rate among pregnant women (0.5%) to the highest prevalence in state opioid-substitution therapy beneficiaries (91.3%) (See the figure). Infection is also highly prevalent in people with hemophilia (62.5%) and people living with HIV (39.7%).

Conclusion: More than one third of the adult population has been screened in Georgia and about half of estimated number of anti-HCV positive adult population were identified. Although, to reach the national strategy goals, it is required to increase screening coverage and reach the people who have never been tested, as well as raise awareness among population and improve infection control in medical and non-medical facilities to prevent transmission and reduce the number of new infections.

Figure: HCV screening in different population groups (April 2015-April 2018)



* State Opioid-Substitution Program beneficiaries screened on HCV

2. Piloting of integrated HCV, TB and HIV screening model at primary care level in Georgia

Abstract Presented at EASL, 2019; Vienna, Austria.

Authors:

Irma Khonelidze,[1] Amiran Gamkrelidze,[1] Maia Lagvilava,[2] Maka Danelia,[1] Ketevan Stvilia,[1] Ekaterine Ruadze,[1] Maia Tsereteli,[1] Irina Karosanidze,[3] Vladimer Getia, [1] Nana Odisharia, [4] Anzor Kobalia [4]

1 National Center for Disease Control and Public Health, Tbilisi, Georgia

2 Ministry of Internally Displaced People from Occupied Territories, Labour, Health and Social Affairs, Tbilisi, Georgia

3 National Family Medicine Training Center, Tbilisi, Georgia

4 Public Health Unit of Samegrelo-Zemo Svaneti Region, Zugdidi, Georgia

Background and Aims: In 2018, with support of the Global Fund Georgia started a pilot project in one of the regions of Georgia (Samegrelo-Zemo Svaneti) to test the potential for integration of HCV, HIV and TB screening services at the regional level and to engage primary healthcare providers in detection and management of all three diseases under the "one umbrella."

Methods: The integrated screening protocol and training module were developed and almost all primary healthcare providers (440 professionals) in the region were trained to ensure the quality of diagnostic procedures, ethical conduct, and accurate recording and reporting through web-based platform. Trained primary health care physicians currently offer triple screening to patients seeking for care at medical facilities, and also pursue active case finding using door to door approach for individual houses, congregate settings or public establishments. In case of AB positive test result, individuals were asked to provide vein blood samples for RNA testing at the point of care. Local government has invested in incentives for physicians and nurses providing screening. The horizontal integrated model has involved local public health department staff as well that along with the National Family Medicine Training Center was providing supportive monitoring and supervision.

Results: In three years before the pilot initiation only 58 500 people were screened for HCV in Samegrelo-Zemo Svaneti Region. In 7 months of the pilot project implementation 88, 178 people (90% of the annual target) were screened, including 66% tested in the rural areas of the region. 2279 (2.58%) were HCV antibody positive (anti HCV+), 1393 (61%) were RNA tested, out of which 1277 (91.7%) were confirmed, 718 (56.2%) were registered at HCV treatment sites and 499 (39%) were enrolled in treatment. The integrated screening program has allowed 60% increase of the local population number screened on HCV infection. In addition, within the pilot 37 HIV AB positive

individuals and 192 presumptive TB cases were identified and referred for further confirmation and treatment.

Conclusion: The project implementation enabled development of sustainable public-private partnership for effective integration of TB/HIC/HCV screening and early disease detection with engagement of Central government, the local municipalities, the Global Fund as a donor and local service providers. It has also become the first precedent of local government contribution to priority health initiatives. The pilot motivated service providers to explore patient-centered approaches to case detection and supported decentralization of diagnostic services (HIV and HCV confirmation tests) to district level non-specialized facilities. Based the promising results obtained during the pilot in Samegrelo-Zemo Svaneti, It is planned to standardize and roll-out the approach countrywide in 2019-2020.

3. HCV care cascade of PWIDs reached within the Global Fund needle and syringe program in Georgia

Abstract Presented at EASL, 2019; Vienna, Austria.

Authors:

Ketevan Stvilia[1], Irma Khonelidze[2], Amiran Gamkrelidze[1], Alexander Asatiani[2], Marine Gogia[3], Guranda Jikia[3], Khatuna Kutateladze[3]

1 National Center for Disease Control and Public Health, Tbilisi, Georgia;

2 National Center for Disease Control and Public Health, Global Fund Programs Implementation Unit, Tbilisi, Georgia;

3 Georgian Harm Reduction Network, Tbilisi, Georgia

Background and aims: Within the Global Fund HIV Program HCV screening is integrated in the PWID comprehensive service package to support Georgian hepatitis C elimination program. HCV AB screening positive PWIDs were followed across the HCV care to develop PWID HCV care cascade for 2018

Method: HCV AB rapid test screening is provided by nurses at the Needle and Syringe Program (NSP) Drop-in centers (16 sites) and mobile ambulatories (6 units) as well as by peer PWIDs countrywide in Georgia. PWIDs who agree to provide personal ID are registered in the National hepatitis C

elimination database, others are registered in the HIV prevention program database with 15 digit unique identifier number.

All HCV AB positive PWIDs are referred for HCV RNA testing to HCV treatment sites or collected samples for core-Ag confirmatory testing are sent to the National Reference Laboratory (Lugar Center). The National Hepatitis C Elimination Database allows tracking of those PWIDs who are registered by personal ID across full continuum of HCV care.

Results: During 10 months of 2019 total 23914 PWIDs were reached within the NSP program out of which 13, 836 were screened on HCV AB with 3324 (24%) positive results. 1221 PWIDs agreed to provide personal ID for registration in hepatitis C elimination database, out of which 865 (70.8%) were HCV AB positive and were enrolled in the HCV care cascade analysis. HCV RNA testing was performed for 608 (70.2%) PWIDs with 84% (511) positivity rate. 255 (49.9%) PWIDs were enrolled in HCV treatment with a mean of 59.7 (±54) days of led time from confirmation to treatment. Mean time from HCV AB testing to RNA testing was 16.7 days (±37.8 days). Mean time for full HCV care cascade of PWIDs from screening to enrollment in treatment program was 74 days (±51.1 days), with the minimum the same day enrollment and the maximum of 298 days prior initiation of treatment.

Conclusion: Despite the continues efforts to support hepatitis C elimination program through the Global Fund Needle and Syringe Program in Georgia, the number of PWIDs enrolled in HCV treatment remains small. Due to criminalization of drug use PWIDs are reluctant to provide personal information that complicates the monitoring of PWIDs across HCV care. More community based peer accompanied referral interventions and/or NSP integrated HCV treatment programs are necessary to increase the number of PWIDs enrolled in the treatment as well as to decrease the time from HCV AB screening to HCV treatment initiation.

4. Evaluation of hepatitis C treatment outcome among people who inject drugs in Georgia

Abstract Presented at 8th International conference on Hepatitis care in substance users, 2019; Montreal, Canada.

Authors:

M. Butsashvili[1], G. Kamkamidze[1], M. Kajaia[1], L. Gulbiani[1], L. Gvinjilia[2], T. Kuchuloria[2], A. Gamkrelidze[3], E. Adamia[4], M. Nasrullah[5], F. Averhoff[5]

[1]Health Research Union/Clinic NEOLAB, [2]TEPHINET, Tbilisi, Georgia, [3]National Center for Disease Control and Public Health, Tbilisi, Georgia, [4]Ministry of internally displaced persons from the occupied territories, labor, health and social affairs of Georgia, [5]Division of Viral Hepatitis, National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention, CDC, Atlanta, United States.

Background

Georgia embarked on hepatitis C elimination in April 2015. People who inject drugs (PWID) represent a major share of hepatitis C burden in the country. Ensuring access to treatment for HCV infected PWID is needed to reach elimination goals. Integration of treatment services into harm reduction (HR) settings could facilitate access for HCV infected PWID.

Description of model of care

The Ministry of Health established a working group for integration of hepatitis C treatment services into HR settings in early 2018. Four pilot HR centers were selected to implement hepatitis C integrated treatment: one oral substitution therapy (OST) site in Tbilisi and three needle syringe programs (NSP)-one each in Tbilisi, Zugdidi, and Batumi. Three sites conduct HCV antibody screening and have HCV RNA testing (using GeneXpert) available on-site. A simplified laboratory testing algorithm was introduced, and patients having FIB4>1.45 are referred to specialized clinics for treatment while patients with FIB4<1.45 are treated at HR center. Sofosbuvir/ledipasvir (for genotype1) and sofosbuvir/velpatasvir (for genotype 2/3) regimens are used for treatment. We analyzed data from HR program and the national treatment program. In addition, providers at pilot sites were surveyed to assess acceptability of treatment integration.

Results:

During the first two months of treatment services at HR sites, 155 clients tested HCV RNA positive, of whom 44(28.4%) had FIB4>1.45 and were referred to specialized clinics and 111 patients (71.6%) began treatment at HR centers. No patients had completed treatment as of March 2019. Overall, 62 HR staff were surveyed. The majority of respondents (n=60; 96.7%) were supportive of hepatitis C treatment integration into HR centers. The most common reason cited for why they favored treatment integration was “patient/client convenience,” reported by 57/60(95%) of respondents.

Conclusion

Integration of hepatitis C care with HR services is likely feasible at HR centers and it is highly acceptable for personnel who provide HR services.

5. Hepatitis C treatment integration with harm reduction services in Georgia: preliminary findings

Abstract Presented at 8th International conference on Hepatitis care in substance users, 2019; Montreal, Canada.

Authors:

M. Butsashvili[1], G. Kamkamidze[1], M. Kajaia[1], L. Gulbiani[1], L. Gvinjilia[2], T. Kuchuloria[2], A. Gamkrelidze[3], E. Adamia[4], M. Nasrullah[5], F. Averhoff[5]

[1]Health Research Union/Clinic NEOLAB, [2]TEPHINET, Tbilisi, Georgia, [3]National Center for Disease Control and Public Health, Tbilisi, Georgia, [4]Ministry of internally displaced persons from the occupied territories, labor, health and social affairs of Georgia, [5]Division of Viral Hepatitis, National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention, CDC, Atlanta, United States.

Background

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Results:

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Conclusion

Integration of hepatitis C care with HR services is likely feasible at HR centers and it is highly acceptable for personnel who provide HR services.

6. Progress in Hepatitis C Testing as Part of the Hepatitis C Elimination Program in Georgia

International Viral Hepatitis Elimination Meeting, 2019; Amsterdam, the Netherlands.

Authors:

Amiran Gamkrelidze[1], Alexander Turdziladze[1], Irma Khonelidze[1], Maia Tsereteli[1], Vladimer Getia[1], Sophia Surguladze[1]

[1]National Center for Disease Control and Public Health of Georgia

Introduction

The country of Georgia, with a population of 3.7 million, initiated the world's first national hepatitis C elimination program in April 2015, which aims to reduce hepatitis C virus (HCV) prevalence by 90% by 2020. In 2015, a seroprevalence study was conducted which estimated that 150,000 Georgian adults were infected by HCV (5.4% of the population). Through the elimination program, screening for hepatitis C is available to all citizens free of charge. The aim is to describe progress in hepatitis C testing as part of hepatitis C elimination program.

Material and Methods

All Georgian citizens have a personal national identification number (ID) assigned at birth which is used for tracking citizens for the different purposes, including healthcare. Information system was created to collect data from the elimination program utilizing the national ID to monitor and evaluate program performance and surveillance. This analysis utilizes data from the national screening registry and treatment databases linked by national ID, and 2014 general population census.

Results

As of June 30 2019, 1,415,804 adults identified with the national ID have been tested for hepatitis C (49.5% of the adult population), of whom 116,622 (8.2%) were anti-HCV positive. In 2015 the positivity rate averaged 27.0%, but has fallen to 4.4% in the first half of 2019. Overall, 92,333 individuals received diagnostic testing to determine viremia, and 75,733 (82.0%) were found to have chronic HCV.

Screening rates are similar for men and women – 49.1% (657,062 individuals) of adult males and 49.8% (758,742 individuals) of adult females have been tested for anti-HCV. Screening coverage is the highest for men (52.0%) in the population aged ≥60 and is the lowest in men aged 30-60 (48.0%) which is also the age group with the highest positivity rate - 20.3%. The lowest positivity rate is seen in men aged 18-29 at 2.3% and the overall positivity rate for adult males is 13.0% which means that 87,427 men have been found to be anti-HCV positive.

Screening coverage is the highest for women (60.3%) in the population aged 18-29 and is the lowest in women aged ≥60 (46.8%) which is also the age group with the highest positivity rate - 5.6%. The lowest positivity rate is seen in women aged 18-29 at 1.1% and the overall positivity rate for adult females is 3.4% which means that 29,195 women have been found to be anti-HCV positive

Conclusions

About half of the adult population has been screened in Georgia and half of estimated number of adults with chronic HCV infection was identified. The highest screening positivity rate was observed in the first year of the program and since then the positivity rate has been declining annually. To gain access to hard-to-reach populations program plans to expand integrated HCV testing and treatment services at the primary healthcare and harm reduction settings throughout the country.

7. Efforts to increase HCV viremia testing uptake to reach 2020 hepatitis C elimination goals in Georgia

International Viral Hepatitis Elimination Meeting, 2019; Amsterdam, the Netherlands.

Authors:

Amiran Gamkrelidze[1], Paata Imnadze[1], Maia Alkhazashvili[1], Maia Tsereteli[1], Vladimer Getia[1], Nazibrola Chitadze[1], Tinatin Kuchuloria[2], Lia Gvinjilia[2], Irina Tskhomelidze[2], Shaun Shadaker[3], Muazzam Nasrullah[3]

[1]National Center for Disease Control and Public Health of Georgia
[2]TEPHINET for Georgia National Hepatitis C Elimination Program
[3]Division of Viral Hepatitis, National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention, CDC

Background

In April 2015, the country of Georgia launched the world's first national program to eliminate hepatitis C, defined as a 90% reduction in prevalence by 2020. In 2017, the data suggested that although large numbers of Georgians were being screened for hepatitis C, the proportion of HCV antibody (anti-HCV) positive persons receiving diagnostic testing to determine current infection was insufficient to meet elimination goals. At that time, although treatment and screening was free for program enrollees, Georgians were required to pay for nucleic acid testing (NAT) to determine current infection. At the end of 2017 the government of Georgia made regulatory changes aimed at improving access to free-of-charge HCV viremia testing through the use of HCV core antigen (HCVcAg). The aim is to describe efforts in Georgia's hepatitis C elimination program to increase HCV viremia testing uptake to reach 2020 elimination goals.

Material & Methods

Regulatory changes pertaining to Georgia's national hepatitis C elimination program enacted from December 2017 to March 2018 were reviewed. Additionally, we analyzed data from the national hepatitis C screening registry and treatment database during September 2017 – August 2019.

In December 2017, the government of Georgia approved HCVcAg testing as an alternative to NAT for diagnosing current HCV infection and made all diagnostics including hepatitis C screening and viremia testing (qualitative or quantitative PCR, HCVcAg) free of charge.

The Lugar Center, the national reference laboratory of the National Center for Disease Control and Public Health (NCDC) has provided reflex HCVcAg test-based viremia testing for all anti-HCV positive blood donors and pregnant women identified through state funded programs since January 1, 2018, and for all anti-HCV positive inpatients and persons screened positive at NCDC laboratory sites since March 10, 2018. To facilitate viremia testing uptake, mandatory sample collection from anti-HCV positive inpatients became the responsibility of all inpatient service providers licensed in the country. Since March 1, 2018, hospitals report both screening results and data pertaining to sample collection and transportation to the Lugar Center directly into the hepatitis C screening registry within 24 hours from the service provision.

Results

From December 2017 through August 2019, 24,205 Georgians received HCVcAg testing to determine viremia, an average of 1,153 tests per month. Those tested had a median age of 52 (interquartile range 41-64) and the majority (67.1%; n=16,240) were male. Overall, 72.9% of HCVcAg tests were positive, resulting in the identification of 17,638 individuals needing treatment.

After the introduction of HCVcAg testing among patients of hospitals, the average number of persons receiving viremia testing increased by 58.7%, from 1,195 per month during September 2017 – February 2018 to 1,897 per month during March 2018 – August 2019. This reversed a downward trend since a peak in July 2016, when 2,641 were tested for current HCV infection.

Conclusions

This report highlights policy initiatives aimed at improving rates of HCV viremia and their impact on viremia testing uptake. Introduction of free-of-charge viremia testing paired with reflex HCVcAg testing among hospitals, antenatal clinics, and blood banks improved HCV viremia testing uptake.

Posters

Barriers of linkage to hepatitis C care among people who inject drugs in Georgia

N141

M. Butsashvili1, T. Abzianidze1, G. Kamkamidze1, L. Gvinjilia2, T. Kuchuloria2, I. Tskhomelidze2, M. Gogia3, M. Tsereteli4, V. Miollany5, T. Kikvidze5, M. Nasrullah6, F. Averhoff6

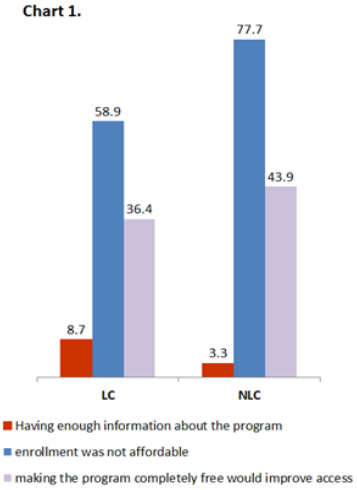
Background

Georgia is the first country embarking on hepatitis C elimination. People who inject drugs (PWID) are responsible for disproportionate share of hepatitis C burden and need access to treatment in order to reduce transmission and achieve elimination.
Barriers to seeking diagnostic follow-up and enrollment into the program among HCV antibody (anti-HCV) positive PWID are not well understood.

Methods

Study participants were enrolled from 12 harm reduction (HR) sites. We compared anti-HCV positive PWID obtaining HCV RNA or core-antigen tests (defined as linked to care [LC]), to anti-HCV positive PWID not receiving confirmatory tests within 90 days of their positive anti-HCV test (not linked to care [NLC]). LC and NLC PWID were contacted and asked about potential barriers to seeking additional care.

Chart 1.



Results

A total of 500 PWID were enrolled, 245 LC and 255 NLC. There were no differences between the two groups by gender, employment status, education level, knowledge of anti-HCV status, and confidence/trust in elimination program (p>.05). PWID aged≥35 years were more likely to be linked compared to those<35 (p<0.05). Having enough information about the program was associated with linkage to care with 8.7% of NLC compared to 3.3% of LC stating they did not have sufficient information (p<0.05). More NLC (77.7%) than LC (58.9%) reported that enrollment was not affordable (p<0.0001). More NLC (43.9%) compared to LC (36.4%) stated that making the program completely free would improve access (p<.05). In addition, more NLC (16.1%) than LC (3.3%) stated that having more treatment provider clinics could improve access (p<.05).

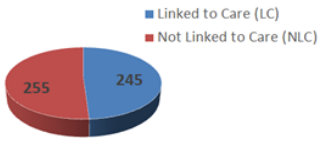
Conclusions

In Georgia, barriers to linkage to care among anti-HCV positive PWID include perceived high cost of care, lack of information on elimination program, perceived lack of access to treatment sites, and younger age. Educational programs in HR sites to address misconceptions about the program may improve linkage to care among PWID.

	Linked to Care	Not Linked to are
Age		
<35	32	39
≥35	213	216
Gender		
Male	224	232
Female	21	23
Education		
University/Post graduate	80	91
Other	160	159
Employment		
Employee	92	87
Unemployed	150	166

Table 1.

Chart 2.



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Progress towards achieving hepatitis C elimination in the country of Georgia, April 2015 – August 2018

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1 INTRODUCTION

In April 2015, Georgia with the support of U.S. CDC and Gilead Sciences, launched the world's first HCV elimination program[1]. A key strategy is nationwide HCV screening, linkage to care, provision of treatment for all HCV persons and effective prevention interventions. A national serosurvey conducted in 2015 estimated 150,000 persons with chronic HCV in the country[2].

To achieve the elimination goal by 2020, a 90% reduction in prevalence of HCV, there are objectives including: diagnosing 90% of HCV-infected persons, treating 95% of those diagnosed and curing 95% of those treated. Progress towards the goal will be assessed by monitoring the HCV care continuum.

2 AIM

We aimed to assess progress towards 90-95-95 targets after 3 years into the elimination program.

3 METHOD

A hepatitis C care cascade was constructed using data from the national HCV treatment program (Figure). The program collects data on all persons registered with the treatment program.

Data on persons tested for chronic HCV infection through sustained virologic response (SVR) were extracted as of August 31, 2018. SVR rates were calculated using both per-protocol (PP) and intent-to-treat analysis (ITT).

4 RESULTS

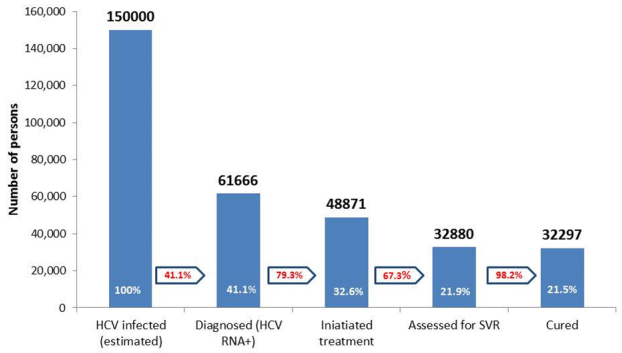
Among estimated 150,000 adults living with chronic hepatitis C in Georgia, 61,666 (41.1%) were diagnosed and registered with the treatment program. Among those registered in the program, 48,871 (79.3%) have initiated treatment with either sofosbuvir or ledipasvir/sofosbuvir based regimens, of which 45,088 (92.2%) have completed treatment.

Among 41,734 persons eligible for SVR assessment 32,880 (78.8%) returned for final evaluation. In PP analysis SVR rate achieved was 98.2% (32,297/32,880) while 77.4% (32,297/41,734) of persons achieved SVR in ITT analysis.

High cure rates were achieved for all HCV genotypes: 98.5% in genotype 1, 98.4% in genotype 2 and 97.7% in most challenging to treat genotype 3.

Treatment effectiveness was comparable among persons with advanced fibrosis (F3 and F4) with 97.3% achieving SVR, and among patients with mild or no liver fibrosis (≤ F2), SVR= 98.8%.

Figure. Hepatitis C care cascade as of August 31, 2018



5 CONCLUSIONS

Georgia has made substantial progress towards eliminating hepatitis C, with over 40% of persons with HCV infection identified and registered for treatment. High cure rates have been achieved among those who received SVR testing.

Efforts to identify and link to care persons with HCV infection, and implement prevention interventions are needed to achieve the elimination goals.

6 ACKNOWLEDGEMENTS

- Authors acknowledge generous support from Gilead Sciences that donated Sofosbuvir, Ledipasvir/Sofosbuvir and Velpatasvir/Sofosbuvir for National Hepatitis C Elimination Program at no costs.
- Authors are grateful to the U.S. Centers for Disease Control and Prevention (CDC) for exceptional technical assistance necessary for initiation and implementation of National Hepatitis C Elimination Program.

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8 CONTACT

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Improvement in liver fibrosis among patients with hepatitis C who achieved sustained viral response after Direct Acting Antivirals treatment, in country of Georgia

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1 INTRODUCTION

Georgia, a country of 3.7 million in the Caucasus region, has a high HCV prevalence of 7% among general adult population.

In April 2015, Georgia initiated the National Hepatitis C Elimination Program, a demonstration program that aims to use both prevention and treatment strategies to reduce HCV prevalence to 0.5% by 2020.

2 AIM

The aim of the study was to assess the long-term health outcome among patients with advanced liver fibrosis treated with direct acting antivirals (DAAs) after achieving sustained viral response (SVR).

3 METHOD

Four clinics providing HCV diagnostic and treatment services under HCV elimination program were participating in the study.

Patients treated with DAAs through elimination program in Georgia and having advanced liver fibrosis level by elastography (>=F3) or FIB4 score (>=3.25) were recruited.

Patients enrolled in the program during May-December 2015, completing full course of the DAA treatment and achieving SVR at week 12-24 post treatment were eligible for the study.

The follow up visits were performed during November 2017 – June 2018 (2 years after SVR was achieved, on average).

Baseline and post treatment changes in liver fibrosis level (in kpa or FIB4 score), ALT, AST, platelet count (PLT), spleen sizes and existence of ascites were evaluated among enrolled patients.

4 RESULTS

A total of 600 patients were recruited and met the eligibility criteria.

Mean age of participants was 52.2 years (range 27-85) and the majority 515/600 (85.8%) were male.

Liver stiffness, defined as kpa, decreased a mean of 8.6 kpa (from 23.89 to 15.26) from baseline to follow-up (p<.0001).

Among those whose fibrosis was measured by FIB4, the mean decrease was 1.41, from 3.52 to 2.11, (p<.0001).

Mean ALT and AST levels decreased from 111.5 to 30.8 (p<.0001) and 89.7 to 30.3 (p<0.05), respectively.

The mean PLT count increased from 159 000 to 182 300 per microliter (p<0.0001). Mean spleen sizes decreased significantly from 136X56 mm to 132X53 mm (p<.001).

Among those with ascites at baseline (n=17), 10 (58.8%) experienced resolution, while among the 583 patients without ascites at baseline, 9 (1.5%) were noted to have ascites during the follow-up examination

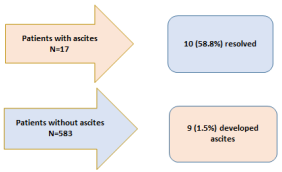
Demographic characteristics of the sample

Characteristic	N	%
Age		
18 – 49	250	41.7
≥ 50	350	58.3
Gender		
Female	85	14.2
Male	515	85.8

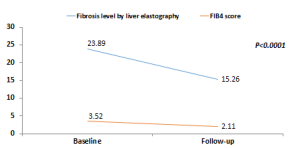
Baseline clinical characteristics of the sample

Characteristic	N	%
Liver fibrosis		
F3	80	13.3
F4	450	75.0
Ascites		
Present	12	2.0
Not present	586	97.7

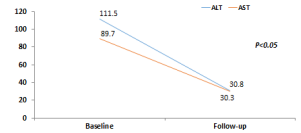
Characteristic	Mean
FIB4 score	3.52
ALT	111.55 u/ml
AST	89.75 u/ml
HB	14.79 g/dL
PLTs	159 10^9/L
Spleen size	136X56 mm



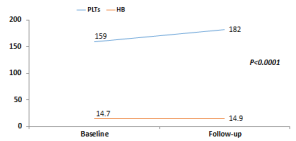
Changes in mean liver fibrosis level



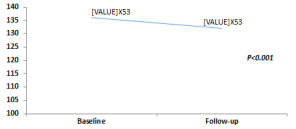
Changes in mean serum ALT and AST levels



Changes in mean PLT count and HB level



Changes in mean spleen size



5 CONCLUSIONS

Significant improvement of liver fibrosis level and different clinical and laboratory parameters was observed 2 years after achieving SVR among patients with advanced liver fibrosis treated with DAAs through HCV elimination program.

6 ACKNOWLEDGEMENTS

Georgia HCV elimination program is conducted under the leadership from the Georgia Ministry of Internally Displaced Persons from the Occupied Territories, Labor, Health, and Social Affairs with strong stakeholder support, including partnership and technical assistance from CDC, and commitment from Gilead Sciences to donate direct-acting antiviral HCV medications (DAAs).

The study was supported by CDC Foundation, grant # 807-17 SC.

The study was also supported by Shota Rustaveli National Science Foundation grants # FR17_371 and # 217998.

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LDV/SOF/RBV is an effective first-line DAA regimen as well as retreating option for RF1_2k/1b patients within Georgian national hepatitis C elimination program

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Infectious Diseases, AIDS and Clinical Immunology Research Center

ABSTRACT

Background and Aims: HCV RF1_2k/1b patients make up to 76.0 % among HCV genotype 2 patients receiving care at the Georgian national hepatitis C elimination program. These patients are treated with either Sofosbuvir/Ribavirin (SOF/RBV) or Ledipasvir/Sofosbuvir/Ribavirin (LDV/SOF/RBV) since 2015 within this program. Our aim was to evaluate baseline and retreatment outcomes among HCV genotype 2 patients receiving HCV care within national hepatitis C elimination program.

Method: Study included 401 adult patients with HCV genotype 2 as determined by 5'UTR/Core genotyping assay. NS5B sequencing was also performed for genotype clarification. Confirmation of breakpoint positions among selected RF1_2k/1b patients was performed by whole genome sequencing. Study patients were treated with either Sofosbuvir/Ribavirin (SOF/RBV) or Ledipasvir/ Sofosbuvir/Ribavirin (LDV/SOF/RBV regimens) from September, 2015 to August, 2018. Re-treatment was performed with LDV/SOF/RBV for 24 weeks.

Results: Of total 401 patients enrolled 305 (76.1%) had RF1_2k/1b strain and 96 (23.9%) had HCV 2a, 2k, or 2c subtypes. Of total patients, 354 (88.3%) were males with a median age of 49.9 years (IQR-42.1-55.5%), and 88 (21.9%) had liver cirrhosis. As of August 2018, sustained virologic response (SVR) was available for 304 individuals. SVR rate was 97.3% (72/74) among genotype 2 and 89.1% (205/230) among RF_2k/1b patients (p=0.05), with an overall SVR rate of 91.1% (277/304). Highest SVR rate was observed among patients treated with LDV/SOF/RBV among both genotypes (99.5%). For patients with cirrhosis SVR was 94.1% (16/17) among genotype 2 compared to 83.7% (41/49) among RF1_2k/1b (p=0.43) patients. Among non-cirrhotic patients, SVR was 98.2% [56/57] among genotype 2 as compared to RF1_2k/1b (SVR 90.6% [164/181]) (p=0.08). Statistically significant difference was observed in response rates among patients treated with SOF/RBV (94.4% for genotype 2 vs. 64.6% for RF1_2k/1b, p=0.02). Among patients with RF1_2k/1b LDV/SOF/RBV had higher SVR rate (100 % [147/147%) vs. SOF/RBV (SVR 64.6% [42/65], p<0.0001). All 27 failing patients were re-treated with LDV/SOF/RBV for 24 weeks yielding SVR rate of 100 %.

Conclusion: LDV/SOF/RBV was found to be highly effective both as baseline regimen as well as retreating option for HCVRF1_2k/1b patients within Georgian national hepatitis C elimination program.

OBJECTIVES

We aimed to evaluate baseline and retreatment outcomes among HCV genotype 2 patients receiving HCV care within national hepatitis C elimination program.

METHODS

Method: Study included 401 adult patients with HCV genotype 2 as determined by 5'UTR/Core genotyping assay. NS5B sequencing was also performed for genotype clarification. Confirmation of breakpoint positions among selected RF1_2k/1b patients was performed by whole genome sequencing. Study patients were treated with either Sofosbuvir/Ribavirin (SOF/RBV) or Ledipasvir/ Sofosbuvir/Ribavirin (LDV/SOF/RBV regimens) from September, 2015 to August, 2018. Re-treatment was performed with LDV/SOF/RBV for 24 weeks.

RESULTS

Table 1. SVR rates by treatment regimen and genotype among persons with complete SVR data (n=304)

Treatment regimen	All	Genotype		
		2	RF1_2k/1b	p value
SOF/RBV	71.1% (59/83)	94.4% (17/18)	64.6% (42/65)	0.02
IFN/SOF/RBV	90.0% (18/20)	100% (2/2)	88.9% (16/18)	0.99
LDV/SOF/RBV	99.5% (200/201)	98.1% (53/54)	100% (147/147)	0.27
Total	91.1% (277/304)	97.3% (72/74)	89.1% (205/230)	0.03

Figure 1. Treatment uptake

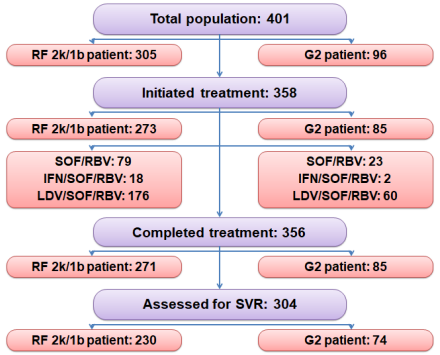

Table 2. SVR rates by treatment regimen, genotypes and liver damage (n=304)

Treatment regimen	Patients without cirrhosis				Patients with cirrhosis			
	HCV Genotype							
	All	2	RF1_2k/1b	p value	All	2	RF1_2k/1b	p value
SOF/RBV	71.2% (42/59)	100% (15/15)	61.4% (27/44)	0.003	70.8% (17/24)	66.7% (2/3)	71.4% (15/21)	0.99
IFN/SOF/RBV	100% (9/9)	0	100% (9/9)	NA	81.8% (9/11)	100% (2/2)	77.8% (7/9)	0.99
LDV/SOF/RBV	99.4% (169/170)	97.6% 41/42)	100% (128/128)	0.24	100% (31/31)	100% (12/12)	100% (19/19)	NA
Total	92.4% (220/238)	98.2%(56/57)	90.6% (164/181)	0.08	86.4% (57/66)	94.1% (16/17)	83.7% (41/49)	0.43

CONCLUSION

LDV/SOF/RBV was found to be highly effective both as baseline regimen as well as retreating option for HCVRF1_2k/1b patients within Georgian national hepatitis C elimination program.

ACKNOWLEDGEMENTS

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Its contents are solely the responsibility of the authors and no not necessarily represent the official views of the Centers for Disease Control and Prevention or the Department of Health and Human Services.

Evaluation of the hepatitis C care cascade in the country of Georgia: monitoring 4 years of progress towards elimination

Tengiz Tsertsvadze,[a] Lali Shanavaz,[a] Nikoloz Chkhartishvili,[a] Amiran Gamkrelidze,[a] Lia Gvinjilia,[a] Akaki Abutidze,[a] Maia Butsashvili,[a] David Metreveli,[a] Vakhtang Kenchadze,[a] Shaun Shadaker,[a] Muazzam Nasrullah,[a] Tamar Gobunia,[a] Ekaterine Adamia,[a] Stefan Zazanov,[a] Nezam Afdhal,[a] Sanjeev Arora,[a] Karla Thornton,[a] Fiandaca Averhoff[a]

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Background

With technical assistance of the U.S. CDC and support from Gilead Sciences, Georgia launched the world's first national hepatitis C elimination program in April 2015 [1,2].

Key strategies include nationwide HCV screening, active case finding, linkage to care, decentralized care, provision of treatment for all HCV persons and effective prevention interventions.

The elimination program aims at achieving 90-95-95 targets by 2020: a) diagnose 90% of HCV-infected persons, b) treat 95% of those diagnosed, and c) cure 95% of those treated [3].

Objectives

We report progress towards elimination targets 4 years into the elimination program

Methods

The estimated number of persons living with HCV infection was based on 2015 population-based national sero-prevalence survey, which showed that 5.4% of adult general population has chronic HCV infection (approximately 150,000 persons).

We analyzed data among adults in the national HCV screening registry, and treatment database during April 2015 to August 2019.

Conclusions

Georgia has made substantial progress towards eliminating hepatitis C. Over 51% of persons with HCV infection were diagnosed, most have initiated treatment and high cure rates are being achieved regardless of fibrosis status. Challenges remain in identifying and linking to care persons living with HCV in Georgia.

Nationwide integrated, decentralized model of HCV treatment, which is already implemented, will be critical to improve linkage to care and close the gaps in HCV cascade.

Results

As of August 31, 2019, overall 116,755 persons tested positive for HCV antibodies and of those 93,514 (80.1%) underwent HCV confirmatory testing.

77,092 (82.4%) of persons tested had chronic HCV infection – 51.4% of the estimated 150,000 adults living with HCV. A total of 60,263 persons initiated treatment – 46.9% of the estimated target population to be treated (128,250).

Of the 39,663 patients who were evaluated for sustained virologic response (SVR), 39,128 (98.7%) tested negative for HCV by PCR, indicative of cure, representing 32.1% of the estimated target population to be cured (121,837).

High cure rates were achieved in patients with all prevalent HCV genotypes in the country: 98.9% in genotype 1, 98.9% in genotype 2, and 98.2% in difficult-to-treat genotype 3. SVR rate was 98.0% in persons with advanced fibrosis (F3/ F4) vs. 99.0% in patients with mild or no liver fibrosis (≤F2), ($p<0.0001$).

Figure: Georgia Hepatitis C Elimination Program Care Cascade, April 28, 2015 – August 31, 2019

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BACKGROUND

With technical assistance of the U.S. CDC and support from Gilead Sciences, Georgia launched the world's first national hepatitis C elimination program in April 2015 [1.2].

Key strategies include nationwide HCV screening, active case finding, linkage to care, decentralized care, provision of treatment for all HCV persons and effective prevention interventions.

The elimination program aims at achieving 90-95-95 targets by 2020: a) diagnose 90% of HCV-infected persons, b) treat 95% of those diagnosed, and c) cure 95% of those treated [3].

OBJECTIVES

We report progress towards elimination targets 4 years into the elimination program

METHODS

The estimated number of persons living with HCV infection was based on 2015 population-based national sero-prevalence survey, which showed that 5.4% of adult general population has chronic HCV infection (approximately 150,000 persons).

We analyzed data among adults in the national HCV screening registry, and treatment database during April 2015 to August 2019.

RESULTS

As of August 31, 2019, overall 116,755 persons tested positive for HCV antibodies and of those 93,514 (80.1%) underwent HCV confirmatory testing.

77,092 (82.4%) of persons tested had chronic HCV infection – 51.4% of the estimated 150,000 adults living with HCV. A total of 60,263 persons initiated treatment – 46.9% of the estimated target population to be treated (128,250).

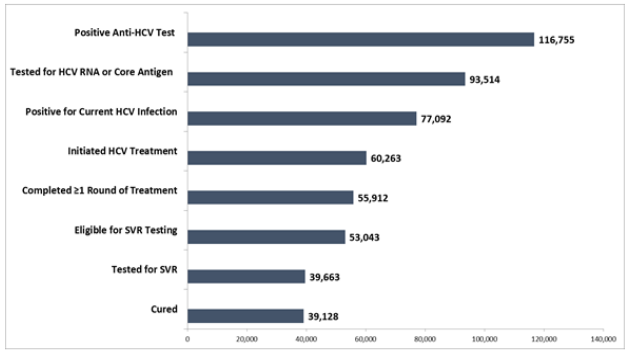
Of the 39,663 patients who were evaluated for sustained virologic response (SVR), 39,128 (98.7%) tested negative for HCV by PCR, indicative of cure, representing 32.1% of the estimated target population to be cured (121,837).

High cure rates were achieved in patients with all prevalent HCV genotypes in the country: 98.9% in genotype 1, 98.9% in genotype 2, and 98.2% in difficult-to-treat genotype 3.

SVR rate was 98.0% in persons with advanced fibrosis (F3/ F4) vs. 99.0% in patients with mild or no liver fibrosis (≤F2), ($p<0.0001$).

RESULTS (cont.)

Figure: Georgia Hepatitis C Elimination Program Care Cascade, April 28, 2015 – August 31, 2019



CONCLUSIONS

Georgia has made substantial progress towards eliminating hepatitis C. Over 51% of persons with HCV infection were diagnosed, most have initiated treatment and high cure rates are being achieved regardless of fibrosis status. Challenges remain in identifying and linking to care persons living with HCV in Georgia.

Nationwide integrated, decentralized model of HCV treatment, which is already implemented, will be critical to improve linkage to care and close the gaps in HCV cascade.

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Authors gratefully acknowledge Gilead Science for donating Sofosbuvir, Ledipasvir/Sofosbuvir and Velpatasvir/Sofosbuvir to the national hepatitis C elimination program at no cost. Authors are grateful to the U.S. CDC for exceptional technical assistance necessary for initiation and implementation of National Hepatitis C Elimination Program.

Management of Hepatitis C in primary healthcare in the country of Georgia

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BACKGROUND

In April 2015, with a partnership with Gilead Sciences and technical assistance from U.S. CDC, Georgia launched the world's first hepatitis C elimination program [1,2].

By August 31, 2019, more than 60,000 persons initiated treatment, achieving >98% cure rates [3].

Broad access to direct acting antivirals (DAAs) resulted in rapid increase in treatment uptake in 2016, which has since declined due to barriers in diagnosis and linkage to care [3].

To address this issue Georgia initiated service decentralization in 2018 by integrating hepatitis C virus (HCV) screening and treatment in primary healthcare centers (PHCs).

OBJECTIVES

We report preliminary results of an integrated model of HCV care in PHCs.

METHODS

By August 2019, a total of 10 PHCs provided HCV care services throughout the country. The integrated model was based on a "one stop shop" approach, by which patients received all HCV screening, treatment and care services at the PHCs.

PHCs provided care to HCV treatment-naïve patients with no or mild fibrosis (FIB-4 score<1.45) using simplified diagnostics (figure 1) and a treatment monitoring (figure 2) approach, while persons with advanced liver fibrosis/cirrhosis were referred to specialized clinics.

Patients received Sofosbuvir/Ledipasvir and/or Sofosbuvir/Velpatasvir for 12 weeks. Sustained virological response (SVR) was defined as undetectable HCV RNA 12-24 weeks after end of therapy.

Figure 1: Pre-treatment evaluation

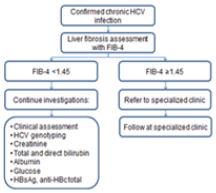


Figure 2: Monitoring algorithm during antiviral therapy

Simplified treatment monitoring procedures				
Measurements	Treatment Duration (weeks)			After treatment completion (weeks)
	4	8	12	12 or 24
Clinical assessment	X	X	X	X
HCV RNA quantitative				X
Complete blood count	X*	X*	X*	
ALT	X	X	X	

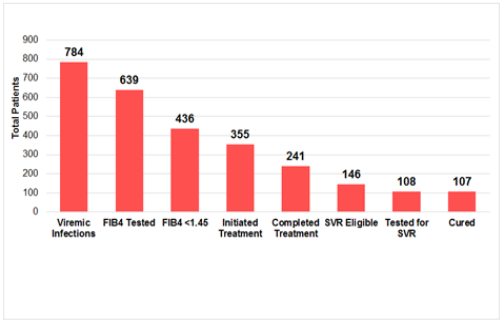
** only for patients receiving Ribavirin containing regimens*

RESULTS

From August 2018 through August 2019, overall 784 persons were tested positive for HCV RNA or core antigen in PHCs; of those, 639 (81.5%) were linked to care (tested for FIB-4 score). Among these, 436 (68.2%) had FIB4 score<1.45; of them, 355 (81.4%) initiated treatment.

A total of 241patients completed treatment. 108 patients had been tested for SVR at the time of analysis, and 107 achieved SVR (99% cure rate).

Figure 3: HCV care cascade in PHC , August 31, 2019



CONCLUSIONS

Our study reported the feasibility and effectiveness of integrating a simplified HCV diagnostic and treatment model in PHCs. Countrywide expansion of this model is warranted to bridge the gaps in the HCV care continuum and ensure high rates of treatment uptake towards achieving elimination targets.

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FACTORS ASSOCIATED WITH SUSTAINED VIRAL RESPONSE AMONG PATIENTS TREATED WITH DIRECT ACTING ANTIVIRALS, GEORGIA ELIMINATION PROGRAM

***George Kamkamidze**, Maia Butsashvili, Tinatin Abzianidze, Ana Gamezardashvili, Lasha Gulbiani, Sofo Bluashvili.*
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AASLD THE LIVER MEETING® NOVEMBER 8-12 2019 BOSTON

INTRODUCTION

Georgia has a high burden of hepatitis C virus (HCV) infection. In 2015, Ministry of health of Georgia with National Center for Disease Control and Public Health (NCDC) and US Centers for Disease Control and Prevention (CDC) conducted the study where a national probability sample of approximately 6000 adults in Georgia was tested for HCV infection, yielding a prevalence estimate of 7.7% for chronic HCV with an estimated 5.4% of adults currently infected.

On April 28, 2015, in collaboration with CDC, Gilead Sciences and other partners, Georgia launched a comprehensive, national HCV elimination program that included free of charge treatment for all HCV infected persons. If successful, the viral reservoir will be substantially reduced and will dramatically decrease the risk of HCV transmission in the country.

AIM

The purpose of this study was to evaluate factors associated with sustained viral response (SVR) among patients treated with direct acting antivirals (DAA) within HCV elimination program in Georgia.

MATERIAL & METHODS

The Elimination Program requires participating clinics and treatment sites to collect pre-treatment socio-demographic, clinical and laboratory data, prescribed medications, treatment adherence and monitoring data.

These data are collected using standardized protocols, and entered in information management system STOP-C - Georgia's national electronic treatment database, developed for the HCV elimination program.

Data collected includes HCV genotype and viral load, level of liver fibrosis, risk factors for HCV infection and treatment-related laboratory data, including SVR at week 12-24 after completion of treatment.

The Elimination Program requires all patients to have a pre-treatment FIB4 score, which is computed from age, ALT, AST and platelet count. A FIB4 score is interpreted as follows: below 1.45 (low), 1.45-3.25 (equivocal), and greater than 3.25 (advanced fibrosis). For those in the equivocal range, a liver elastography is conducted and results recorded.

Data were extracted from the HCV treatment program database of clinic Neolab, one of the major clinical sites providing HCV care and treatment as part of the HCV elimination program.

For all patients included in the program, pretreatment sociodemographic and clinical data, treatment regimen, adherence and monitoring data are collected. Treatment is provided by sofosbuvir/ribavirin (SOF/RBV) with or without interferon (IFN) and sofosbuvir/ledipasvir (LDV) with or without RBV. Treatment outcomes were analyzed by demographic and clinical data, including the degree of liver fibrosis with patients defined as having advanced liver fibrosis (>=F3 by liver elastography or >3.25 by FIB4 score) and treatment regimen. Multivariate analysis using logistic regression was conducted.

RESULTS

During April 28, 2015 – January 30, 2019, a total of 4610 individuals with positive HCV RNA test were included in the treatment program.

SVR result was available for 3352 patients by the time of data analysis. Overall, SVR was achieved in 95.9 % of patients.

By bivariate analysis, variables significantly associated with SVR were:

- Treatment regimen (83.6 % cure rate for SOF/RBV and 99.1% for SOF/LDV or SOF/LDV/RBV regimen),
- Genotype (with genotype 3 having highest cure rate of 96.6% compared to 95.0% and 94.6% for genotypes 2 and 1, respectively)
- Liver fibrosis stage (99.4% SVR among patients with low fibrosis level compared to 90.1% among patients with advanced fibrosis)
- Age (99.7% for age<35 with 95.1% for older patients)
- Gender (98.2% for females and 95.5% for males),
- Platelet count, ALT, AST and weight.

After adjustment, significant association of SVR was observed with:

- Genotype (for genotype 3, aOR=2.39, 95% CI: 1.28-4.44, for genotype 2, aOR=1.96, 95% CI: 1.01-3.79),
- Treatment regimen (aOR=5.59, 95% CI: 2.83-11.06),
- Fibrosis stage (low vs. high fibrosis aOR=5.56, 95% CI: 2.04-14.49).

CONCLUSION

The presented study showed that by multivariate analysis age, gender, weight and liver enzymes were not associated with SVR, while genotype, fibrosis stage and treatment regimen were independent predictors of the treatment outcome.

ACKNOWLEDGEMENTS

Georgia HCV elimination program is conducted under the leadership from the Georgia Ministry of Labor, Health, and Social Affairs [MoLHSA] with strong stakeholder support, including partnership and technical assistance from CDC, and commitment from Gilead Sciences to donate direct-acting antiviral HCV medications (DAAs).

The study was supported by the Shota Rustaveli National Science Foundation of Georgia (SRNSFG) grants # 217998 and FR17_371 and the Fulbright Research Scholarship Program, Bureau of Educational and Cultural Affairs, United States Department of State with the cooperation of the Institute of International Education (IIE # PS00284872).

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DISCLOSURES

None

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Oral Presentations

1. Best practice talk - Georgia, Amiran Gamkrelidze

   Presented at International Viral Hepatitis Elimination Meeting, 2018; Amsterdam, the Netherlands

2. Hepatitis C care cascade in the country of Georgia: monitoring progress towards elimination, Tengiz Tsertsvadze

   Presented at International Viral Hepatitis Elimination Meeting, 2018; Amsterdam, the Netherlands

3. The road to elimination in Georgia, April 2015- August 2018, David Sergeenko

   Presented at International Liver Congress, 2019; Vienna, Austria

4. The critical role of partnerships in HCV elimination, Georgia, April 2015- August 2018, David Sergeenko

   Presented at International Liver Congress, 2019; Vienna, Austria

5. The HCV care cascade and treatment outcomes, April 2015- August 2018, Tengiz Tsertsvadze

   Presented at International Liver Congress, 2019; Vienna, Austria

6. HCV micro-elimination among people who inject drugs in pursuit of national elimination, April 2015- August 2018, Maia Butsashvili

   Presented at International Liver Congress, 2019; Vienna, Austria

7. Beyond treatment: HCV elimination provides collateral benefits to the health system. April 2015 - August 2018, Francisco Averhoff

   Presented at International Liver Congress, 2019; Vienna, Austria

8. Key role of partnerships in global HCV elimination, April 2015 - August 2018, Muazzam Nasrullah

   Presented at International Liver Congress, 2019; Vienna, Austria

9. Key challenges and strategies to reach HCV elimination, April 2015 - August 2018, Amiran Gamkrelidze

   Presented at International Liver Congress, 2019; Vienna, Austria

10. HIV, Hepatitis C and harm reduction in Georgia, Marina Gogia

    Presented at International Forum on Infectious Diseases, 2019; Istanbul, Turkey

11. Scaling-up of an effective model of harm reduction-based and peer-supported hepatitis C treatment for PWID in Georgia, George Soselia

    Presented at International Harm Reduction Conference, 2019; Porto, Portugal

12. HBV/HCV co-infection among patients enrolled in HCV elimination program in Georgia, Maia Butsashvili

    Presented at 2nd Transcaucasus Symposium on HBV Infection, 2019; Tbilisi, Georgia

13. Progress towards eliminating hepatitis C in Georgia: overcoming challenges through decentralization of services, George Kamkamidze

    Presented at Translating science to end HIV in Eastern Europe and Central Asia, AIDS 2018 Post-Conference Symposium, 2019; Tbilisi, Georgia

14. Approaches to providing hepatitis C viremia testing to PWIDs in Georgia. HEAD start project in Georgia, Maia Japaridze

    Presented at 8th International conference on Hepatitis care in substance users, 2019; Montreal, Canada

15. Georgian experience in HCV elimination – is that a way towards HBV elimination?, Francisco Averhoff

    Presented at 2nd Transcaucasus Symposium on HBV Infection, 2019; Tbilisi, Georgia

16. Progress towards hepatitis C elimination in Georgia, Tengiz Tsertsvadze

    Presented at International Meeting on HCV Micro-Elimination in HIV/HCV Co-Infection, 2019; Tbilisi, Georgia

17. Integrating HCV care in primary healthcare, Akaki Abutidze

    Presented at International Meeting on HCV Micro-Elimination in HIV/HCV Co-Infection, 2019; Tbilisi, Georgia

18. Longer-term liver outcomes among HIV/HCV co-infected patients after curing hepatitis C, Natalia Bolokadze

    Presented at International Meeting on HCV Micro-Elimination in HIV/HCV Co-Infection, 2019; Tbilisi, Georgia

19. HBV re-activation in HBV/HCV co-infected patient, Lali Sharvadze

    Presented at International Meeting on HCV Micro-Elimination in HIV/HCV Co-Infection, 2019; Tbilisi, Georgia

20. Perspectives of HCV Micro-elimination in HIV/HCV Co-infection in Georgia, Nikoloz Chkhartishvili

Presented at International Meeting on HCV Micro-Elimination in HIV/HCV Co-Infection, 2019; Tbilisi, Georgia

21. HCV reinfection among HIV patients after DAA therapy in the country of Georgia, Pati Gabunia

    Presented at International Meeting on HCV Micro-Elimination in HIV/HCV Co-Infection, 2019; Tbilisi, Georgia

22. Integrating HCV care in harm reduction services, Maia Butsashvili

    Presented at International Meeting on HCV Micro-Elimination in HIV/HCV Co-Infection, 2019; Tbilisi, Georgia

23. Evaluation of the Hepatitis C Care Cascade in the Country of Georgia: Monitoring Progress towards Elimination, Tengiz Tsertsvadze

    Presented at International Viral Hepatitis Elimination Meeting, 2019; Amsterdam, the Netherlands

Appendix 4.

Publications Related to the Hepatitis C Elimination Program

Abstracts

1. **Confidence in the Georgia national HCV elimination program among women of reproductive age**
   Georgian Med News. 2019 October;(295):105-109

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   Abstract

Georgia is among the countries with a very high prevalence of hepatitis C virus (HCV) infection. The recent availability of highly effective, direct-acting antivirals (DAAs) capable of curing >90% of persons treated has made HCV elimination a possibility. All adult citizens infected with HCV are eligible to receive free DAAs through the Georgia National HCV Elimination Program (Program). From April 2015 to December 2018, 54,087 persons were enrolled in the Program throughout the country. However, more than 20,000 individuals are aware of their HCV antibody positive status but did not have HCV RNA testing, a necessary step to determine treatment needs. We hypothesized that a reason for hesitance to enroll in the Program may be a low level of trust of the Program. A cross-sectional study was conducted in Tbilisi, the capital of Georgia. Reproductive aged women were randomly selected from three maternity care centers during prenatal care. The self-administered questionnaire included questions on socio-demographic information, knowledge about HCV infection and trust in the Program. A total of 2185 women of reproductive age were enrolled in the study. The mean age was 28.5 (age range: 17-46) years. The majority of the study participants (76.4%) had a university degree. The vast majority of study participants (>95%) were married and 95.1% were Georgian ethnicity. Almost 90% of the participants were aware of their HCV infection status. Most women (85.3%) had heard of HCV elimination program in Georgia; 74.6% stated that they trust the Program. However, almost 10% of surveyed women stated they would refuse to get enrolled in the

Program if their anti-HCV test result is positive. Trust in the Program was higher among women aged >25 years (80.7%) compared to younger women (68.4%) (p<0.0001). Level of education was also associated with trust to the program: more women with higher education level reported that they trust the Program (78.7%) compared to women with lower education level (68.5%) (p<0.0001). Trust in the Georgia National HCV Elimination Program is not sufficiently high among women of reproductive age in Georgia. Effective educational campaigns are needed to improve trust to the Program for this targeted group.

2. Hepatitis B vaccination: knowledge and attitude among women of reproductive age in Georgia Georgian Med News. 2019 October; (295):109-114

Authors:

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Abstract

Georgia is a country with high prevalence of hepatitis B. Based on a 2015 population serosurvey, the prevalence of hepatitis B surface antigen (HBsAg) is 2.9% and prevalence of anti-HBc is 25.5% in general population. Hepatitis B vaccine has been included in the national immunization schedule of Georgia only since 2002. Thus, most reproductive aged women were not vaccinated during young childhood. Cross-sectional study was conducted in the capital of Georgia, Tbilisi. Reproductive aged women were randomly selected and then recruited from three maternity care centers during prenatal care. The self-administered questionnaire included questions on socio-demographic information, hepatitis B vaccination status and awareness of HBV infection status. A total of 2185 reproductive aged women were enrolled in the study. The mean age was 28.5 (age range 17-46) years. Most (76.4%) had a bachelor and/or master's degree. 20.0% of respondents never heard about HBV. Very few (3.3%) knew they were infected with HBV. We could not determine if women were chronically infected or were exposed and developed antibodies. HBV knowledge was limited: 57.5% were not aware of available HBV treatment; 51.6% didn't know HBV infection could be prevented (35.8% named HBV vaccination, 29.3% named condom use). Only 10% of study participants reported being vaccinated for HBV.

Awareness of HBV infection was higher among women over age 25 (72.1%) compared to women aged 25 years or less (27.9%) ($P<0.0001$). Among women who reported having an HBV infection, 40.6% did not name vaccine as a prevention method and 38.2% did not have information about availability of HBV treatment ($P<0.05$). Based on our study results, knowledge about HBV infection and vaccination is very low among reproductive aged women in Georgia. Women's health centers can be a good place to reach reproductive aged women for counseling on HBV infection and promote vaccination against hepatitis B.

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Research Paper

Direct acting antiviral-based treatment of hepatitis C virus infection among people who inject drugs in Georgia: A prospective cohort study

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ARTICLE INFO

Keywords:
People who inject drugs
Hepatitis C virus
Adherence
SVR
Direct acting antiviral
Middle income country

ABSTRACT

Background: People who inject drugs (PWID) are often excluded from HCV treatment programs due to concerns about their ability to adhere to care. Georgia has a high prevalence of HCV infection (5.4% of chronic cases in general population) with an epidemic concentrated among PWID. We evaluated adherence to care and sustained virologic response (SVR) among PWID in Georgia.

Methods: In this observational study, participants with recent injecting drug use (previous 6 months) and chronic HCV attending a needle- and syringe-program were included. Participants received sofosbuvir and ribavirin +/- pegylated interferon, with peer-based support during treatment. The primary endpoint was undetectable HCV RNA 12 weeks post-treatment (SVR12). Factors associated with SVR were assessed using logistic regression.

Results: Among 244 participants [HCV genotype (GT) 3, 52%; GT2, 25%; GT1, 19%; mixed GT, 4%]; 55% had cirrhosis. Overall, 24% were receiving OST and 50% injected drugs in the previous month. 98% (239 of 244) completed treatment, with 88% (210 of 239) having never delayed a medical appointment and 79% (189 of 239) never missing a dose of medication. Overall, SVR was 84.8% (207 of 244). SVR was 88.5% (207 of 234) among participants who attended 12-week follow up appointment for HCV RNA testing. In multivariate analyses, SVR was significantly associated with adherence (no missed doses) to treatment [vs. missed doses; adjusted OR (aOR) 2.77; 95% confidence interval (95%CI), 1.01–7.51), and genotype (vs. GT1; GT2, aOR 0.27; 95%CI 0.06–1.21; GT3, aOR 1.09; 95%CI 0.27–4.50; and mixed GT, aOR 0.14; 95%CI 0.02-0.97).

Conclusion: In this real-life study in a middle-income country, PWID treated for HCV and receiving a simple peer-support intervention demonstrated an excellent treatment response and good adherence, not associated with injecting drug use during treatment and OST at treatment initiation.

Introduction

People who inject drugs (PWID) account for about 10% of the 71 million chronic HCV cases worldwide, although they represent less than 0.33% of the global adult population (Degenhardt et al., 2017; Nelson et al., 2011; Polaris observatory HCV collaborators, 2017). Also, an estimated 23% of new HCV infections occur among PWID (World Health Organization, 2017a) Almost half of PWID living with HCV infection are from East/Southeast Asia and Eastern Europe (Nelson et al., 2011), where there is overall limited access to evidence-based harm reduction (HR) services (Larney et al., 2017). Alongside criminalization and systematic discrimination, concerns about the ability of PWID to adhere to care and the risk of reinfection after treatment leads to their exclusion from many existing treatment programs or national policies (Wolfe et al., 2015).

The development of simple, tolerable and highly effective direct-acting antiviral (DAA) therapies has created an opportunity for the global elimination of HCV, and countries are updating their national strategy to control the epidemic (World Health Organization, 2018). In 2016, the World Health Assembly adopted the first Global Health Sector Strategy on Viral Hepatitis 2016–2020, with global targets of reducing new viral infections by 90% and deaths due to viral hepatitis by 65% by

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Impact of hepatitis C virus antibody positivity on mortality and causes of death in people living with HIV in Georgia

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Abstract

Hepatitis C co-infection in people living with HIV (PLWH) is common in Georgia. Antiretroviral therapy (ART) is widely available in the country since 2004, and from 2011, patients have unlimited access to hepatitis C virus (HCV) treatment. A retrospective nationwide cohort study included adult PLWH diagnosed between 2004–2016, who were followed up until 31 December 2017. Predictors of mortality were assessed in Cox proportional hazards regression model. A total of 4560 persons contributed 22,322 person-years (PY) of follow-up, including 2058 (45.1%, 10,676 PY) anti-HCV+ patients. After the median 4.1 years of follow-up, 954 persons died, including 615 anti-HCV+ patients. Persons with HCV had higher overall mortality compared to HIV monoinfection (5.76/100 PY vs. 2.91/100 PY, $p < 0.0001$). In multivariable analysis, anti-HCV positivity was significantly associated with mortality (adjusted hazard ratio: 1.42, 95% CI: 1.09–1.85). Among anti-HCV+ persons, liver-related mortality due to viral hepatitis before the availability of HCV therapy (2004–2011) was 2.11 cases per 100 PY and this decreased to 0.79 cases per 100 PY after 2011 ($p < 0.0001$). AIDS remained the leading cause of death prior to and after 2011. Wide availability of ART and anti-HCV therapy translated into a significant decline in mortality including due to liver-related causes. Improving earlier diagnosis will decrease excess AIDS-related mortality among people living with HIV/HCV co-infection.

Keywords

HIV, hepatitis C, antiretroviral therapy, AIDS

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Introduction

Wide-scale availability of antiretroviral therapy (ART) led to significant increase in life expectancy among people living with HIV (PLWH) nearly approaching that of general population.[1] As PLWH live longer, they are more likely to die from non-AIDS complications, including liver-related diseases caused by viral hepatitis.[2] HIV is known to accelerate the progression of liver disease caused by hepatitis C virus (HCV); in turn HCV is associated with increased risk of mortality among PLWH.[3–5]

Georgia is a country where the HIV prevalence is low, with an estimated adult prevalence of 0.4%, while 7.7% of adult general population is anti-HCV-positive.[6,7] Co-infection with HCV is common among PLWH in Georgia with nearly half of them carrying HCV antibodies.[8] For many years, Georgia's HIV epidemic was driven by injection drug use (IDU), but recent trends indicate shift to sexual transmission through both heterosexual contacts and male-to-male sex. The country has made a significant progress in HIV treatment and care ensuring universal access to ART since 2004 through the Global Fund support.[9] This has resulted in significant reduction in all-cause mortality

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Clinical Infectious Diseases

MAJOR ARTICLE

Three Years of Progress Toward Achieving Hepatitis C Elimination in the Country of Georgia, April 2015–March 2018

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Background. In April 2015, in collaboration with the US Centers for Disease Control and Prevention and Gilead Sciences, the country of Georgia embarked on the world's first hepatitis C elimination program. We aimed to assess progress toward elimination targets 3 years after the start of the elimination program.

Methods. We constructed a hepatitis C virus (HCV) care cascade for adults in Georgia, based on the estimated 150 000 persons aged ≥18 years with active HCV infection. All patients who were screened or entered the treatment program during April 2015–March 2018 were included in the analysis. Data on the number of persons screened for HCV were extracted from the national HCV screening database. For the treatment component, we utilized data from the Georgia National HCV treatment program database. Available treatment options included sofosbuvir and ledipasvir/sofosbuvir–based regimens.

Results. Since April 2015, a cumulative 974 817 adults were screened for HCV antibodies; 86 624 persons tested positive, of whom 61 925 underwent HCV confirmatory testing. Among the estimated 150 000 adults living with chronic hepatitis C in Georgia, 52 856 (35.1%) were diagnosed, 45 334 (30.2%) initiated treatment with direct-acting antivirals, and 29 090 (19.4%) achieved a sustained virologic response (SVR). Overall, 37 256 persons were eligible for SVR assessment; of these, only 29 620 (79.5%) returned for evaluation. The SVR rate was 98.2% (29 090/29 620) in the per-protocol analysis and 78.1% (29 090/37 256) in the intent-to-treat analysis.

Conclusions. Georgia has made substantial progress in the path toward eliminating hepatitis C. Scaling up of testing and diagnosis, along with effective linkage to treatment services, is needed to achieve the goal of elimination.

Keywords. HCV; elimination; care cascade; Georgia.

Introduction of highly effective direct-acting antivirals (DAAs) for hepatitis C virus (HCV) with cure rates exceeding 90% have resulted in a paradigm shift in the response to the HCV epidemic [1]. In 2016 the World Health Assembly endorsed the Global Health Sector Strategy on Viral Hepatitis 2016–2021, which calls for the elimination of viral hepatitis as a public health threat by 2030 [2]. The World Health Organization (WHO) defines elimination as 90% reduction in the incidence of HCV infection and 65% reduction in HCV-related mortality, to be achieved through diagnosing 90% of people living with HCV infection and treating 80% of those diagnosed. As of February 2019, 124 countries reported national hepatitis plans to be in place, yet only 12 countries (Australia, Egypt, France, Georgia, Iceland, Italy, Japan, Mongolia, the Netherlands, Spain, Switzerland, and the United Kingdom) were on track to meet the WHO targets [3, 4]. A major barrier on the road to elimination is limited domestic and international investments in hepatitis C programs, particularly in resource-limited countries [5]. Lack of finances affects access to testing, diagnostics, and treatment, resulting in significant gaps in the HCV care cascade. Global progress analysis shows that only 14 million people with chronic hepatitis C were diagnosed and a cumulative 5 million people out of estimated 71 million persons living with chronic hepatitis C globally received DAA treatment [3, 6].

Georgia is a small Eastern European country (population of 3.7 million people), with a lower-middle–income economy and healthcare expenditures accounting for 8.44% of gross domestic product [7]. The country's high burden of hepatitis C has

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STATE OF VIRAL HEPATITIS CARE IN 16 COUNTRIES OF CENTRAL AND EASTERN EUROPEAN REGION

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SUMMARY

Objectives: Survey was conducted to assess state of viral hepatitis care in Central and Eastern Europe (CEE).

Methods: Representatives of 16 CEE countries completed on-line survey in April–May 2017 that collected information on basic epidemiology and availability of key services for HCV and HBV infections. Sources of information provided ranged from national surveillance data to expert opinion.

Results: The burden of viral hepatitis varied between countries, ranging from 6,500 to 2 million for HCV and from 10,000 to 3 million for HBV. Access to routine HCV RNA testing and genotyping was reported by 11 and 9 countries, respectively. HCV resistance testing was available in 7 countries. Direct acting antivirals (DAAs) were available in 13 countries, most frequently Sofosbuvir and Ledipasvir/Sofosbuvir (12 countries apiece) and Ombitasvir/Paritaprevir/Dasabuvir (9 countries). HBV DNA testing and HBV genotyping were routinely available in 10 and 7 countries, respectively. Eleven countries reported available treatment with Tenofovir.

Conclusions: There are gaps in viral hepatitis care in CEE. Despite the availability of registered modern drugs for HCV and HBV, the access to treatment is limited. Ensuring quality health care is essential to reduce the epidemic and achieve the WHO's goal of eliminating viral hepatitis as a major public health challenge.

Key words: viral hepatitis, Central and Eastern Europe, HCV, HBV

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INTRODUCTION

Viral hepatitis due to hepatitis B virus (HBV) and hepatitis C virus (HCV) represent major health challenge globally. Both viruses can cause chronic hepatitis that may lead to cirrhosis and hepatocellular carcinoma (1, 2). The World Health Organization (WHO) estimates that there are more than 300 million people living with chronic HBV and HCV infection globally including 29 million people living in the WHO European Region resulting in 171,000 deaths annually (3, 4).

Currently available prevention and treatment modalities make the goal of viral hepatitis elimination technically feasible (5). This includes highly effective vaccine against HBV, antiviral drugs to control HBV and new generation direct acting antivirals (DAAs) curing >95% of HCV infections (1, 6). However, there are important challenges to overcome, including gaps in prevention, diagnosis and treatment (3).

Latest global hepatitis report shows that only 9% of people living with HBV and 20% of people living with HCV are aware of their status (3). Only 8% of those diagnosed with HBV and HCV infections received antiviral therapy (3). Access to effective treatment is substantially hampered by high costs of both HBV and HCV drugs (7), which are often inaccessible to all patients through health systems. While prevention can reduce the rate of new infections, the number of chronically infected persons would remain high for years, therefore, ensuring testing, virological monitoring and unrestricted access to treatment is crucial for achieving elimination goal.

We conducted survey to assess state of viral hepatitis care within the Euroguidelines in Central and Eastern Europe (ECEE) Network Group, which was formed in 2016 to promote dissemination of European standards of care in HIV and viral hepatitis in Central and Eastern Europe (CEE) (8).

MATERIALS AND METHODS

On-line survey was constructed to elicit information related to HCV and HBV care in CEE region. The survey asked respondent to answer 17 question, including 2 general questions about the country of residence and occupation, 8 questions about HCV epidemiology and availability of HCV diagnostic and treatment

Research Article
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Progress and challenges of a pioneering hepatitis C elimination program in the country of Georgia

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Background & Aims: Georgia, with a high prevalence of HCV infection, launched the world's first national hepatitis C elimination program in April 2015. A key strategy is the identification, treatment, and cure of the estimated 150,000 HCV-infected people living in the country. We report on progress and key challenges from Georgia's experience.

Methods: We constructed a care cascade by analyzing linked data from the national hepatitis C screening registry and treatment databases during 2015–2018. We assessed the impact of reflex hepatitis C core antigen (HCVcAg) testing on rates of viremia testing and treatment initiation (i.e. linkage to care).

Results: As of December 31, 2018, 1,101,530 adults (39.6% of the adult population) were screened for HCV antibody, of whom 98,430 (8.9%) tested positive. Of the individuals who tested positive, 78,484 (79.7%) received viremia testing, of whom 66,916 (85.3%) tested positive for active HCV infection. A total of 52,576 people with active HCV infection initiated treatment and 48,879 completed their course of treatment. Of the 35,035 who were tested for cure (*i.e.*, sustained virologic response [SVR]), 34,513 (98.5%) achieved SVR. Reflex HCVcAg testing, implemented in March 2018, increased rates of monthly viremia testing by 97.5% among those who screened positive for anti-HCV, however, rates of treatment initiation decreased by 60.7% among diagnosed viremic patients.

Conclusions: Over one-third of people living with HCV in Georgia have been detected and linked to care and treatment, however, identification and linkage to care of the remaining individuals with HCV infection is challenging. Novel interventions, such as reflex testing with HCVcAg, can improve rates of viremia testing, but may result in unintended consequences, such as decreased rates of treatment initiation. Linked data systems allow for regular review of the care cascade, allowing for identification of deficiencies and development of corrective actions.

Lay summary: This report describes progress in Georgia's hepatitis C elimination program and highlights efforts to promote hepatitis C virus screening and treatment initiation on a national scale. Georgia has made progress towards eliminating hepatitis C, treating over 50,000 people, approximately one-third of the number infected, and achieving cure for 98.5% of those tested. However, identifying infected individuals and linking them to care remains challenging. Novel approaches to increase diagnostic testing can have unintended consequences further down the care cascade.

Keywords: Georgia; HCV; Hepatitis C diagnostic testing; Screening; Linkage to care; Reflex testing.

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Introduction

Georgia, a small middle-income country with a population of 3.7 million, located at the cross-roads of Europe and Asia, launched the world's first national hepatitis C elimination program in April 2015, with the ambitious goal of a 90% reduction in hepatitis C prevalence by 2020.[1] At the time the program was initiated, a national seroprevalence survey was conducted that estimated 150,000 Georgians (5.4% of the adult population) were living with HCV infection.[2] To achieve the elimination goal, Georgia implemented several strategies, including the identification and treatment of all HCV-infected people in the country.[3] The feasibility of this strategic goal was made possible by an April 2015 memorandum of understanding (MOU) between the government of Georgia and Gilead Sciences, in which Gilead Sciences agreed to provide direct-acting antiviral (DAA) medications free-of-charge for eligible Georgians with HCV infection.[3,4] The cost of DAAs in 2015 was prohibitive; without the MOU with Gilead Sciences this program could not have transpired. A large number of Georgians enrolled in the program during the first 3 years, and cure rates exceeded 95% among those treated and tested for cure (i.e., sustained virologic response [SVR]).[5] Yet, despite the availability of treatment and high cure rates, important challenges remain. We report on progress, key challenges, and lessons learned from Georgia's experience in identifying persons with HCV infection and linking them to hepatitis C care and treatment.

Research Article
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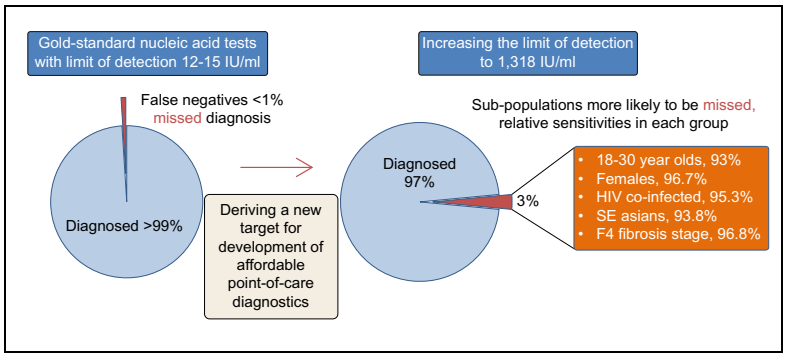
Deriving the optimal limit of detection for an HCV point-of-care test for viraemic infection: Analysis of a global dataset

Graphical abstract



Highlights

- >97% of those with chronic hepatitis C virus have viraemia >1,318 IU/ml.
- Low-level viraemia among 66,640 individuals did not vary significantly by genotype.
- The sensitivity of HCV diagnostic tests was maintained even when increasing the detection limit by 100×.

Authors

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Lay summary

We created and analysed a dataset from 12 countries with 66,640 participants with chronic hepatitis C virus infection. We determined that about 97% of those with viraemic infection had 1,300 IU/ml or more of circulating virus at the time of diagnosis. While current diagnostic tests can detect as little as 12 IU/ml of virus, our findings suggest that increasing the level of detection closer to 1,300 IU/ml would maintain good test accuracy and will likely enable development of more affordable portable tests for use in low- and middle-income countries.

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Research Article
Viral Hepatitis

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Deriving the optimal limit of detection for an HCV point-of-care test for viraemic infection: Analysis of a global dataset

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Background & Aims: Affordable point-of-care tests for hepatitis C (HCV) viraemia are needed to improve access to treatment in low- and middle-income countries. Our aims were to determine the target limit of detection (LOD) necessary to diagnose the majority of people with HCV eligible for treatment, and identify characteristics associated with low-level viraemia (LLV) (defined as the lowest 3% of the distribution of HCV RNA) to understand those at risk of being misdiagnosed.

Methods: We established a multi-country cross-sectional dataset of first available quantitative HCV RNA measurements linked to demographic and clinical data. We excluded individuals on HCV treatment. We analysed the distribution of HCV RNA and determined critical thresholds for detection of HCV viraemia. We then performed logistic regression to evaluate factors associated with LLV, and derived relative sensitivities for significant covariates.

Results: The dataset included 66,640 individuals with HCV viraemia from across the world. The LOD for the 95th and 99th percentiles were 3,311 IU/ml and 214 IU/ml. The LOD for the 97th percentile was 1,318 IU/ml (95% CI 1,298.4–1,322.3). Factors associated with LLV, defined as HCV RNA <1,318 IU/ml, were younger age 18–30 *vs.* 51–64 years (odds ratios [OR] 2.56; 95% CI 2.19–2.99), female *vs.* male sex (OR 1.32; 95% CI 1.18–1.49), and advanced fibrosis stage F4 *vs.* F0-1 (OR 1.44; 95% CI 1.21–1.69). Only the younger age group had a decreased relative sensitivity below 95%, at 93.3%.

Conclusions: In this global dataset, a test with an LOD of 1,318 IU/ml would identify 97% of viraemic HCV infections among almost all populations. This LOD will help guide manufacturers in the development of affordable point-of-care diagnostics to expand HCV testing and linkage to care in low- and middle-income countries.

Lay summary: We created and analysed a dataset from 12 countries with 66,640 participants with chronic hepatitis C virus infection. We determined that about 97% of those with viraemic infection had 1,300 IU/ml or more of circulating virus at the time of diagnosis. While current diagnostic tests can detect as little as 12 IU/ml of virus, our findings suggest that increasing the level of detection closer to 1,300 IU/ml would maintain good test accuracy and will likely enable development of more affordable portable tests for use in low- and middle-income countries.

Introduction

Globally, viral hepatitis is responsible for 1.34 million deaths[1,2] and more than 50 million of the estimated 70 million cases of chronic hepatitis C virus (HCV) occur in low and middle-income countries (LMICs).[3] The World Health Organization (WHO) defined goals towards the elimination of viral hepatitis as a public health threat, with a 90% reduction in new infections, and a 65% reduction in mortality by 2030.[1,4] Achievement of these targets requires scale-up of access to affordable testing and treatment alongside interventions for HCV prevention (harm reduction and safe blood donation and injections).[5] Progress in treatment scale-up is encouraging with more than 3 million treated with direct-acting antivirals since 2015, however, testing coverage and diagnosis rates are still less than 10% in LMICs.[6]

Keywords: Hepatitis C virus; Diagnosis; Point-of-care; Limit of detection; Viraemia, Affordable.
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Approximately 15–45% of people infected with HCV will spontaneously clear the virus[7,8] and therefore confirmation of HCV viraemia is necessary to identify those needing treatment. The standard diagnostic algorithm recommended by the WHO includes an initial HCV antibody test followed by confirmatory testing for viraemia with either a nucleic acid test (NAT) for HCV RNA or core antigen (HCVcAg) where RNA tests are not available.[9–11] High proportions of those with positive antibody fail to have confirmatory testing and are never linked to treatment.[12,13] Further, available tests for viraemia are expensive, and require advanced laboratory facilities, electricity, water, and refrigerated reagents. Few LMICs have testing policies or the requisite laboratory infrastructure in place[13–15]

Innovations in testing technology, and research to inform optimal implementation strategies for HCV in LMICs are needed.[9,16,15] A rapid, affordable, easy-to-use test for confirmation of HCV viraemia at the point-of-care (POC) that can be deployed on a large scale has the potential to improve outcomes across the diagnosis and care continuum, particularly in high HCV prevalence settings.[16–18]

Presently, there are no data to determine a limit of detection (LOD) for WHO prequalification criteria for a POC HCV viraemia test. Thus, POC tests are held to the same standards as laboratory-based NATs. The laboratory-based Abbott RealTime HCV viral load test, for example, is able to detect and measure HCV RNA down to 12 international units per milliliter (IU/ml) with >99% sensitivity; similarly, the Roche COBAS®TaqMan® HCV Test reports an LOD of 15 IU/ml.[19] The laboratory-based Abbott ARCHITECT HCVcAg test has an LOD corresponding to 3,000 IU/ml with 93.4% sensitivity.[20] Requiring POC assays to achieve the same prequalification criteria as laboratory assays may limit the ability to expand HCV testing and treatment in LMICs. The POC Genedrive® HCV assay, however, acquired European *in vitro* diagnostics approval this year with an LOD of 2,362 IU/ml,[21] but is not yet WHO prequalified. Additionally, Cepheid Xpert® HCV Viral Load finger-stick assay detects as little as 40 IU/ml and can utilise consolidated near-patient Xpert platforms or the POC Omni version.[22]

A consensus target product profile in 2017 outlined price targets and operational characteristics for a near-patient HCV viraemia test[18] including but not limited to: a minimal LOD of 1,000–3,000 IU/ml, minimal test sensitivity of 95%, test cost <$15 though ideally <$5, and instrument cost <$20,000 but ideally <$2,000. Currently, available platforms struggle to meet these price targets. Data are needed to estimate the clinical sensitivity of the potential minimum LOD recommendations. Integrating NAT data outlined above with the goals from the target product profile, we hypothesise that a POC assay with an LOD of 1,000 IU/ml (3 log IU/ml) would have >97% clinical sensitivity for confirming HCV viraemia. A single-step POC test would allow for accessible, low-cost testing of viraemia without loss to follow-up in LMICs, despite having a lower analytical sensitivity.[18,23,24] Our objective is to determine the requisite LOD for an affordable POC assay to diagnose the majority of people with chronic HCV, and to identify characteristics of those with low-level viraemia (LLV) who might be missed by a less sensitive test.

Patients and methods

Study design

We assembled a cross-sectional dataset of the first available HCV RNA measurement for HCV antibody positive persons with viraemia from high, moderate, and low HCV prevalence settings in 12 countries (Cambodia, Cameroon, Canada, Egypt, Georgia, India, Indonesia, Malaysia, Mozambique, Pakistan, Thailand, and Vietnam) with representation of the 6 major HCV genotypes, a broad range of liver fibrosis stages, and varying prevalence of human immunodeficiency virus (HIV) and hepatitis B virus (HBV) co-infection. To test our hypothesis, we analyzed the distribution of HCV RNA at the time of diagnosis, and performed bivariate and multivariable analyses to identify demographic and clinical characteristics associated with LLV, defined as those in the lowest 3% of the distribution of HCV viral load (*i.e.*, those missed by a test with 97% clinical sensitivity).

We performed a cross-sectional analysis of initial HCV viral load data and linked demographic (age, sex, country of testing) and clinical (HIV and HBV co-infection, HCV genotype, fibrosis stage) data collected between January 1, 2007 and June 1, 2017. We included males and females of all ages with detectable quantitative HCV RNA. We excluded participants with missing age or sex demographics and those on HCV treatment. We grouped countries by WHO regions: African, Americas, Eastern Mediterranean, European, South East Asia, and Western Pacific.

Data sources

We identified potential patient cohorts for inclusion from 2 main sources: the WHO global hepatitis programme contacts database that includes implementing partners and international HCV researchers, and a PubMed literature search using the search terms “HCV RNA quantification” and “cohort study” to identify additional cohorts of people with HCV infection. Criteria for potential inclusion in this analysis were available HCV RNA quantification linked to comprehensive demographic and clinical data among populations outside of the United States. We contacted study authors and established a working group with all respondents who agreed to share data. Fig. S1 shows a flow-chart of contributing sites and countries, and Table 1 summarises characteristics of the source data, including: HCV epidemiology of the country or region of origin (prevalence, population affected, World Bank country classification), patient inclusion and exclusion criteria if from a research cohort, and reason for HCV testing.

We determined the main source of patient samples and basis for HCV testing from study protocols or direct communication with collaborators. Reasons for testing were categorised as: i) targeted among specific high-risk populations (people who inject drugs, birth cohorts, healthcare workers), or ii) clinically indicated (*i.e.* testing of those with clinical signs or symptoms or laboratory features suggestive of hepatitis), or iii) routine as part of large-scale screening programmes (*i.e.* antenatal clinics, blood donors, seroprevalence surveys). We included data from 1 large reference laboratory in a high-income setting (Canada) as a comparison to LMICs.

Data concatenation

We predefined a protocol for data concatenation. We outlined categories and associated dummy variables for all categorical variables (age, sex, country, WHO region, HCV genotype, fibrosis stage). HCV viral load measurements at each site were reported in IU/ml. Sample specifics (serum or plasma) and platform used for quantification were collected where available. We determined fibrosis stage either from transient elastography (Fibroscan®) results reported in Metavir stage, or calculated

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Table 1. Data source characteristics.

Site, Location, Region	Dates of Collection	Country HCV Epidemiology,[3,39] Economy[40]	Sample Size, Population	Testing Purpose*	Inclusion/Exclusion Criteria and Cohort Notes
Centre Pasteur, Yaoundé, Cameroon, African	2010–2016	Viraemic prevalence: 0.7% Pop. Infected: baby boomers, iatrogenic Genotype Distribution: G1 44.8%, G2 24.3%, G4 30.7% Economy: Lower-middle	4,861, Specialty clinics	Clinical	
British Columbia Center for Disease Control Hepatitis C Testers Cohort (BC-HTC), Vancouver, Canada, Americas	Jan. 2007–Dec. 2016	Viraemic prevalence: 0.6% Pop. Infected: IDU, ex-IDU, iatrogenic, unknown. Incident infections are occurring in PWID, males 2× more likely than females Genotype Distribution: G1 50.3%, G2 15.4%, G3 22.3%, G4 2.3% Economy: High	27,448, General	Reference laboratory	BC-HTC includes data for >95% of all individuals tested for HCV in the province of British Columbia. Data is collected and merged from the province public health laboratory[41]
Egyptian Liver Research Institute and Hospital, Mansoura, Egypt, Eastern Mediterranean		Viraemic prevalence: 6.3–14.7% Pop. Infected: general, iatrogenic Genotype Distribution: G1 3.8%, G3 0.8%, G4 93.1% Economy: Lower-Middle	1,063, General		
Georgia HCV Elimination Program, Tbilisi, Georgia, European	April 2015–May 2017	Viraemic prevalence: 4.2–7.7% Pop. Infected: IDU, iatrogenic transmission, 50% of prison population Genotype Distribution: G1 61%, G2 11.0%, G3 27% Economy: Lower-Middle	29,568, General	Mixed: targeted, routine, clinical	The Georgia HCV Elimination Program is a partnership between the Georgia Ministry of Health, the US Centers for Disease Control, and Gilead Sciences[42–44]
Médecins Sans Frontières (MSF), 1. Cambodia, Western Pacific 2. Mozambique, African 3. Pakistan, Eastern Mediterranean	Sept.–Dec 2016	Cambodia Viraemic prevalence: 2.3% Pop Infected: IDU, MSM, iatrogenic Genotype Distribution: G1 24.0%, G3 20.0%, G6 56.0% Economy: lower-middle Mozambique Viraemic prevalence: no data Genotype Distribution: no data Economy: low Pakistan Viraemic prevalence: 3.8–6.7% Pop. Infected: IDU, iatrogenic Genotype Distribution: G1 10.9%, G2 3.8%, G3 79%, G41.6%, G5 0.1%, G6 0.1%, Mixed 8.3% Economy: lower-middle	Cambodia: 1737, general Mozambique: 13, HIV infected Pakistan: 1293, general	Targeted	Cambodia & Mozambique: Observational cohorts. Inclusion: ≥18 years old, detectable HCV RNA, able to provide written informed consent Pakistan: Retrospective analysis of operational data. Inclusion: ≥18 years old, detectable HCV RNA
TREAT Asia, Kirby Institute Jakarta, Indonesia; Kuala Lumpur, Malaysia; Bangkok, Thailand; Hanoi, Vietnam South East Asia	Dec 2013-Jan 2015	Viraemic prevalence: Region = 0.7–1.2% Pop. Infected: IDU, MSM, iatrogenic Genotype Distribution: G1 35.2%, G2 11.1%, G3 19.9%, G4 0.9%, G5 0.4%, G6 30.8%, Mixed 1.7% Economy: Indonesia – Lower-Middle Malaysia – Upper-Middle Thailand – Upper-Middle Vietnam – Lower-Middle	413, HIV infected	Targeted	Inclusion: HIV-infected patients under care at participating sites. Detectable HCV antibody within 6 months of enrollment. Exclusion: <18 years old, CD4 count <200, Child-Pugh score >A, ascites, encephalopathy, bleeding esophageal varices, liver cancer, pregnant, breastfeeding or the male partner of a pregnant female[45]

(*continued on next page*)

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Table 1 (*continued*)

Site, Location, Region	Dates of Collection	Country HCV Epidemiology,[3,39] Economy[40]	Sample Size, Population	Testing Purpose*	Inclusion/Exclusion Criteria and Cohort Notes
Y.R. Gaitonde Centre for AIDS Research and Education, Chennai, India, South East Asia	2010–2016	Viraemic prevalence: 0.5% Pop. Infected: IDU, iatrogenic Genotype Distribution: G1 24.0%, G3 54.4%, G4 5.8%, G5 0.2%, Mixed 15.6% Economy: Lower-middle	5,476, IDU, MSM, HIV infected	Mixed: targeted and routine	Four study cohorts: 1. Respondent-driven sampling strategy used for recruitment. Inclusion: >18 years old, self-report of IDU in prior 2 years, provide informed consent, valid referral coupon.[46] 2. Inclusion: >18 years old, provide written informed consent, report IDU in prior 6 months.[47] 3. CDOT[48] 4. Inclusion: >18 years old, provide informed consent, self-reported history of IDU in prior 5 years, no intention of migrating for 2 years during study period[49]

Including site, country, World Health Organization region, dates of sample collection, country HCV epidemiology and World Bank economy classification, sample size, sample population, testing purpose* (targeted, clinical, routine, reference laboratory, mixed), and enrolment inclusion and exclusion criteria (for research cohorts).
Pop = Population; IDU = injection drug user(s); G1 = genotype 1; G2 = genotype 2; G3 = genotype 3; G4 = genotype 4; G5 = genotype 5; G6 = genotype 6; US = United States; HIV = human immunodeficiency virus; AIDS = acquired immunodeficiency syndrome.
*1) Targeted among specific high-risk populations (injection drug users, birth cohorts, healthcare workers), 2) clinical (testing of those with clinical signs or symptoms or laboratory features suggestive of hepatitis), 3) and routine from large-scale screening (antenatal clinics, blood donors, seroprevalence surveys).

from Fibrosis-4 score[25,26] as these scores correlate well with Fibroscan.[27–29] For those with a Fibrosis-4 score <1.45, we assigned Metavir stage F0-F1. For scores between 1.45 and 3.25, we assigned stage F2-F3, and scores above 3.25 we assigned to stage F4.

Statistical analysis

We employed descriptive statistics to derive the HCV viral load distribution in $\log_{10}$ IU/ml for initial HCV RNA among all patients in the combined dataset. From this distribution, we identified the LOD levels of HCV RNA in IU/ml corresponding to the 95th, 97th, and 99th percentiles, *i.e.* the level of HCV RNA below which the infection would be missed. To estimate the 95% CI for each LOD, we performed bootstrap and Markov chain Monte Carlo method[30] to randomly simulate a population of 10,000 patients from the total dataset. We then calculated the LOD at the 95th, 97th, and 99th percentiles from this sample population, and repeated the procedure 10,000 times to obtain an LOD range for each percentile. We then calculated the 95% CIs from these sample distributions.

We defined LLV as HCV RNA in the lowest 3% of the distribution, below the LOD corresponding to the 97th percentile determined above. We then calculated summary statistics for covariates of interest and tested associations between each covariate and the odds of having LLV. We used a stepwise approach to construct a multivariable logistic regression model of the odds of LLV. Covariates remained in the multiple logistic regression model when their p value was ≤0.05 and we found no substantial multicollinearity. We tested for effect modification with predefined stratified analyses: i) HIV subset analysis, ii) HBV subset analysis, iii) fibrosis stage with transient elastography data only. We also assessed the effect of varying the fibrosis classification thresholds of the Fibrosis-4 score. First, we shifted the cut-offs toward F4: scores <1.20, we assigned stage F0-F1, 1.20 to 3.0 stage F2-F3, and scores >3.0 stage F4. We then shifted the cut-offs away from F4: scores <1.60 stage F0-F1, 1.60 to 3.45 stage F2-F3, and scores >3.45 stage F4.

Next, we performed data imputation for the missing exposures of interest (HIV co-infection, HBV co-infection, HCV genotype, fibrosis stage) to create a dataset for sensitivity analyses. We employed parametric regression imputation with a prediction model to impute the missing values for fibrosis stage.[31] We utilised prevalence data specific to each country for HCV genotype, HIV and HBV co-infection, and imputed missing data for these variables within each country cohort. For example, we used the genotype distributions described in each country as the probabilities of having each genotype, we then employed Markov chain Monte Carlo techniques to stochastically assign a genotype to each individual. We used the same method adapting country and sex specific HIV and HBV prevalence data.

We then used the imputed dataset to test associations between each covariate and the odds of having LLV with bivariate and multivariable logistic regression, and compared the results with the non-imputed total population dataset. Finally, we quantitatively compared the performance of the LOD from the total population dataset among the covariates with significant associations with LLV in the imputed dataset by deriving the relative percentiles from HCV RNA distributions for subsets from each significant covariate. We used R version 1.0.136 to perform all statistical analyses.

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Results

Dataset characteristics

The dataset included 66,640 individuals with HCV viraemia from Cambodia (2.6%), Canada (40.9%), Cameroon (0.4%), Egypt (1.6%), Georgia (44.4%), India (8.1%), Indonesia (0.2%), Malaysia (0.05%), Mozambique (0.02%), Pakistan (1.3%), Thailand (0.2%), and Vietnam (0.1%) (Fig. S1). Table 1 contains data source characteristics and summarises country-level HCV prevalence data and genotype distribution.

Characteristics for the total population cohort (TPC) are presented in Table 2. Females comprised 24.4% (16,320) of participants with a median age of 48 years. Among those also tested for HIV (54.3%) and HBV (50.7%), 10.9% (3,945) were HIV co-infected, and 21.4% (7,221) were HBV co-infected. We identified the HCV genotype distribution as follows: 40.9% (27,245) genotype 1, 13.9% (9,287) genotype 2, 22.7% (15,157) genotype 3, 3.0% (2,030) genotype 4, <1% (13) genotype 5, 1.3% (889) genotype 6, <1% (170) with mixed genotype, and 17.8% (11,849) with

Table 2. Characteristics of 66,640 participants in a combined cross-sectional dataset.

Variable	Total cohort N (Col%)	Low-level viraemia* n (Row%)	OR (95% CI)	aOR[1] (95% CI)
Age				
<18	75 (0.1)	4 (5.3)	2.39 (0.73–5.79)	1.73 (0.52–4.22)
18–30	5,883 (8.8)	396 (6.7)	**3.06 (2.68–3.49)**	**2.56 (2.19–2.99)**
31–50	31,724 (47.6)	962 (3.0)	**1.33 (1.19–1.48)**	**1.30 (1.16–1.45)**
51–64	24,173 (36.3)	556 (2.3)	Ref	Ref
≥65	4,785 (7.2)	84 (1.8)	**0.76 (0.60–0.95)**	**0.75 (0.59–0.94)**
Sex				
Female	16,320 (24.4)	526 (3.2)	1.1 (1.00–1.22)	**1.32 (1.18–1.49)**
Male	50,320 (75.5)	1,476 (2.9)	Ref	Ref
Country				
Cambodia	1,730 (2.6)	34 (1.9)	**0.66 (0.46–0.92)**	
Cameroon	293 (0.4)	3 (1.0)	**0.34 (0.08–0.89)**	
Canada	27,277 (40.9)	805 (3.0)	Ref	
Egypt	1,063 (1.6)	5 (0.5)	**0.16 (0.06–0.34)**	
Georgia	29,569 (44.4)	780 (2.6)	**0.89 (0.81–0.98)**	
India	5,430 (8.1)	360 (6.6)	**2.33 (2.05–2.65)**	
Indonesia	141 (0.2)	2 (1.4)	0.47 (0.08–1.49)	
Malaysia	34 (0.05)	1 (2.9)	1.51 (0.08–7.35)	
Mozambique	13 (0.02)	1 (7.7)	4.16 (0.23–22.02)	
Pakistan	854 (1.3)	11 (1.3)	**0.43 (0.22–0.74)**	
Thailand	142 (0.2)	1 (0.7)	0.23 (0.01–1.04)	
Vietnam	94 (0.1)	1 (1.1)	0.35 (0.02–1.59)	
WHO Region				
African	306 (0.5)	3 (1.0)	**0.33 (0.08–0.85)**	**0.21 (0.05–0.65)**
Americas	27,277 (40.9)	805 (3.1)	Ref	Ref
E. Mediterranean	1,917 (2.9)	16 (0.8)	**0.28 (0.16–0.44)**	**0.05 (0.02–0.09)**
European	29,569 (44.4)	780 (2.6)	**0.89 (0.81–0.98)**	**0.13 (0.07–0.27)**
S.E. Asia	5,841 (8.8)	364 (6.2)	**2.19 (1.92–2.48)**	**0.66 (0.54–0.81)**
W. Pacific	1,730 (2.6)	34 (1.9)	**0.66 (0.46–0.92)**	**0.21 (0.12–0.36)**
HIV				
Co-infected	3,945 (5.9)	191 (4.8)	**1.57 (1.34–1.84)**	1.01 (0.83–1.21)
Negative	32,253 (48.4)	1,012 (3.1)	Ref	Ref
Missing data	30,442 (45.7)	799 (2.6)	NA	NA
HBV				
Co-infected	7,221 (10.8)	214 (3.0)	**1.08 (0.92–1.25)**	1.14 (0.97–1.34)
Negative	26,579 (39.9)	734 (2.8)	Ref	Ref
Missing data	32,840 (49.3)	1,054 (3.2)	NA	NA
HCV Genotype				
Genotype 1	27,245 (40.9)	623 (2.3)	Ref	Ref
Genotype 2	9,287 (13.9)	261 (2.8)	**1.24 (1.07–1.43)**	**1.25 (1.07–1.45)**
Genotype 3	15,157 (22.7)	405 (2.7)	**1.17 (1.03–1.33)**	**1.17 (1.03–1.34)**
Genotype 4	2,030 (3.0)	28 (1.4)	**0.59 (0.39–0.86)**	1.14 (0.75–1.67)
Genotype 5	13 (0.02)	1 (7.7)	3.55 (0.19–18.08)	4.22 (0.05–17.15)
Genotype 6	889 (1.3)	12 (1.3)	**0.58 (0.31–0.99)**	0.61 (0.31–1.12)
Mixed	170 (0.3)	4 (2.4)	1.03 (0.32–2.44)	0.97 (0.29–2.3)
Missing	11,849 (17.8)	669 (5.6)	NA	NA
Fibrosis stage				
F0-F1	12,460 (18.7)	313 (2.5)	Ref	Ref
F2-F3	11,923 (17.8)	242 (2.0)	**0.80 (0.68–0.95)**	0.89 (0.76–1.07)
F4	8,366 (12.5)	239 (2.9)	1.14 (0.96–1.35)	**1.43 (1.19–1.70)**
Missing	33,891 (50.9)	1,115 (3.4)	NA	NA

Data from patients with chronic HCV in Cambodia, Canada, Cameroon, Egypt, Georgia, India, Indonesia, Malaysia, Mozambique, Pakistan, Thailand, and Vietnam. The association of covariates with low-level viraemia, HCV RNA <1,318 IU/ml, is indicated by the bivariate ORs and aORs with 95% CI – statistically significant OR are in bold font. Col%, column percent; Row%, row percent; Ref, reference group; OR, odds ratio; aOR, adjusted OR; NA, not applicable; WHO, World Health Organization, E., eastern; S.E., South East; W., western; HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus.

*Low-level viraemia = HCV RNA <1,318 IU/ml.

[1]aOR derived from a multivariable model adjusting for age, sex, country, HCV genotype, and fibrosis stage.

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missing genotype data. We categorised 12,880 (38.1%) individuals as Metavir fibrosis stage F0-F1, 12,242 (36.3%) as F2-F3, and 8,644 (25.6%) as F4 among the 33,766 individuals with available fibrosis staging data (Fibroscan or Fibrosis-4 score).

HCV viral load distribution & limit of detection analyses

The HCV RNA (log_{10} IU/ml) frequency distribution is depicted in Fig. 1. We derived the LOD for the 95th, 97th and 99th percentiles as: 3,311 IU/ml (95% CI 3,256.3–3,368.0), 1,318 IU/ml (95% CI 1,298.4–1,322.3), and 214 IU/ml (95% CI 207.1–218.6) respectively. We further visualised the HCV RNA distribution to compare the mean HCV RNA for each covariate with violin plots (Fig. 2). Violin plots depict a box plot where a circle denotes the median and the interquartile range is shown by a box in solid black. Overlaid on this box plot is a kernel density plot indicating more data where the plot is thicker and less where it narrows. We then derived violin plots for each country to illustrate the viral load distribution by site as a surrogate approach to control for variation in quantification platforms and sampling techniques (Fig. S2). The mean RNA lies between 5 and 6 log IU/ml in all cohorts.

Identification of subgroups with low-level viraemia

We derived the odds of association with LLV for each covariate with the following groups selected as a reference because each contained the largest volume from the reference laboratory dataset in Canada: 51–64 years of age, male sex, Canada, Americas, genotype 1. Bivariate analyses indicated increased odds of LLV <1,318 IU/ml for those aged 18–30 and 31–50 years, participants from India, the South East Asian region, and those with HIV co-infection or genotype 2 and 3 infection (Table 2). The OR was highest between those aged 18–30 years and the reference group aged 51–64 years, at 3.06 (95% CI 2.68–3.49). India had an OR of 2.33 (95% CI 2.05–2.65) compared to Canada. South East Asia had an OR of 2.19 (95% CI 1.92–2.48) compared to the Americas. HIV co-infected persons had an OR for LLV of 1.57 (95% CI 1.34–1.84) compared to those without HIV. Lastly, genotype 2 had an OR of 1.24 (95% CI 1.07–1.43) and genotype 3 OR 1.17 (95% CI 1.03–1.33) compared to genotype 1.

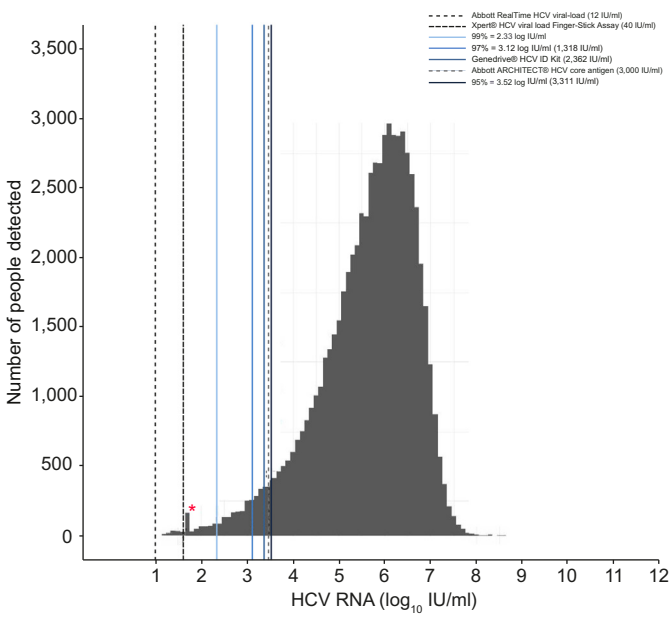

Fig. 1. Frequency distribution of HCV RNA (log_{10} IU/ml) among participants in a combined cross-sectional dataset. Data from patients with chronic HCV in Cambodia, Canada, Cameroon, Egypt, Georgia, India, Indonesia, Malaysia, Mozambique, Pakistan, Thailand, and Vietnam. The analytic level of detection for: a) centralized NAT Xpert® HCV Viral Load (40 IU/ml) and Abbott RealTime HCV Viral load (12 IU/ml), b) point-of-care NAT Genedrive® HCV ID Kit (2,362 IU/ml) and c) Abbott ARCHITECT HCV core antigen (HCVcAg) test (in IU/ml; 3,000 IU/ml approximately equivalent to 3 fmol/L) are marked in comparison to the LOD derived for the 99th, 97th, and 95th percentiles in the dataset. *Marks the lower LOD for tests performed in India that were detected but not quantified. HCV, hepatitis C virus; LOD, limit of detection; NAT, nucleic acid test.

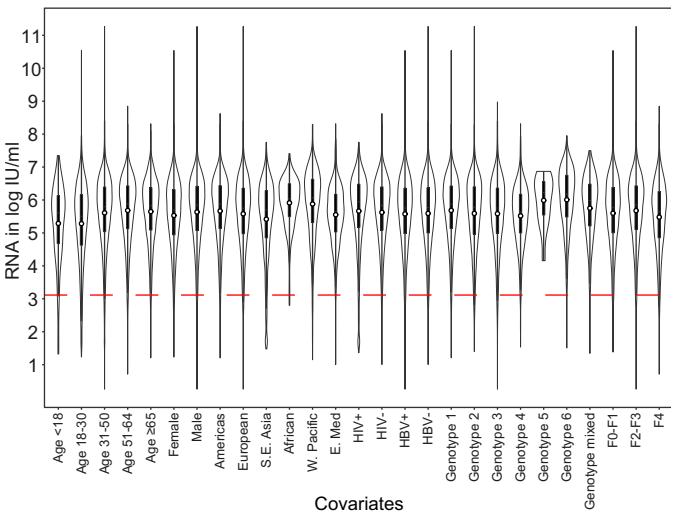

Fig. 2. Violin plot of the HCV RNA distribution (log_{10} IU/ml) for each covariate in the total population cohort. In each violin plot, a circle denotes the median and the interquartile range is shown by box in solid black. Overlaid on this box plot is a kernel density plot indicating more data where the plot is thicker and less where it narrows. The dashed horizontal marker indicates the 1,318 IU/ml level of detection derived from the HCV RNA frequency distribution. HCV, hepatitis C virus.

In a multivariable model controlling for age, sex, WHO Region, HIV and HBV co-infections, genotype, and fibrosis stage, the 18–30-year age group, female sex, genotypes 2 and 3, and fibrosis stage F4 remained associated with increased odds for LLV (Table 2). Persons 18–30 years of age had an adjusted OR (aOR) of 2.56 (95% 2.19–2.99) compared to the 51–64-year-old age group. For female sex, the aOR was 1.32 (95% CI 1.18–1.49) compared to males. The aORs for genotype 2 and 3 compared to genotype 1 were 1.24 and 1.17, respectively. Lastly, for advanced fibrosis stage F4, the aOR increased to 1.44 (95% CI 1.21–1.69) compared to stage F0-1. We did not detect significant interactions between: i) sex and fibrosis stage, ii) genotype and country, iii) genotype and sex, iv) genotype and age group.

Stratified and sensitivity analyses

Stratified analyses for HIV and HBV co-infection did not suggest an effect measure modification for either covariate (Tables S2 and S3). A subset analysis of those with Fibroscan results did not differ from that of the total dataset population (Table S4). Similarly, sensitivity analyses varying the cut-off thresholds for fibrosis stage classification by Fibrosis-4 scores did not impact the associations found for fibrosis stage and LLV (data not shown).

Characteristics for the cohort after missing data imputation for HIV, HBV, genotype, and fibrosis stage are presented in Table S5. Now 6.3% (4,169) are classified as HIV-coinfected (compared to 5.9% in the TPC and 10.9% among those tested,

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Table 2), and 12.2% (8,161) as HBV co-infected (10.8% in TPC, 21.4% among those tested). The genotype distribution was similar to the TPC. Fibrosis stage categories were also similar to those with data in the TPC. In the imputation regression analyses, significant associations with LLV remained after multivariable adjustment for: groups aged 18–30 (aOR 2.44) and 31–50 (aOR 1.29) years, female sex (aOR 1.31), participants from South East Asia (aOR 1.59), and fibrosis stage F4 (aOR 1.14) (Table S5). The increased odds among HIV co-infection, and HCV genotypes 2 and 3 in the TPC attenuated in the imputed dataset.

Relative percentiles for significant covariates

While an HCV RNA of 1,318 IU/ml correlated to the 97th percentile in the total population dataset, the relative percentiles corresponding to the 1,318 IU/ml LOD for significant covariates were: 93% for age group 18–30, 96.7% for females, 93.8% for participants from South East Asia, 95.3% for HIV co-infected, and 96.8% for fibrosis stage F4 (Fig. 3A). Though genotypes 2 and 3 had increased odds for LLV, the relative percentiles remained >97%. All percentiles were similar in the imputed dataset sensitivity analyses (Fig. 3B).

Discussion

This dataset of 66,640 individuals from 12 countries representative of 6 global regions represents the largest and most comprehensive dataset assembled to address the issue of clinical sensitivity of different LODs for detection of HCV viraemia. Our data confirm that with an LOD of 1,318 IU/ml (3.12 log IU/ml), 97% of viraemic HCV infections would be identified. These data further support the recent European Association for the Study of the Liver recommendation for an LOD of 1,000 IU/ml among diagnostic nucleic acid assays for use in LMICs.[32] While several covariates were associated with increased odds for LLV below 1,318 IU/ml, we report a relative sensitivity below 95% only for the 18–30-year age group (93.6% sensitivity) and among participants in South East Asia (93.8% sensitivity); genotypes 2 and 3 were associated with LLV but the relative sensitivity remained >97%. The prevalence of LLV among the 18–30-year age group in this study may reflect fluctuating viraemia that occurs with early HCV infection.[33,34] Of note, many of the participants from sites in South East Asia were active injection drug users and may also have had early HCV infection. We have insufficient data in the TPC to conduct a subset analysis of people who inject drugs.

Our findings differ from previous studies that evaluated HCV viral load quantification as many were designed to evaluate predictors of high-level viraemia; however, the degree of LLV we describe is similar to an evaluation of 2,472 people with genotype 1 infection.[35] Another study of 148 people with HCV infection found lower levels of circulating HCV RNA among those with decompensated cirrhosis.[36] We captured a trend toward LLV, but this was not sufficient to alter the relative sensitivity of the LOD in this sub-population. From the available data, we could not identify those who had decompensated cirrhosis within the F4 stage. Therefore, the OR may be slightly diminished by the number of participants with compensated cirrhosis in this group who still have abundant healthy hepatocytes that allow for HCV replication. Prior studies reported higher HCV RNA levels among those with HIV.[37,38] In contrast, our data suggest increased odds for LLV among those with HIV co-infection and a decrease in the sensitivity of the LOD to 95.2%. Data on

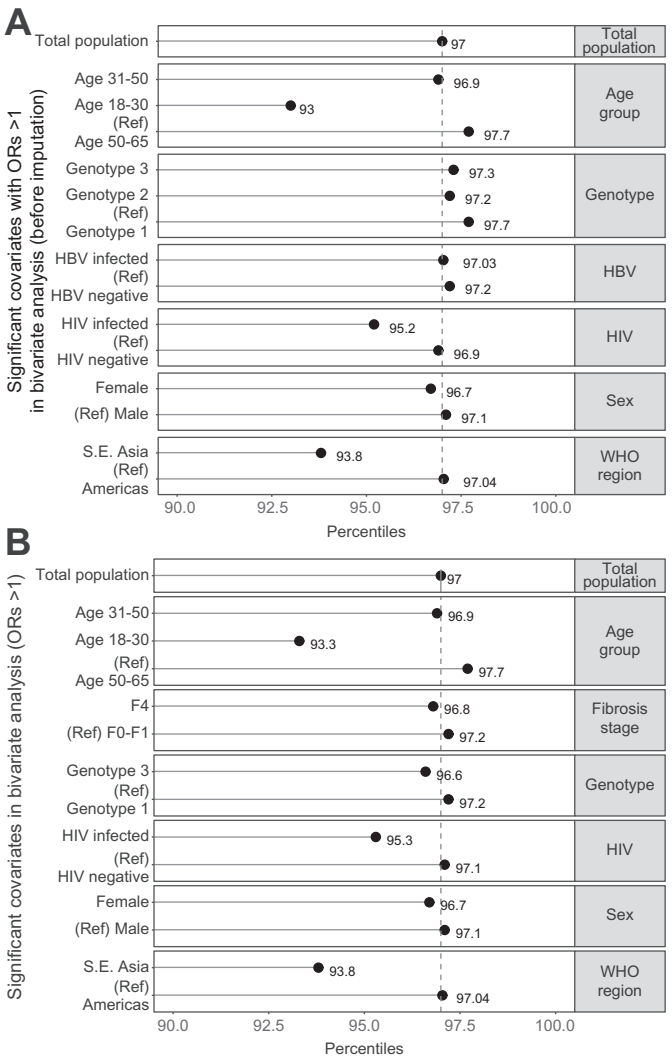

Fig. 3. Graph of relative percentiles of HCV viraemia corresponding with the limit of detection derived from the total population dataset (1,318 IU/ml). For covariates significantly associated with low-level viraemia in the (A) total population dataset and (B) imputed dataset. The reference (ref) groups are included for each category. The dashed vertical line marks the 97th percentile from the total population dataset. HCV, hepatitis C virus.

use of antiretroviral therapy and level of viral load suppression were not available from all data sources, and therefore the level of HCV viral load among those with advanced stage HIV either not receiving or failing on therapy, could not be compared to those with well-controlled HIV infection on effective antiretroviral therapy. Lastly, these studies were designed to investigate outcomes or treatment predictors and had much smaller sample sizes that limit their power to evaluate the LLV frequency.

The main strengths of this study are the large sample size powered to investigate covariates of interest and the wide representation of different geographic regions and genotypes. Regions with high HCV prevalence (Egypt, Georgia) were well represented as well as lower prevalence settings (Cameroon).

There are several limitations to this study. Identified and included patient cohorts were those with available HCV RNA linked with clinical and demographic data and therefore may not be generalisable. We conducted a secondary analysis of data from populations that were tested for HCV for a range of reasons. There were also different methods for data collection at

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each site. While some data represent a broad sample of tests performed in the general population at a reference laboratory, other data were collected as part of research protocols with strict inclusion and exclusion criteria. There were missing data for several covariates (HIV and HBV co-infection, HCV genotype, fibrosis stage) in 20–52% of the participants. We performed sensitivity analyses including a comparative regression model using imputed data to better characterise bias introduced by missing data and found the introduced bias to be limited overall.

This study investigated the viral load distribution among those with chronic HCV infection from 12 countries in different geographic regions to estimate the requisite clinical sensitivity of a POC test for HCV diagnosis and inform sub-populations that may be at risk of false negative testing. Our findings suggest that a test with an LOD of 1,318 IU/ml, which is about 100 times higher (less sensitive) than the current gold-standard NATs, will likely detect 97% of viraemic HCV infections. While an increase in LOD may not impact cost and development of near-patient molecular technologies, it sets an achievable LOD for immunoassays such as those that involve HCV core antigen detection. Comparative and cost-effectiveness analyses will be needed to investigate settings that may benefit the most, and to quantify how a less sensitive test might impact the diagnosis, treatment and cure cascade in LMICs. A product specification that allows for an LOD of 1,318 IU/ml could facilitate development of an affordable non-molecular POC test that could dramatically increase rates of HCV testing and treatment initiation in LMICs, thus substantially impacting health outcomes for chronic HCV infection on a population-level.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Concept and design: Freiman, Wang, Easterbrook, Horsburgh, Marinucci, White, Denkinger, Linas. Data collection and procedures: Freiman, Kamkamidze, Krajden, Loarec, Njouom, Nguyen, Shiha, Soliman, Tsertsvadze, Wang, White. Writing of article: Dr. Freiman is the first author with Drs. Denkinger and Linas contributing equally as senior authors. All authors contributed to the preparation of the manuscript.

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Supplementary data

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The global campaign to eliminate HBV and HCV infection: International Viral Hepatitis Elimination Meeting and core indicators for development towards the 2030 elimination goals

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Abstract

Hepatitis B virus (HBV) and hepatitis C virus (HCV) affect more than 320 million people worldwide, which is more than HIV, tuberculosis (TB) and malaria combined. Elimination of HBV and HCV will, therefore, produce substantial public health and economic benefits and, most importantly, the prevention of 1.2 million deaths per year. In 2016, member states of the World Health Assembly unanimously adopted a resolution declaring that viral hepatitis should be eliminated by 2030. Currently, few countries have elimination programmes in place and even though the tools to achieve elimination are available, the right resources, commitments and allocations are lacking. During the fifth International Viral Hepatitis Elimination Meeting (IVHEM), 7–8 December 2018, Amsterdam, the Netherlands, an expert panel of clinicians, virologists and public health specialists discussed the current status of viral hepatitis elimination programmes across multiple countries, challenges in achieving elimination and the core indicators for monitoring progress, approaches that have failed and successful elimination plans.

Keywords: hepatitis C virus, elimination, World Health Organization, hepatitis B virus, viral hepatitis

Introduction

Hepatitis B virus (HBV) and hepatitis C virus (HCV) affect more than 320 million people worldwide, which is more than HIV, tuberculosis (TB) and malaria combined [1,2]. Elimination of HBV and HCV will, therefore, produce substantial health and economic benefits and, most importantly, the prevention of over 1.2 million deaths annually [1].

In 2016, the World Health Assembly (WHA) unanimously adopted the resolution that viral hepatitis should be eliminated by 2030. In addition, the World Health Organization (WHO) published the Global Health Sector Strategy on hepatitis to reach this goal [1]. The International Task Force for Disease Eradication (ITFDE) adapted and endorsed the elimination goals of WHO, and HBV and HCV infections are recognised as feasible targets for elimination. In addition, WHO established a framework to guide implementation of the key interventions at a national level to achieve the global elimination goals. At the start of the elimination era for viral hepatitis, few countries are on track to meet the 2030 elimination goals. Moreover, in 2017, only 28% and 48% of countries are reported to have elimination plans in place for HBV and HCV, respectively [3,4].

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HBV and HCV infection meet accepted criteria for disease elimination. However, appropriate resources, commitment and allocation are currently lacking. If the right parties work together, including governments, international organisations, the private sector and civil society, great success can be achieved. Modelling studies have indicated that if core interventions are implemented with sufficient service coverage, elimination could be accomplished. This will require collecting strategic information, planning of programmes with involvement of all stakeholders, engaging civil society, arranging financial support and implementing appropriate strategies for target populations [5]. Key for the viral hepatitis response is to be integrated within countries' efforts to achieve universal health coverage as part of the 2030 Sustainable Development Goals.

During the fifth International Viral Hepatitis Elimination Meeting (IVHEM), 7–8 December 2018, Amsterdam, the Netherlands, an expert panel of clinicians, virologists and public health specialists discussed what progress is needed to achieve elimination, what major challenges are still to be faced and, in addition, the core indicators for monitoring progress. IVHEM brought together current or proposed HBV and HCV prevention and elimination programmes to share local experiences in planning and implementation of the key interventions recommended by WHO. Through information sharing, the goals of the meeting were to help programmes improve performance and guide development of new elimination programmes.

The investment challenges

A major barrier towards elimination is the lack of funding. Viral hepatitis is significantly underfunded compared to HIV, TB and malaria. Currently, there is no significant support from the Global Fund, PEPFAR, the Gates Foundation or other similar international funders outside of the setting of HIV co-infection. Without some support from these, or similar organisations it is unlikely that the 2030 elimination targets will be achieved [4].

Several reasons have been postulated as to the lack of funding for viral hepatitis. First, there is limited knowledge about the high cost of the viral hepatitis epidemic that will continue to grow in future years if current trends in testing and treatment continue. Reaching the 2030 elimination targets by increasing testing and treatment can, however, stop these increasing costs. In fact, achieving viral hepatitis elimination will produce a positive return on investment by 2028 from savings due to the removal of indirect cost associated with viral hepatitis [4]. Additionally, some countries are likely to obtain an even greater health benefit with their current investment. Egypt for instance is currently undertaking massive screening programmes for HCV, but has built into this screening for multiple diseases including HBV, obesity, diabetes and hypertension. In the first 20 days in October, over 4 million people were screened with 140,000 HCV cases detected; as well as more than 1 million cases of obesity and 20,000 diabetic patients were identified.

A second likely reason for the lack of investment is that, viral hepatitis infects many minorities who are often highly vulnerable and underrepresented at a political level. Due to their vulnerability these groups are often not in position to advocate for support and funding. HIV is an example where involvement of civil society drove the HIV movement and resulted in awareness, political support and funding. Work needs to be done to support civil society and community organisations to be engaged and advocating for funding. Only with enough community advocacy will the political leadership start to support the matter and the pledge for a global fund can begin.

Whilst the viral hepatitis response would benefit from the support of international funding organisations, it is key that individual countries take responsibility for supporting the investment in elimination. China is a good example. Sustainable HBV programmes were established with support from private partnerships and leadership [4]. GAVI was one of the organisations that supported universal hepatitis B immunisation of infants in China. In addition, organisations such as GAVI, which recently announced prioritised investment in HBV birth-dose vaccines, can make a tremendous difference with raising awareness particularly through immunisation campaigns, especially in low- and middle-income countries. Georgia's HCV response is another example where a strong government leadership, combined with private investment from Gilead Sciences and technical support from the US Centers for Disease Control and Prevention and FIND/Unitaid led to successes.

The lack of national and international investment in viral hepatitis programmes, especially in low- and middle-income countries, means that national hepatitis programmes are underfunded. As a result, testing programmes are hampered and only small numbers of individuals therefore have access to treatment [6]. In order to establish a strong hepatitis response and strengthen healthcare systems, especially in low- and middle-income countries, financial support is needed to lay the groundwork for elimination by providing essential research and support [6].

Strategic information of successful countries on track towards the elimination goals

There are several countries that have developed elimination plans [3,4]. One of the most successful countries is Egypt, where many are already cured, and mass testing programmes are identifying the millions of individuals who are unaware of their infection [7]. Not only adults are included in these programmes: Egypt is also including children and adolescents. By testing and treating the young population, parents are also engaged in testing. In addition, adolescents tend to strengthen the community by raising awareness and advocacy. During the testing programme, stigma in schools or when parents where asked for consent for testing of their child has been identified. By working together with organisations such as the national mother and child organisation, knowledge is gained regarding the protection of children from discrimination and stigma. This approach can be an example for other countries, since worldwide over 11 million children (under the age of 15) have HCV infection [8].

Georgia is another country that has successes in eliminating viral hepatitis. There is a high prevalence of HCV infection (5.4% of adults have HCV) [9]. Since 2015, an HCV elimination programme has been in place, based on six main principles: (1) advocacy, awareness and education, and partnerships for HCV-associated resources; (2) HCV transmission reduction; (3) identification of those with HCV; (4) HCV laboratory diagnostics; (5) HCV care and treatment; and (6) HCV surveillance. The programme receives funding from the Global Fund, and is constantly evolving to meet the beneficiaries' needs. Georgia uses an integrated approach by combining testing protocols and care for HIV, TB and HCV. By integrating viral hepatitis care into existing platforms, costs are reduced. To improve coverage and maximise the number of the target population, Georgia decentralises HCV-related services. This improves accessibility for persons living in rural areas. In addition, primary healthcare workers and non-specialised settings near patients' homes are involved in the management of uncomplicated HCV cases.

Iceland is also leading in elimination and, according to mathematical models, could potentially reach the WHO elimination targets by 2020 [10]. A nationwide programme has been established, Treatment as Prevention for Hepatitis C (TraP HepC), where universal access to direct-acting antivirals (DAAs) is combined with intensified screening and harm-reduction efforts. One central virology laboratory serves the entire country and reports all new HCV infections directly to a national HCV registry. Emphasis is on early case finding and treatment of high-risk groups such as persons who inject drugs (PWID) and prisoners, as well as patients with advanced liver disease. Using the treatment-as-prevention (TasP) approach, previously described as a good tool for HIV prevention and described as effective for HCV, the aim is to not only offer a cure to patients but also to reduce the domestic HCV incidence by 80% prior to the WHO elimination goals for 2030 [11–13]. The programme has already resulted in a major decrease of HCV prevalence among key risk groups such as PWID and prisoners.

In Athens (Greece), a fast-track intervention to seek-test-link-treat PWIDs has been established, based on a programme established during an outbreak of HIV among persons who inject drugs [14,15]. Athens accounts for 8700 high-risk drug users, of whom 2450 had actively injected in the past 30 days [16]. Harm-reduction programmes with opioid substitution therapy (OST) and needle syringe programmes (NSP) are in place, but waiting times are long. In addition, DAAs have been available without restriction since September 2018. However, they are only accessed by a small percentage of PWIDs. The current programme is used

to increase diagnosis and treatment for HCV and HIV infection among PWIDs. Chain-referral sampling is used to bring individuals into care (a single individual from a target population is invited and requested to invite three other recruits from their network) [17]. A combination of rapid identification, fibroscans and biochemical testing are used in a single visit to avoid losing individuals in the care cascade (Table 1). Specially trained clinicians visit the study site, to improve linkage to care. In addition, PWIDs are assigned a peer-navigator, who accompanies them to their first liver or infectious diseases clinic appointment. Similarly to Iceland, a national HCV treatment registry is used to monitor progress and to improve linkage to care.

In the United States the Veterans Administration (VA) uses Lean as a strategic methodology to improve HCV care (Table 1). Lean is a business methodology that promotes the flow of value (care) to the customer (patient), through continuous improvement, and increases access to information to ensure responsible decision-making. Currently, 8.9 million veterans receive VA care, and the VA leadership has identified HCV as a priority. 'Hepatitis Innovation

Table 1. The challenges, failures, lessons learned and solutions from different countries in efforts to eliminate viral hepatitis

Country	Challenge and/or failures	Solutions and lessons learned
Egypt	High HCV prevalence, treated all patients and screening programmes were running behind, cost of diagnosis, number of PCR tests was a bottleneck	• Before 2014: established data networking centre and political will to eliminate HCV. Since, 2016 pledge from the president to eliminate HCV [7] • National plan since 2014 including HCV treatment centres • Generic DAAs • Decentralising the screening project by using mobile units and different testing sites • Negotiated for a lower PCR price given number fo tests required • Loan from the World Bank and private sector cooperation • Companies helped to develop dried blood spot test • Simplify the monitoring strategy
Georgia	High HCV prevalence, need to identify the missing millions, reaching the younger population, cost, linkage to care	• Integrated hepatitis care into HIV, TB and malaria care • Scaling-up advocacy for hepatitis, HIV and TB • Decentralisation of healthcare (screening and treatment) using primary healthcare • Massive screening programmes, focusing on affected age group of males (30–60 years) and high-risk groups • Universal screening in harm-reduction networks • Used medical university students as extra help in these harm-reduction networks • When elimination was feasible the authorities were on board • Strengthen the healthcare system through the support of Global Fund • More enrolment of public health specialists for linkage-to-care process
Australia	Reaching the younger population, decline in number of people accessing treatment [18]	• Decentralising care and bringing care to the community where patients access services (community care/primary care) [19] • Point-of-care test in needle and syringe programmes (RAPID-EC) • Increase awareness about new HCV treatments • Increase coordination between services, for example community and prisons • Support enhanced data management
France	Prioritisation of treatment, high drug cost, high HCV prevalence and HCV transmission among PWIDs [20]	• Established mathematical models to gain further insight into the best treatment strategies and harm-reduction programmes [21–23] • Price negotiations allowing the significant decrease in drug costs
United States	High HCV prevalence, optimising HCV in the VA	• System redesign using LEAN methodology [26,27]
Netherlands	Linkage to care of the high-risk group, retention in care	• Involving target group in establishing linkage-to-care strategies • Using affected community in building online and offline information platform [28] • Development of play-safe chemsex toolkit
Canada	Projects stalled due to constant data gathering required by health authorities, screening programmes were successful but the labs could not process the numbers	• Not everything has to be perfect • Negotiating is power, important to get all the major players in the room. The leadership must push the agenda forward; in addition, the industry must also understand the needs and can support the gaps in care
Myanmar	Low general awareness and in key populations, rural areas hard to reach, low vaccine coverage	• Aiming for high advocacy by increasing the political will • Decentralisation of healthcare
Rwanda	Receiving funding	• Government acknowledged viral hepatitis as a major health problem and sought funding • Strengthening of the programme by the Global Fund
Greece	Small numbers of PWIDs accessed care, waiting lists for harm-reduction programmes are long	• Established a fast-track intervention to seek-test-link-treat PWIDs [14,15] • Used previous HIV programmes as an example • Chain-referral sampling to engage individuals into care [17] • Rapid identification, fibroscans and biochemical testing all in a single visit • Peer-navigators to improve linkage to care
Iceland	Some actively injecting drug users remain difficult to engage in treatment and maintain on treatment; visitors from abroad, such as asylum seekers and foreign prisoners with pre-existing chronic HCV infections; patients at an increased risk of infection and re-infection (MSM, persons sharing needles)	• Incentives (including financial) for difficult patients. Adherence support • Screening of immigrants and asylum seekers. Collaboration with the chief epidemiologist and immigration authorities. • Scale-up of HCV testing and harm-reduction efforts, including increased access to needles and syringes (NSP)

Box 1. Essential components of HCV elimination programmes

- Data are used to assess HCV disease burden and health system capacity
- Plan of action with time limited numerical targets
- Civic and political support for implementing partners and target populations
- Capacity to deliver appropriate interventions to target populations
- Sustainable models for financing programmes
- Integration of services in existing health systems
- Strategic data to monitor programme performance and progress towards elimination goals
- Participation in operational research

Teams' (HIT) were installed at each hospital, comprising doctors, pharmacists, nurse practitioners, physician assistants, research nurses, clerks and system redesign personnel. Their aim is to improve HCV care by redesigning care and the delivery processes with the lean methodology, which makes it feasible to measure improvements in variability, access, quality of HCV care and problems with HCV screening. Each year, the HIT leadership teams set national goals for HCV testing rates and treatment rates. In addition, they have constructed HCV dashboards, where providers have clear 'real-time' access to patient data. Moreover, HITs established different testing interventions such as: clinical reminders; reflex HCV-RNA testing; performance indicators for healthcare executives; and multimedia marketing. Special programmes are focused on at-risk groups by educating and partnering with mental health and substance use treatment providers and homeless stand-downs. Challenges are that many of the remaining untreated patients have barriers to receiving treatment, such as homelessness, substance use, refusal of treatment, other co-morbidities (e.g. cancer), or do not use VA services at this time.

Gaps in the treatment cascade

Finding the missing millions

Care-cascade analysis is an essential evaluation tool for the challenges on the way to cure. The cascade of care for HBV and HCV showed that one of the major difficulties on the road to elimination is finding the missing millions affected by the illnesses. While Egypt was very successful in treating all known individuals with HBV and HCV, there were many who were undiagnosed and massive testing programmes were needed to identify the missing millions [7]. With major support from the president, successful negotiations with several companies saw reduced prices for *in vitro* diagnosis tests. By simplifying diagnostics and the costs of follow-up programmes, the cost for each case of HCV elimination declined. Subsequently, the lack of polymerase chain reaction machines created the next bottle neck, limiting the number of specimens that could be tested. To solve the capacity problem, a change to diagnosis and screening using point-of-care tests was made. This allowed decentralised testing using mobile units and local testing sites, tackling the issue region by region rather the whole country at once.

In Rwanda, there is a strong political will to eliminate hepatitis, due to the higher mortality from viral hepatitis than from HIV. The Rwandan government supported hepatitis elimination programmes by allocating $9 million and obtained support from the Global Fund. HBV and HCV prevalence is estimated to vary around 3.1–4.5% and 4.6–8.9%, respectively (total population of 12 million) [29]. HIV programmes form a successful model for service delivery and platforms for testing (viral load and genotyping). Therefore, hepatitis screening services have been successfully integrated into existing HIV care. In addition, DAAs are freely available. In Rwanda, 280,000 individuals were tested, 9000 patients were treated, and television and radio were used to target individuals aged 45 and older for hepatitis testing to reach the missing millions.

One major barrier in finding the missing millions is the lack of awareness of viral hepatitis. Globally, 9-out-of-10 individuals are unaware of their infection status, as most have no well-defined symptoms and many do not classify themselves as belonging to at-risk groups [1]. In addition, millions of people have been, and continue to be, infected, accidentally and unnoticed, by unscreened blood transfusions and unsterilised equipment [30]. Although certain countries have established massive testing programmes, there is still limited experience on how to engage with large numbers of undiagnosed individuals, and it is likely to vary between countries and regions depending on which risk behaviours are driving the epidemic.

A good insight into country-specific epidemics is essential as a baseline for the development of testing approaches. The HCV epidemic in Canada, for instance, is concentrated around birth cohorts and most people are unaware of their risk. Targeted testing in birth cohorts, therefore, would be a perfect strategy, although this would be an insufficient strategy in Egypt, where HCV exists among the whole population. Solely testing the birth cohort results in many undiagnosed infections, so screening programmes should be implemented more widely. By contrast, in Australia, former and current PWIDs are aware of their infection but unaware of the availability of curative DAAs. This does not require a testing programme but linkage to care. Mathematical models can help to identify the most cost-effective testing strategy [23].

Improving linkage to care

Linkage to care is crucial and an important precursor to retention. Cascade analysis with recent data is fundamental to improve linkage to care. As an example, in African countries, cascade analysis pointed to a more pronounced treatment gap compared to other regions [1,10,31]. A common reason for delaying health services among people living with HIV/AIDS was 'medical pluralism', the use of multiple health systems including traditional healers in sub-Saharan Africa [32,33]. Many lessons can be learned from HIV care, which can be used in determining viral hepatitis linkage-to-care programmes. In particular, viral hepatitis testing can be integrated into the already existing delivery models for HIV and primary care.

Several minorities also face linkage-to-care issues, often due to stigmatisation and low political commitment. This results in limited service penetration and a lack of engagement of healthcare providers. In the UK for example, homeless persons, are estimated to be 50 times more likely to have chronic HCV infection, but only 3% receive treatment [34]. PWIDs also have difficulties in finding health care, which is a significant barrier in linkage to care. There is also a lack of specialised services and programmes for younger people who would particularly benefit from earlier treatment and care. Currently, only Egypt has a testing and treatment programme for adolescents, and more countries should advocate for treatment programmes among this age group. Calling attention to marginalised populations is appropriate since HBV and HCV are often the result of poor healthcare and a problem for civil society as a whole. Public education can build awareness of the burden of disease and linkage to liver cancer to promote greater advocacy by civil society to call on political leaders to commit national resources to HCV and HBV elimination.

In the Netherlands, linkage to care for high-risk groups was one of the major challenges (Table 1) and the community generated

innovative ideas. New HCV infections are concentrated among men who have sex with men (MSM) [35,36] while new cases of HCV among PWIDs are very low: in 2016 there were 44 cases in MSM with fewer than five associated with injection drug use [37]. Since 2015, DAAs have become available without restriction, which resulted in a decline in incidence of 70% among MSM [11,38]. However, re-infections are still high and predominantly related to the involvement of MSM in high-risk sexual activities (including chemsex). MSM are, therefore, the key group for interventions. Currently, innovative harm-reduction strategies are used in close collaboration with the community to achieve HCV elimination. NoMoreC is a good example of a community platform where MSM educate other MSM on HCV and safe sex. In addition, play-safe toolboxes can be ordered as well as free HCV home tests, based on dry bloodspot testing [28]. The aim of this platform is to increase awareness and knowledge, encourage regular and timely testing, and offer tailored advice to MSM to reduce their risk of acquiring HCV [28].

HCV treatment uptake in Australia was initially high, but has begun to fall over the past 12 months [39]. Several barriers for linkage to care were identified, such as: a shortage of healthcare practitioners in some area (particularly rural and regional Australia), lack of coverage services; stigma and discrimination; accessing tertiary care services; and HCV being not a priority [18] (Table 1). As a solution, Australia redefined linkage to care models towards the community, where patient access to services and care was decentralised. Several studies, for example, the PRIME study and RAPID-EC, showed that patients were more likely to engage in care when DAAs were given in primary care compared to tertiary hospitals [19,40]. Prescribing rules were changed and, by 2018, most DAAs were prescribed by general practitioners.

HBV care is neglected compared to HCV

HBV care is 'neglected' compared to HCV in terms of treatment and, in addition, there is still limited recognition of the illness. There are several reasons why. First, the greatest HBV morbidity and mortality is found in low- and middle-income countries. In many of these countries HIV had been a major contributor to morbidity and mortality until the development of good coverage of antiretroviral therapy. Additionally, with the advent of DAAs, HCV has become a treatable condition; however, HBV has been left behind. Second, there is no community movement, as there was with HIV, to bring the condition into the spotlight. Civil society is very important for creating advocacy and raising awareness. With the availability of DAAs, this awareness has increased for HCV, although mostly led by drug company treatment campaigns rather than by the affected community. Third, HBV testing needs to be more accessible and cost barriers need to be reduced. HBV monitoring is also difficult with many different steps. Additionally, the timely use of HBV vaccination at birth is a challenge in certain countries, particularly in sub-Saharan Africa where coverage is around 10%.

Monitoring progress

Monitoring progress is an important element in the elimination effort to ascertain if interventions, such as vaccination programmes and other prevention efforts are being effective, whether testing is increasing, and if those testing positive are being linked to care as necessary. Without monitoring, progress cannot be measured, and the impact of the epidemic cannot be understood. WHO recommend three elements for surveillance and 10 core indicators [30]. For surveillance: (1) enhanced case reporting of acute hepatitis describes incidence trends and identifies who acquire hepatitis; (2) biomarker surveys generate reliable population-based estimates of the prevalence, preferably by age; and (3) sequelae surveillance captures mortality from viral statistics and the attributable fraction describes mortality trend [30]. Cascade monitoring relies on aggregated or individual data. If it is not possible to obtain new data, existing data can be extrapolated to provide working estimates to allow the establishment of elimination programmes.

WHO plans to monitor progress towards elimination by requesting countries to report on their progress by core indicators [30]. WHO is to publish new simplified, consolidated guidelines on hepatitis strategic information that will propose a simplified approach for conducting rapid data extraction to report progress towards elimination in the Global Reporting System for Hepatitis (GRSH) [30]. WHO will monitor what is new, policy uptake, cascade of care and sequelae. With this information, WHO will provide a global system of centralised data.

What further steps are needed

Hepatitis B vaccination of infants, blood safety programmes and universal precautions in healthcare settings have already greatly reduced HBV and HCV incidence. However, morbidity and mortality are still increasing. What is further needed is to prioritise the full implementation of timely HBV vaccinations, drug addiction therapies, safe injection equipment and HCV treatment for persons who inject drugs, and assured access to testing, care and treatment for those with HBV and HCV.

In addition, countries should establish elimination programmes with action plans that have time-limited numerical targets and the capacity to deliver appropriate interventions to target populations, with Egypt and Australia as good examples. Moreover, services should be integrated in existing health systems, as successfully achieved in Georgia, and strategic data should be used to monitor programme performance and progress towards elimination goals with Iceland and the VA as examples. Countries should also participate more in operational research.

Furthermore, a global coalition, as recommended by the ITFDE, can help by building the capacity and advocacy towards elimination [41]. Large elimination campaigns are often supported by coalitions of implementing programmes, funding organisations, technical experts, and even international organisations such as WHO. A global coalition, guided by the ITFDE and experiences of other elimination programmes can provide the knowledge and experience, and can establish dynamic evidence-based meetings such as IVHEM, which can provide assistance from technical experts and opportunities for generating new knowledge.

Conclusion

During IVHEM, key elements, such as linkage to care, finding the missing millions, awareness, stigma, cost, and lack of funding were discussed as challenges to elimination programmes. The experience gained from previous and current disease elimination initiatives revealed the essential components of effective elimination programmes, including action plans, building capacity, integrated services, collecting strategic data, and monitoring progress.

Examples from several countries were given on how costs were lowered and existing healthcare systems were used. For example, the VA fully integrated HBV and HCV care into existing services and Georgia integrated and decentralised towards primary care. Other methods for lowering costs were discussed, such as in Egypt, where negotiations with companies reduced the cost of

testing due to the large volume required and generic DAAs were manufactured locally. In addition, Australia more affordable interventions and diagnostics were negotiated and primary care services are being used to deliver treatment.

In order to establish elimination, collection of strategic information, involvement of all stakeholders, engagement with civil society, and arrangement of financial support were considered important elements. Iceland was given as a good example of where public and private partnership, in combination with a HCV registry, led to a successful nationwide elimination programme.

To improve linkage to care, appropriate strategies for the target population should be established as for example in the Netherlands where the community was engaged in creating a programme.

Most importantly, in order to achieve elimination, we need more involvement from the community, and bring the right parties together because only the voice of millions can really drive the movement forward.

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Conflict of interest

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MvdV: participated in ad boards with fees paid to his institution for: Abbvie, Gilead, J&J, MSD, ViiV; received independent research grants from: Abbvie, Gilead, MSD, J&J.

MES: PI in a Gilead Sciences-sponsored investigator-initiated trial (received no PI fees).

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Hepatitis C prevalence and risk factors in Georgia, 2015: setting a baseline for elimination

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Abstract

Background: The country of Georgia launched the world's first Hepatitis C Virus (HCV) Elimination Program in 2015 and set a 90% prevalence reduction goal for 2020. We conducted a nationally representative HCV seroprevalence survey to establish baseline prevalence to measure progress toward elimination over time.

Methods: A cross-sectional seroprevalence survey was conducted in 2015 among adults aged ≥18 years using a stratified, multi-stage cluster design ($n = 7000$). Questionnaire variables included demographic, medical, and behavioral risk characteristics and HCV-related knowledge. Blood specimens were tested for antibodies to HCV (anti-HCV) and HCV RNA. Frequencies were computed for HCV prevalence, risk factors, and HCV-related knowledge. Associations between anti-HCV status and potential risk factors were calculated using logistic regression.

Results: National anti-HCV seroprevalence in Georgia was 7.7% (95% confidence interval (CI) = 6.7, 8.9); HCV RNA prevalence was 5.4% (95% CI = 4.6, 6.4). Testing anti-HCV+ was significantly associated with male sex, unemployment, urban residence, history of injection drug use (IDU), incarceration, blood transfusion, tattoos, frequent dental cleanings, medical injections, dialysis, and multiple lifetime sexual partners. History of IDU (adjusted odds ratio (AOR) = 21.4, 95% CI = 12.3, 37.4) and blood transfusion (AOR = 4.5, 95% CI = 2.8, 7.2) were independently, significantly associated with testing anti-HCV+ after controlling for sex, age, urban vs. rural residence, and history of incarceration. Among anti-HCV+ participants, 64.0% were unaware of their HCV status, and 46.7% did not report IDU or blood transfusion as a risk factor.

Conclusions: Georgia has a high HCV burden, and a majority of infected persons are unaware of their status. Ensuring a safe blood supply, implementing innovative screening strategies beyond a risk-based approach, and intensifying prevention efforts among persons who inject drugs are necessary steps to reach Georgia's HCV elimination goal.

Keywords: Hepatitis C virus, HCV, HCV elimination, Georgia, HCV prevention, Global health security

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Background

Globally, there are an estimated 71 million people living with hepatitis C virus (HCV) infection and 411,000 HCV-attributable deaths annually [1]. HCV is bloodborne and transmitted most often through unsterile medical equipment, infected blood and tissue used for medical procedures, and shared drug injection equipment. HCV infection often progresses asymptomatically for 20–30 years, and most HCV-related deaths result from liver cirrhosis or hepatocellular carcinoma decades after the incident HCV infection [2–6]. HCV accounts for an estimated 27% of cirrhosis and 25% of hepatocellular carcinoma cases worldwide [7].

Georgia is an Eastern European, middle-income country with 3.7 million residents [8]. A 2002 survey in the capital city of Tbilisi found that 6.7% of the general population and 70.4% of persons who inject drugs had antibodies to HCV (anti-HCV, evidence of past or current HCV infection) [9], suggesting that HCV prevalence in Georgia could be among the highest globally. In 2015, Georgia launched the world's first HCV elimination program, aiming to provide universal access to curative, direct-acting antiviral (DAA) treatment at no cost to patients, and to implement nationwide prevention measures to curb transmission [10]. Existing prevalence data have been instrumental in engaging the government's strong support to combat the country's HCV burden, but are outdated and not nationally representative. Data documenting updated nationwide HCV prevalence and risk factors for infection are necessary to effectively plan treatment and prevention services supporting Georgia's HCV elimination goals, and to establish a baseline to track progress toward elimination over time.

This paper presents the results of the first nationally representative HCV seroprevalence survey in Georgia, conducted in 2015 by Georgia's National Center for Disease Control and Public Health (NCDC) in collaboration with the United States Centers for Disease Control and Prevention (CDC). The Georgian government is using these results to plan and implement HCV surveillance, education, prevention, screening, care, and treatment efforts. A follow-up survey is planned to assess the impact of interventions designed to achieve HCV elimination. In addition, planning and conducting this national serosurvey provided an important opportunity to strengthen the public health capacity in Georgia and thereby enhance global health security.

Methods

Sample design

A cross-sectional, nationally representative seroprevalence survey was conducted in Georgia from May–August 2015 among adults aged ≥18 years using a stratified, multi-stage cluster design. A sample size of 7000 was calculated based on estimated 6.7% anti-HCV seroprevalence [9], a design effect of 2, and an anticipated 70% response rate. The sample was designed to yield a nationwide HCV prevalence estimate, independent prevalence estimates in six pre-selected major cities, and in urban vs. rural areas overall. Region-level estimates were also calculated where sample size was sufficient.

The country was divided into 16 mutually exclusive sampling strata (six major cities and ten regions). Strata defined by a region contained both urban and rural areas, but excluded any of the six major cities that lie within the region's boundaries. The occupied territories of Abkhazia and South Ossetia were excluded.

The sampling frame was a full list of Georgia's 9503 census tracts, provided by Georgia's National Statistics Office (GeoStat). These census tracts served as the primary sampling units (clusters) within each stratum. Equal size tracts were assumed since a size measure was not available during sample selection. To reach a sample size of 7000, 280 clusters were selected across the 16 strata, 25 households were selected within each cluster, and one participant was selected from each household. The six major cities were oversampled (120 clusters) to increase precision of point estimates. The remaining 160 clusters were allocated to the ten regions proportionally based on their population size. The specific clusters sampled within each stratum were randomly selected from the list provided by GeoStat.

Within each selected cluster, 25 households were systematically selected using an algorithm based on the cluster's total number of year-round households. Within each household, the Kish method was applied to randomly select one adult for participation [11]. Household members aged ≥18 years who had spent the previous night in the house were eligible; temporary guests and household members living outside the home were excluded. If the selected individual was unavailable, two revisit attempts were made; no replacement participants were selected if the individual was unavailable after revisits or refused participation.

Data collection

Interviewers trained and supervised by NCDC and CDC epidemiologists administered a structured questionnaire to participants who provided informed consent. The questionnaire was given verbally in participants' preferred language (Kartuli/Georgian, Russian, Armenian, or Azeri) and included demographics, medical history, lifestyle/behavioral history, and knowledge of HCV. Data were entered into hand-held electronic devices in real time and uploaded to a secure database. Survey questions were vetted by local staff to ensure cultural appropriateness and suitability for laypersons with a primary

school education. Field and laboratory procedures, questionnaires, and informed consent forms were piloted in rural and urban areas.

Nurse-phlebotomists collected 10 mL blood specimens from consenting participants. Specimens were centrifuged in the field, transported to public health laboratories for processing and testing, and stored at the Georgian National Reference Laboratory in Tbilisi. Each participant's specimen and questionnaire data were linked using a unique barcode. Personal identifying information was obtained strictly to report laboratory test results to participants, and was removed before epidemiologic analysis.

Laboratory methods

Anti-HCV and HCV RNA testing were performed in Georgian public health laboratories. CDC laboratory staff monitored protocols and processes for quality assurance/quality control. All specimens were tested for anti-HCV by enzyme-immunoassay (HCV Ab v4.0 EIA *IVD*, Dia.Pro. Diagnostic Bioprobes Srl, Italy). Anti-HCV-positive specimens were tested for HCV RNA (Sacace™ HCV Real-TM Qual, Sacace Biotechnologies Srl, Italy). Anti-HCV-positive/RNA-negative specimens underwent confirmatory anti-HCV testing using a third generation line immunoassay (INNO--LIA™ HCV Score, *IVD*, Innogenetics N.V., Belgium); specimens that tested positive or indeterminate for anti-HCV in confirmatory testing were re-tested for HCV RNA in the CDC Division of Viral Hepatitis Assay Development and Diagnostic Reference Laboratory in Atlanta, Georgia, USA using a highly sensitive, FDA-licensed assay (COBAS Ampliprep/COBAS Taqman® CAP/CTM v2.0, *IVD,* Roche, Indianapolis, IN, USA); specimens testing HCV RNA negative in the CDC laboratory were re-tested for anti-HCV using the FDA-licensed VITROS Immunodiagnostic System (aHCV, *IVD*, Ortho Clinical Diagnostics, Raritan, NJ, USA) to identify false positives. All specimens were tested for hepatitis B virus and human immunodeficiency virus; results are not reported in this manuscript.

Laboratory test results were reported securely to participants via the Georgian Post; to receive the mailing, participants were required to present a national identification card matching the name of the addressee. Participants with a positive HCV RNA test received written instructions for accessing Georgia's national HCV treatment program in the same mailing.

Statistical methods

Statistical analyses were conducted using SAS 9.3 (Cary, North Carolina, USA). Data were weighted based on probability of selection at cluster, household, and individual levels, and adjusted to represent Georgia's national population by sex, age, and geographic distribution using 2014 census data. Analyses used complex survey procedures accounting for stratification, clustering, and unequal sample weights. Variance was calculated using Taylor series linearization.

Anti-HCV prevalence was calculated by demographic characteristics and potential HCV risk factors; weighted prevalence estimates and 95% confidence intervals (CI) are presented. Bivariate associations between anti-HCV positivity and demographic and risk factor characteristics were examined using Rao-Scott chi-square tests; associations were considered significant when $p < .05$. An unconditional logistic regression model was utilized to explore the relationship between anti-HCV positivity and multiple risk factors that were significantly associated with anti-HCV status in bivariate analyses. Backward elimination was used to reduce the full model; variables were retained if the Wald F test $p < .05$. Variables without significant, independent associations with anti-HCV positivity were retained as confounders if they changed parameter estimates for other significant predictor variables in the main effects model by ≥10%. All potential pairwise interactions in the final model were examined and considered significant if the Wald F test $p < .05$. The final model was assessed for multicollinearity. Odds ratios and 95% CI are presented. Weighted percentages and 95% CI were computed for HCV knowledge variables. Unweighted percentages were computed for HCV treatment history variables.

This survey was determined to be a routine public health activity for public health surveillance by CDC's Human Subjects Research Office and therefore judged to not involve human subjects research.

Results

Of 7000 adults selected, 6296 (89.9%) consented to participate, and 6014 (85.9%) provided both questionnaire responses and a blood specimen. Response rates exceeded 70% in all strata. Three specimens were hemolyzed during processing, and one returned inconclusive anti-HCV results. Demographic analyses include all 6296 participants; HCV-specific analyses include the 6010 participants who provided both questionnaire responses and a blood specimen yielding interpretable serologic test results.

Participant demographics and exposures

Participants' median age was 45 years; 53.8% were female, and 56.7% lived in urban areas (Table 1). 90.9% had completed secondary school or higher, and 19.5% were unemployed. Approximately two-thirds (64.0%) reported an annual household income less than the national average (12,268 Georgian Lari/$5254 US dollars) [12] .

Table 1 Demographic characteristics and reported exposures among survey participants, Georgia HCV serosurvey, 2015

Characteristic	n	Weighted % (95% CI)
Total Sample	6296	100.0
Sex		
Female	3868	53.8 (52.0, 55.5)
Male	2428	46.2 (44.5, 48.0)
Missing	0	
Age		
18–29	1115	19.4 (18.2, 20.7)
30–39	1177	19.4 (17.9, 20.9)
40–49	1070	18.6 (17.2, 20.0)
50–59	1140	16.5 (15.4, 17.7)
≥ 60	1790	26.1 (24.5, 27.8)
Missing	4	
Geography		
Urban	3350	56.7 (52.7, 60.6)
Rural	2946	43.3 (39.4, 47.3)
Missing	0	
Employment status		
Employed	2120	37.8 (35.6, 39.9)
Student	172	3.6 (2.9, 4.4)
Homemaker	1483	19.1 (17.7, 20.6)
Retired	1405	20.0 (18.7, 21.5)
Unemployed (able to work)	1110	19.5 (18.0, 21.1)
Missing	6	
Highest level of education completed		
Completed less than elementary/primary school	43	0.7 (0.5, 1.1)
Completed elementary/primary school	612	8.5 (7.3, 9.8)
Completed secondary school	2567	40.2 (38.1, 42.3)
Completed professional/technical school	1157	16.6 (15.3, 18.0)
Completed university/college or higher	1912	34.0 (31.6, 36.4)
Missing	5	
Yearly household income		
≤ 6000 GEL/year (≤ 4400 USD)	2867	45.6 (43.0, 48.3)
6001–12,000 GEL/year (4400–6800 USD)	953	18.5 (16.8, 20.3)
12,001–24,000 GEL/year (6800–13,600 USD)	724	12.6 (11.3, 13.9)
> 24,000 GEL/year (> 13,600 USD)	1339	23.3 (21.1, 25.8)
Missing	413	
Ever injected drugs		
Yes	208	4.2 (3.5, 5.2)
No	6042	95.8 (94.8, 96.5)
Missing	46	
Ever incarcerated		
Yes	240	4.6 (3.8, 5.7)
No	6037	95.4 (94.3, 96.2)
Missing	19	

Table 1 Demographic characteristics and reported exposures among survey participants, Georgia HCV serosurvey, 2015 *(Continued)*

Characteristic	n	Weighted % (95% CI)
Have any tattoos		
Yes	639	12.2 (10.9, 13.7)
No	5645	87.8 (86.3, 89.1)
Missing	12	
Ever received a blood transfusion		
Yes	459	7.0 (6.1, 7.9)
No	5828	93.0 (92.1, 93.9)
Missing	9	
Ever received kidney dialysis		
Yes	17	0.3 (0.2, 0.6)
No	6255	99.7 (99.4, 99.8)
Missing	24	
Number of medical injections received in last 6 months		
0	3857	62.8 (60.7, 64.8)
1	557	9.5 (8.4, 10.7)
> 1	1701	27.8 (26.0, 29.6)
Missing	181	
Frequency of dental cleanings		
Twice/year	199	4.4 (3.6, 5.3)
Once/year	491	9.0 (7.8, 10.2)
Less than once/year	1170	20.3 (18.5, 22.3)
Never	4370	66.3 (64.0, 68.5)
Missing	66	
Number of lifetime sexual partners		
0–2	4232	75.0 (73.1, 76.8)
> 2	1026	25.0 (23.2, 26.9)
Missing	1038	
Men who have sex with men (MSM)		
Yes	0	0
No	2185	90.0
Missing	243	10.0

When asked about risk factors for HCV infection, 4.2% reported a history of injection drug use (IDU), 7.0% reported receiving a blood transfusion, and < 1% reported receiving dialysis; 4.6% reported a history of incarceration, and 12.2% reported having at least one tattoo. None identified as men who have sex with men (MSM), and 25.0% reported having > 2 lifetime sexual partners.

HCV prevalence

Of the 6010 participants providing a usable blood specimen, 433 (7.7, 95% CI = 6.7, 8.9) tested anti-HCV positive, and 311 (5.4, 95% CI = 4.6, 6.4) tested HCV RNA positive (indicating chronic infection). Anti-HCV prevalence was higher in urban vs. rural areas (9.5% vs. 5.4%, $p < 0.0001$) (Table 2); the highest regional prevalence was in Samegrelo-Zemo Svaneti region in northwest Georgia (10.9%), particularly in the city of Zugdidi (14.0%) (Fig. 1). Anti-HCV prevalence was approximately three times higher among men vs. women (12.1% vs. 3.8%, $p < 0.0001$) and varied by age (Table 2); among men, prevalence peaked at 22.7% in the 40–49 age group, while it increased steadily with age among women to a maximum of 5.4% among those ≥60 years of age (Fig. 2).

Table 2 Anti-HCV prevalence by demographic and exposure subgroup in unadjusted and adjusted models, Georgia HCV serosurvey, 2015

Characteristic		Anti-HCV Prevalence		Unadjusted Models		Final Adjusted Model	
	Total n	n	Weighted % (95% CI)	Crude OR (95% CI)	*p-value*	Adjusted OR (95% CI)	p-value
Demographics							
Sex							
Female	3671	145	3.8 (3.0, 4.9)	1			
Male	2339	288	12.1 (10.2, 14.3)	3.5 (2.5, 4.8)	< 0.0001		
Missing	0						
Age							
18–29	1063	23	2.4 (1.5, 4.0)	1			
30–39	1140	94	8.8 (6.8, 11.3)	3.9 (2.2, 6.8)	< 0.0001		
40–49	1026	128	14.0 (11.1, 17.6)	6.5 (3.9, 11.1)	< 0.0001		
50–59	1096	79	7.0 (5.2, 9.5)	3.0 (1.6, 5.8)	0.0006		
60+	1681	109	6.7 (5.0, 9.0)	2.9 (1.6, 5.4)	0.0007		
Missing	4						
Geography							
Urban	3155	290	9.5 (8.0, 11.4)	1.8 (1.4, 2.5)	< 0.0001		
Rural	2855	143	5.4 (4.4, 6.6)	1			
Missing	0						
Employment Status							
Employed/student/ homemaker/unpaid worker/retired	4939	286	5.9 (5.0, 7.1)	1			
Unemployed*	1065	147	15.0 (12.3, 18.1)	2.8 (2.1, 3.7)	< 0.0001		
Missing	6						
Exposures							
Ever injected drugs							
Yes	205	150	66.5 (56.0, 75.6)	37.6 (23.5, 60.0)	< 0.0001	21.4 (12.3, 37.4)	< 0.0001
No	5762	283	5.0 (4.3, 5.9)	1			
Missing	43						
Ever incarcerated							
Yes	236	98	42.0 (32.8, 51.7)	11.3 (7.5, 17.1)	< 0.0001		
No	5757	335	6.0 (5.1, 7.0)	1			
Missing	17						
Have any tattoos							
Yes	626	104	16.2 (12.2, 21.1)	2.8 (1.9, 4.0)	< 0.0001		
No	5372	329	6.5 (5.5, 7.6)	1			
Missing	12						
Number of medical injections in last 6 months							
0	3656	233	6.7 (5.6, 7.9)	1			
1	541	40	6.6 (4.3, 10.2)	0.99 (0.60, 1.65)	0.98		
> 1	1648	144	9.5 (7.5, 12.1)	1.48 (1.10, 1.99)	0.01		
Missing	165						

Table 2 Anti-HCV prevalence by demographic and exposure subgroup in unadjusted and adjusted models, Georgia HCV serosurvey, 2015 *(Continued)*

Characteristic		Anti-HCV Prevalence		Unadjusted Models		Final Adjusted Model	
	Total n	n	Weighted % (95% CI)	Crude OR (95% CI)	*p-value*	Adjusted OR (95% CI)	p-value
Ever received a blood transfusion							
Yes	447	69	21.4 (15.6, 28.5)	3.8 (2.6, 5.5)	< 0.0001	4.5 (2.8, 7.2)	< 0.0001
No	5554	364	6.7 (5.8, 7.7)	1			
Missing	9						
Received a blood transfusion before or after 1997							
Before 1997	225	36	25.3 (16.2, 37.3)	1.6 (0.7, 3.7)	0.27		
In or after 1997	222	33	17.4 (10.7, 27.1)	1			
Ever received kidney dialysis							
Yes	17	3	27.6 (7.9, 62.9)	4.6 (1.0, 20.4)	0.04		
No	5972	430	7.7 (6.7, 8.8)	1			
Missing	21						
Frequency of dental cleanings							
Twice/year	193	15	15.0 (8.1, 26.2)	2.1 (1.1, 4.4)	0.04		
Once/year	478	27	6.7 (3.9, 11.5)	0.9 (0.5, 1.6)	0.66		
Less than once/year	1108	84	6.9 (5.0, 9.4)	0.9 (0.6, 1.3)	0.58		
Never	4173	304	7.6 (6.5, 8.8)	1			
Missing	58						
Number of lifetime sexual partners							
0–2	4020	157	3.8 (3.0, 4.7)	1			
> 2	991	129	11.9 (9.1, 15.4)	3.4 (2.4, 5.0)	< 0.0001		
Missing	999						

Note: Anti-HCV related analyses include only participants who submitted both questionnaire data and a usable blood specimen ($n = 6010$)
*Unemployed includes those able or unable to work

Factors associated with HCV infection

In bivariate analysis, anti-HCV positivity was significantly associated with male sex, unemployment, and urban residence, as well as history of IDU, incarceration, blood transfusion, tattoos, frequent dental cleanings, medical injections, dialysis, and having multiple lifetime sexual partners (Table 2). Among participants who reported a history of blood transfusion, no significant difference in anti-HCV prevalence was detected between those who reported receiving a transfusion before vs. in/after 1997 (when Georgia began testing donated blood for HCV) (Table 2). Other medical and community exposures including hospitalization, surgery, body piercings, and manicures/pedicures were not significantly associated with anti-HCV positivity (data not shown).

In the adjusted model, history of IDU (adjusted odds ratio (AOR) = 21.4, 95% CI = 12.3, 37.4) and receipt of a blood transfusion at any date (AOR = 4.5, 95% CI = 2.8, 7.2) were the only risk factors that were significantly, independently associated with anti-HCV positivity, controlling for sex, age, urban vs. rural residence, and history of incarceration (Table 2). [Note: A dichotomous blood transfusion variable (ever vs. never received transfusion) was used in the multivariate model.] There were no significant interactions in the final model.

Of the 433 anti-HCV positive participants, 38.2% reported IDU, and 19.7% reported receiving a blood transfusion. Nearly half of anti-HCV positive participants (46.7%) did not report either of these risk factors. Overall, 66.5% of anti-HCV positive participants were male, and 43.4% were ≥ age 50. The sex and age breakdown was similar among anti-HCV positive participants reporting a blood transfusion (63.2% male and 55.7% ≥ age 50) and among anti-HCV positive participants who did not report either IDU or history of blood transfusion (60.6% male and 46.2% ≥ age 50). Anti-HCV positive participants reporting IDU were mostly male (98.3%) and concentrated in the 30–49 age range (70.0%), with 16.3% ≥ age 50.

HCV diagnosis and treatment

Among the 433 participants who tested anti-HCV positive, 156 (36.0%) already knew their HCV status prior to the survey. Awareness of HCV status was more likely

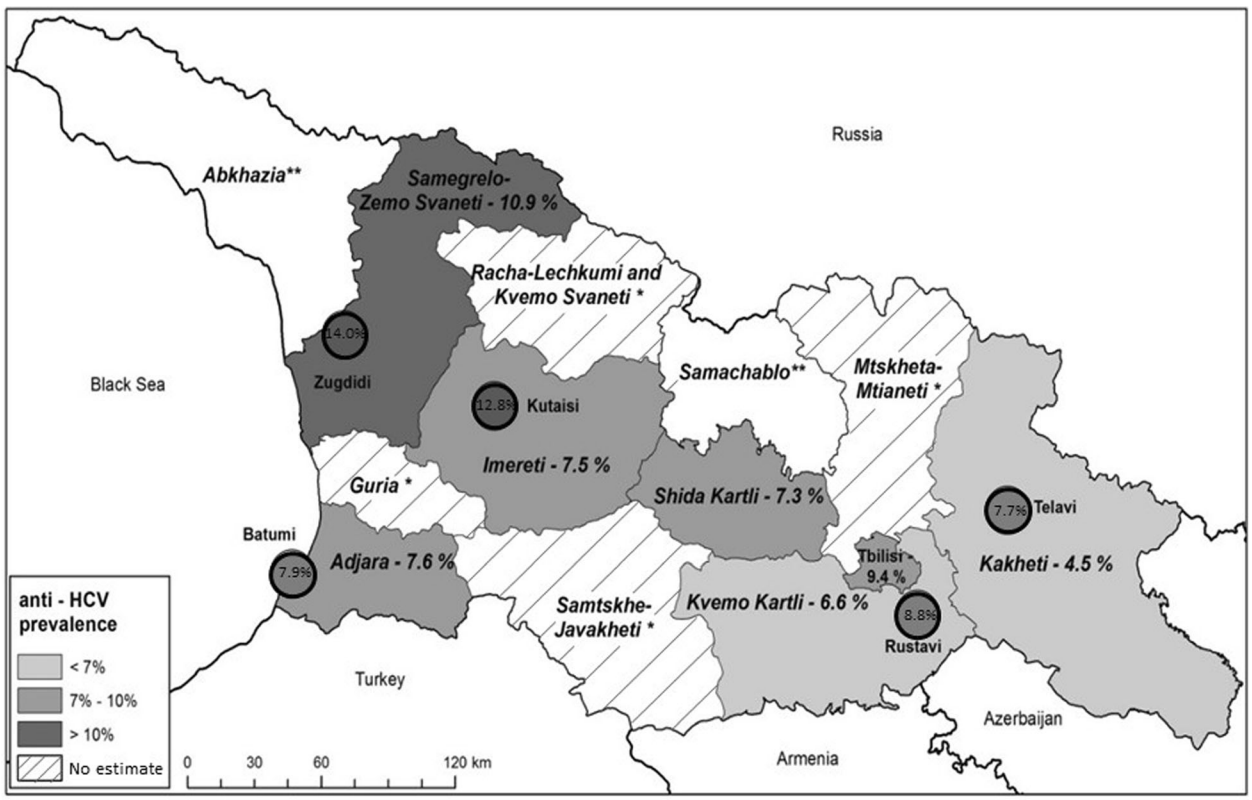

Fig. 1 Anti-HCV prevalence in major cities and regions of Georgia. The highest regional anti-HCV prevalence was found in Samegrelo-Zemo Svaneti region in northwest Georgia (10.9%), particularly in the city of Zugdidi (14.0%, nearly double the national prevalence of 7.7%). In general, anti-HCV prevalence was higher in cities than in the surrounding rural areas. [Notes: *Anti-HCV prevalence estimates were not calculated for Guria region, Mtskheta-Mtianeti region, Racha-Lechkumi/Kvemo Svaneti region, or Samtskhe-Javakheti region due to insufficient sample size. **The occupied territories of Abkhazia and Samachablo (South Ossetia) were not included in the survey]

among anti-HCV positive participants reporting IDU compared to those not reporting IDU (55.3% vs. 28.5%, p = 0·0002). Among participants aware of their HCV infection, 50 (32.1%) reported initiating treatment prior to the survey, 32 (64.0%) of those who reported initiating treatment reported completing it, and 6 (18.8%) of those who reported completing treatment reported being cured (Fig. 3). A cross-check of self-reports against laboratory test results revealed that 14 participants reporting treatment completion tested HCV RNA negative

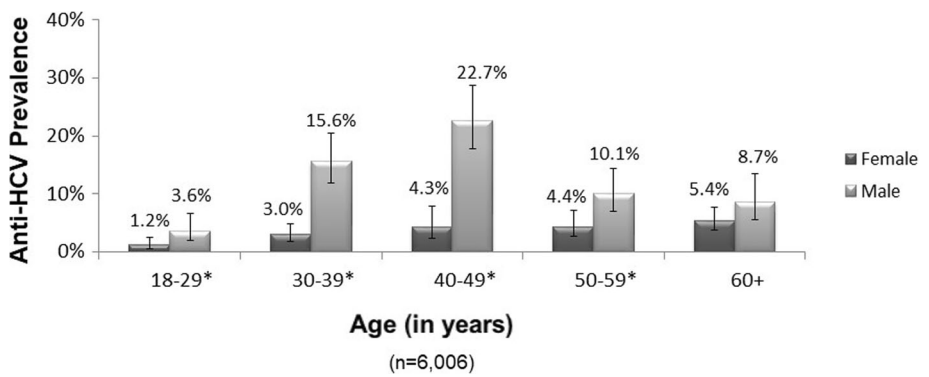

Fig. 2 Anti-HCV prevalence by age and sex. Anti-HCV prevalence was approximately three times higher among men vs. women overall (12.1% vs. 3.8%) and varied by age; among men, prevalence peaked at 22.7% in the 40–49 age group, while it increased steadily with age among women to a maximum of 5.4% among those ≥60 years of age. [Note: *Differences in anti-HCV prevalence between male and female respondents were statistically significant in asterisked categories using Rao-Scott Chi-square tests ($p < 0.05$)]

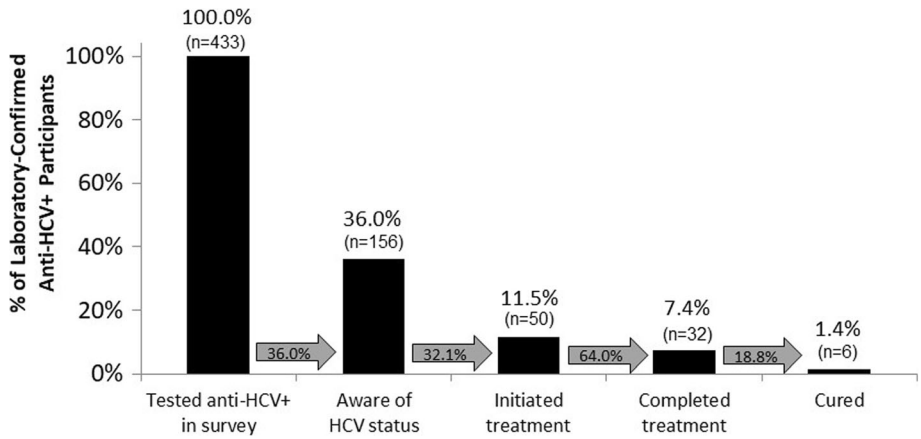

Fig. 3 Self-reported cascade of HCV care among laboratory-confirmed anti-HCV positive participants. Among the 433 survey participants who tested anti-HCV positive, 156 (36.0%) already knew their HCV status prior to the survey. Among participants aware of their HCV infection, 50 (32.1%) reported initiating treatment prior to the survey, 32 (64.0%) of those who began treatment reported completing it, and 6 (18.8%) of those who completed treatment reported being cured

(more than twice the number who reported being cured); however only three of the six who reported a cure actually tested HCV RNA negative.

Among anti-HCV positive participants aware of their infection and reporting no treatment, reasons cited for non-treatment included lack of treatment availability (56.6%), high cost (33.0%), and anticipated side effects (12.3%).

HCV-related knowledge

A majority of participants (56.1%) were aware that HCV can be transmitted through exposure to infected blood; when asked about specific transmission modes, 52.3% identified sharing needles/syringes, 43.6% identified sharing household objects that have had contact with blood, and 31.9% identified sexual contact as possible HCV transmission modes. More than half of participants (57.2%) were aware that HCV can be asymptomatic, and 70.5% knew that HCV is treatable. HCV-related knowledge was higher among participants who were anti-HCV positive, and highest specifically among anti-HCV positive participants reporting a history of IDU (Table 3).

When asked what sources they trust for information about their health, 35.8% of participants identified doctors and other healthcare workers, and 34.0% identified television. Other information sources including the internet, family/friends, medical literature, newspapers, radio, brochures/fliers, pharmacists, and billboards, were each cited as trustworthy by fewer than 15% of participants (data not shown). Participants were able to select multiple responses to this question.

Discussion

HCV elimination has garnered increasing international support since the development of curative HCV drugs in recent years, resulting in the World Health Organization's worldwide HCV elimination plan, the European Union HCV Policy Summit commitment to elimination, and individual elimination programs in Georgia, Australia, Iceland, the Cherokee Nation in the United States, and other areas [13–17]. Georgia was the first

Table 3 HCV-related knowledge by anti-HCV status and reported IDU history, Georgia HCV serosurvey, 2015

	All participants		Anti-HCV+ participants		Anti-HCV+ participants reporting IDU	
	n	Weighted % (95% CI)	n	Weighted % (95% CI)	n	Weighted % (95% CI)
Aware that HCV can be asymptomatic	2458	57.2 (54.9, 59.4)	260	76.4 (69.9, 81.9)	120	83.7 (74.2, 90.2)
Aware that HCV can be treated	3041	70.5 (68.5, 72.5)	287	83.6 (77.5, 88.3)	130	89.0 (80.1, 94.2)
HCV can be transmitted by						
Blood	3295	56.1 (53.9, 58.3)	295	71.1 (64.8, 76.8)	136	89.0 (80.2, 94.1)
Sharing needles or syringes	3056	52.3 (50.0, 54.6)	278	67.1 (60.4, 73.2)	128	87.2 (78.8, 92.6)
Sharing household objects like razors or toothbrushes	2582	43.6 (41.1, 46.1)	249	58.6 (51.7, 65.1)	114	73.4 (62.4, 82.1)
Sexual contact	1875	31.9 (30.1, 33.7)	165	41.4 (35.0, 48.1)	83	57.5 (46.3, 67.9)

country to undertake HCV elimination and has set ambitious targets including a 90% reduction in chronic HCV prevalence by 2020 [10, 18].

This survey confirms that Georgia has a high burden of HCV infection and identifies risk factors that will be essential to address in Georgia's HCV elimination strategy. Applying the 5.4% HCV RNA prevalence found in this survey to Georgia's adult population of 2.78 million results in an estimated 150,340 (95% CI = 128,060, 173,060) people aged ≥18 years living with chronic HCV infection. Because this sample did not include incarcerated or homeless persons, groups known to have high HCV prevalence [19–22], this survey likely underestimates the true HCV burden. Two risk factors measured in this survey were significant, independent predictors of anti-HCV positivity: reported history of IDU and reported receipt of a blood transfusion. However, half of anti-HCV positive participants reported neither exposure, illustrating that screening based on reported risk factors alone will be insufficient to identify most chronically infected persons and eliminate HCV.

Communication about HCV transmission modes and disease course will be important components of efforts to increase screening. Half of all participants were unaware that they could have an HCV infection without experiencing any symptoms, and half were unaware that HCV is transmitted through exposure to infected blood. HCV-related knowledge was highest among participants reporting a history of IDU, possibly due to familiarity with the risks of injecting drugs. Although media coverage of the HCV elimination program within Georgia has likely increased the general public's knowledge about HCV since this survey, these findings highlight the need to further intensify public education efforts to drive screening, particularly in groups less familiar with HCV transmission risks such as injecting drugs. However, identifying effective messaging and modes of communication could be challenging, given that only one-third of participants expressed trust in healthcare professionals as sources of health-related information, and even fewer reported trust in other sources including friends, family, radio, television, or the internet.

History of IDU was the strongest predictor of HCV infection in this survey and was reported by 38.2% of anti-HCV positive participants. IDU was most common among men, likely driving the three-fold difference in anti-HCV prevalence between men vs. women. In particular, men ages 40–49 years had the highest prevalence of both reported IDU (17.4%, data not shown) and anti-HCV (22.7%). (This cohort came of age during a drug trafficking and IDU epidemic in Georgia during the 1990s/early 2000s following the collapse of the former Soviet Union [23]). However, injecting behavior poses an important challenge for HCV elimination regardless of the age of persons injecting, and those actively injecting drugs will be a key target to curb transmission. Increasing access to harm reduction programs, including needle and syringe programs and medication for opioid use disorder, will be essential. In addition, a follow-up study among persons actively injecting drugs would further clarify HCV prevalence and risk behaviors in this sub-group to guide prevention efforts.

History of a blood transfusion also emerged as an independent risk factor for HCV infection and was reported by 20% of anti-HCV positive participants. Although Georgia began testing its donated blood supply for HCV in 1997, there was no detectable difference in anti-HCV prevalence between participants who received a transfusion before vs. after the blood testing program began. To halt HCV transmission and support elimination, it is imperative that Georgia evaluate and improve its blood safety program.

Nearly half of anti-HCV positive participants reported neither IDU nor blood transfusion. Possible explanations include underreporting of risk factors due to stigma, legal concerns, and poor recall, as well as HCV transmission through exposures not identified as potential risk factors in this survey. Suboptimal infection control during healthcare and dental procedures has been hypothesized as an HCV transmission risk in Georgia due to privatization and regulatory challenges in these sectors following the dissolution of the former Soviet Union. However, the cross-sectional nature of this survey and the near-universal utilization of dental and healthcare services make risk association difficult to detect from these exposures. Nonetheless, these data indicate that nearly half of HCV-infected persons in Georgia could be unaware of their risk history or unwilling to report it. Thus, screening strategies beyond a risk-based approach will be necessary for Georgia to identify enough infected persons to reach its elimination targets. In addition, further investigation is warranted to better understand potential HCV transmission risks in Georgia aside from IDU and blood transfusions, as well as differences in risk factors by sex.

Over 60% of participants with evidence of HCV infection learned about their status for the first time through participation in this survey. Among those already aware of their HCV infection, approximately one-third reported prior treatment; most would have been treated with interferon-based regimens, which were the only HCV treatment options available in Georgia prior to the launch of the national elimination program, and were cost-prohibitive for most Georgians. By offering DAA-based treatment to patients at no cost, Georgia's HCV elimination program has addressed the primary treatment barriers cited by survey participants - expense, availability, and anticipated side effects. From the beginning of the elimination program in April 2015 through December 2016, 27,595 persons

initiated treatment, and efforts are ongoing to continue to improve access for those who are aware of their HCV infection [18, 24]. With treatment infrastructure now in place, the greatest opportunity to boost progress toward HCV elimination lies in screening and diagnosing more infected individuals.

This survey has several limitations. Its cross-sectional design limits the ability to draw causal associations between possible exposures and HCV, a chronic infection that could have been acquired at any time before the survey. Further, the necessary reliance on self-reported risk factor data could result in information bias that is unmeasurable. The fact that IDU is illegal in Georgia and is the leading reason for incarceration [25] likely discourages self-reports of injecting behavior; similarly, high levels of MSM stigmatization likely explain the complete absence of self-reported MSM among participants in this survey. Finally, HCV prevalence among participants reporting a history of IDU at some point in their lifetime may not reflect HCV prevalence among persons actively injecting drugs, due to changes in infection dynamics in injecting populations over time.

Conclusions

Georgia is working toward ambitious HCV elimination goals, aiming to screen and diagnose 90% of the estimated 150,000+ Georgians with chronic HCV infection, treat 95% of those identified, and reduce national prevalence of chronic HCV by 90% by 2020 [18]. This survey has provided nationally representative data to guide Georgia's comprehensive HCV elimination strategy, as well as baseline HCV prevalence to evaluate progress toward HCV elimination in the coming years. In addition, conducting the survey provided an important opportunity to strengthen Georgia's public health capacity and thereby enhance global health security

Abbreviations

anti-HCV: antibodies to hepatitis C virus; AOR: adjusted odds ratio; CDC: United States Centers for Disease Control and Prevention; CI: confidence interval; DAA: direct-acting antiviral; Geostat: Georgia National Statistics Office; HCV RNA: hepatitis C virus ribonucleic acid; HCV: hepatitis C virus; IDU: injection drug use; MSM: men who have sex with men; NCDC: Georgia National Center for Disease Control and Public Health

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Availability of data and material

The datasets generated and analysed during this study are not publicly available due to privacy restrictions. Participants were informed during the consent process that the data they provide would be available only to the Georgian Ministry of Labour, Health, and Social Affairs and the US Centers for Disease Control and Prevention.

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About this supplement

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Authors' contributions

FA, JM, AG, and PI conceived of the idea for this survey, and LH, SS, MA, GC, CB, GK, SK, JD, and FA contributed to its design. MA and GC oversaw laboratory procedures in Georgia, and NC and RS conducted laboratory analyses. JD oversaw the overall laboratory component, trained laboratory staff, and conducted laboratory quality assurance/quality control and confirmatory testing at CDC. LH, SS, AK, and MS trained interviewers and phlebotomists and oversaw the field work component. GK obtained data from Geostat to weight survey data. DB conducted follow-up data collection. LH and SR conducted statistical analyses, and LH, SR, CB, SH, and FA interpreted the results. LH and AK designed figures for the manuscript, and LH drafted the initial version of the manuscript. All authors have reviewed and approved the final manuscript.

Ethics approval and consent to participate

Ethical approval was obtained from the Georgia National Center for Disease Control and Public Health Institutional Review Board. This survey was determined to be a routine public health activity for public health surveillance by CDC's Human Subjects Research Office and therefore judged to not involve human subjects research. All participants signed a consent form in their preferred language; the form explained the purpose of the survey, provided contact information for the Principal Investigator, informed participants that they could decline to answer any questions they chose, and assured them that their participation would not influence health care services they receive through the Georgian government.

Consent for publication

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Competing interests

The authors declare that they have no competing interests.

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An evaluation of the hepatitis C testing, care and treatment program in the country of Georgia's corrections system, December 2013 – April 2015

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Abstract

Background: The country of Georgia has a high burden of chronic hepatitis C virus (HCV) infection, and prisoners are disproportionately affected. During 2013, a novel program offering no cost screening and treatment of HCV infection for eligible prisoners was launched.

Methods: The HCV treatment program implemented a voluntary opt-in anti-HCV testing policy to all prisoners. Anti-HCV positive persons received HCV RNA and genotype testing. Transient elastography was also performed on prisoners with positive HCV RNA results. Prisoners with chronic HCV infection who had ≥F2 Metavir stage for liver fibrosis and a prison sentence ≥ 6 months were eligible for interferon-based treatment, which was the standard treatment prior to 2015. We conducted an evaluation of the HCV treatment program among prisoners from the program's inception in December 2013 through April 2015 by combining data from personal interviews with corrections staff, prisoner data in the corrections database, and HCV-specific laboratory information.

Results: Of an estimated 30,000 prisoners who were incarcerated at some time during the evaluation period, an estimated 13,500 (45%) received anti-HCV screening, of whom 5175 (38%) tested positive. Of these, 3840 (74%) received HCV RNA testing, 2730 (71%) tested positive, and 880 (32%) met treatment eligibility. Of these, 585 (66%) enrolled; 405 (69%) completed treatment, and 202 (50%) achieved a sustained virologic response at least 12 weeks after treatment completion.

Conclusions: HCV infection prevalence among Georgian prisoners was high. Despite challenges, we determined HCV treatment within Georgian Ministry of Correction facilities was feasible. Efforts to address HCV infection among prison population is one important component of HCV elimination in Georgia.

Keywords: Chronic hepatitis C, HCV infection, Prisons, Global health security, Linkage to care, Incarcerated, Prisoner

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Background

There are an estimated 71 million people infected with hepatitis C virus (HCV) and 399,000 associated deaths annually worldwide [1, 2]. Georgia is a lower-middle income country located in Eastern Europe, with a population of 3.7 million people and has one of the highest prevalence rates of HCV infection in the world [3]. In 2002, data from a serosurvey found 6.7% of the adult population in the capital city of Tbilisi had antibodies to HCV (anti-HCV) [3, 4]. A recent national serosurvey in 2015 estimated a 7.7% anti-HCV prevalence [5]. Estimates of anti-HCV prevalence among high-risk groups include: 57–92% among people who inject drugs (PWID), 17% among men who have sex with men, and 4–12% among health care workers [6]. Injection-drug use (IDU) is an important risk factor for HCV transmission in Georgia and the most common reason for incarceration [6]. Anti-HCV prevalence among prisoners in most countries is significantly higher than the prevalence in the general population [7–9].

Complaints of inadequate healthcare provided in Georgian prisons led to proceedings adjudicated in 2009 by the European Court of Human Rights, resulting in judgements against Georgia. The Court directed the Georgian government to provide prisoners with access to hepatitis C prevention and treatment and undertake systematic steps to ensure access to testing and treatment [10]. Immediately following elections in 2012, the new administration prioritized prison healthcare as a priority: The "18 months prison healthcare reform" was launched in 2013 and was successfully completed (according to an EU independent evaluation) in 2014. Introduction of the hepatitis C program in prisons was an important part of the prison healthcare reform; providing hepatitis C prevention counseling, testing and treatment services to inmates at no cost.

In this report, we evaluate the effectiveness of the hepatitis C treatment program in Georgian prisons. This evaluation provided an important opportunity to assess the program and through the lessons learned strengthen public health capacity. This will lead to improvements in the prevention and treatment of HCV in Georgia and globally, and thereby enhance global health security. It is anticipated that the challenges and successes identified in this evaluation would be used by public health policy makers to implement a successful prison treatment program which would contribute significantly toward Georgia's national HCV elimination program, which began in April 2015 [11].

Methods

Data were obtained from three sources: 1) Personal communication and interviews with Georgia Ministry of Corrections (MOC) officials; 2) A database maintained by the Georgian MOC that contains prisoner demographic information (age, sex, length of prison sentence, anti-HCV result, liver elastography score, and treatment received); and anti-HCV positive prisoners had additional blood samples sent to a laboratory, where a 3) database maintained by the Infectious Diseases, AIDS and Clinical Immunology Research Center (IDACIR) in Tbilisi that contains laboratory information from prisoners (HCV RNA result, HCV genotype, aspartate aminotransferase [AST], alanine aminotransferase [ALT], and platelet count). Georgian MOC officials merged data from these sources using prisoners' names into one dataset for programmatic analysis, and was de-identified to ensure confidentiality.

Description of the Georgia MOC HCV treatment program

The penitentiary system in Georgia consists of one female prison and ten male prisons and houses approximately 10,000 prisoners at any given time with a maximum capacity of 21,398. The majority of prisoners are male (97%), and 80% are aged 18–45 years.

The MOC launched a program for hepatitis C screening, care and treatment in Georgia's prison system in December 2013. The MOC implemented a voluntary opt-in anti-HCV testing policy to all prisoners. Those who tested positive were offered confirmatory HCV RNA testing and, if positive, received non-invasive liver fibrosis staging with transient elastography (elastography). Liver elastography scores were recorded as categorical liver fibrosis scores that corresponded to Metavir stage; higher liver elastography scores indicate more liver fibrosis. Demographic information and liver fibrosis score were entered into a MOC database. Laboratory testing was only performed on persons with a liver elastography score corresponding to F2 or greater, and included: liver transaminases, platelet count, serial HCV RNA, and HCV genotype, which were entered into the IDACIR database.

Treatment eligibility criteria included: 1) Chronic HCV infection determined by detection of virus by PCR (HCV-RNA-positive) and HCV genotype test; 2) Transient elastography measurement ≥F2; and 3) Prison sentence long enough to complete the treatment, which was usually longer than 6 months. If a prisoner met these criteria, a committee composed of physicians from the MOC and the Ministry of Labour, Health, and Social Affairs, and representatives from community organizations reviewed each case, including medical and psychiatric records to identify any contraindications to interferon-based treatment regimens. After review, a determination was made as to whether the prisoner was eligible for the treatment program. The physicians on that committee determined the specific HCV treatment regimen to administer to each prisoner based on the

American Association for the Study of Liver Diseases (AASLD) 2009 Practice Guidelines [12]. Treatment medications during the evaluation period included pegylated interferon and ribavirin for 24 or 48 weeks depending on the HCV genotype. The program had resources to provide treatment to 500 prisoners free of charge each year. Interferon-free regimens were not available in Georgia prior to April 2015.

Statistical analysis

We described the HCV care cascade among prisoners by calculating the number of prisoners who: a) received anti-HCV testing; b) received confirmatory HCV-RNA and HCV genotype testing, and liver elastography score; c) were deemed eligible for treatment; d) enrolled in HCV treatment; e) began and completed their prescribed treatment course; and f) achieved a sustained virologic response (undetectable HCV RNA) at least 12 weeks post therapy (SVR12). The proportion achieved for each step was calculated using the preceding value as the denominator. We described the demographic characteristics, HCV genotype, and non-invasive liver fibrosis assessments for chronically infected prisoners who were treatment eligible. We calculated other non-invasive fibrosis assessments using the fibrosis-4 (FIB-4) score and AST to Platelet Ratio Index (APRI) for those who had laboratory data available. The FIB-4 score was calculated using the formula: (age [years] x AST [U/L]) / (platelets [10^9/L] x square root ALT [U/L]) in which the age of the patient was the age at the time of the blood draw. FIB-4 scores < 1.45 have a negative predictive value of 90% for advanced fibrosis and scores > 3.25 have a 65% positive predictive value for F3/4 [13]. APRI was calculated using the formula: (AST [IU/L] / AST upper limit of normal [37 IU/L] / platelet count [10^9/L]) × 100. The lower the APRI score (< 1.0) the greater the negative predictive value, and scores > 2.0 have a specificity of 91% for identifying cirrhosis [14]. Analyses were conducted using SAS Institute Inc. version 9.3 (Cary, NC, USA).

Results

This assessment included data from the program's inception in December 2013 through April 2015. The total number of prisoners housed by MOC during the evaluation period was difficult to ascertain, but the MOC estimates 30,000 persons were in the prison system at some time during the evaluation period. Figure 1 illustrates the HCV care cascade. An estimated 13,500 (45%) prisoners received anti-HCV testing, and 5175 (38%) tested positive. Of those who tested positive, 3840 (74%) had confirmatory HCV RNA testing performed, and of those who had RNA testing, 2730 (71%) tested positive and were diagnosed with chronic HCV infection. Of 2730 prisoners diagnosed with chronic HCV infection, 880 (32%) met the eligibility criteria for treatment. Of these, 858 (98%) were male, 155 (18%) had elastography ≥ 12.5 consistent with Metavir F4, and most were infected with HCV genotype 3 (48%). Other characteristics are listed in the Table 1. FIB-4 and APRI identified 52

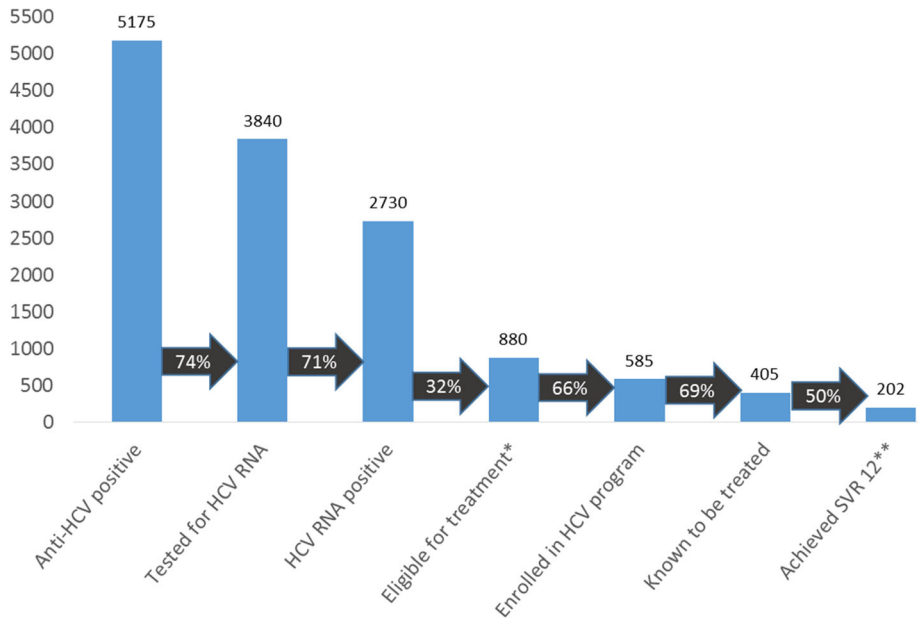

Fig. 1 Chronic Hepatitis C Virus Infection Care Cascade Among Prisoners in Georgian Prisons, December 2013–April 2015. *Eligible for treatment required a transient elastrography result F2 or greater and a prison sentence long enough to complete treatment. **SVR = sustained virologic response, defined as not detectable HCV RNA at least 12 weeks after completion of therapy

and 62 prisoners with advanced fibrosis or cirrhosis, respectively (Table 1). The strength of the agreement for liver elastography was moderate for FIB-4 (kappa = 0.568; 95% CI 0.456 to 0.679) and APRI (kappa = 0.545; 95% CI 0.437 to 0.653).

Of treatment eligible prisoners, 585 (66%) enrolled in treatment (Fig. 1). Of these, 405 (69%) had completed the full treatment course by the end of the evaluation period. Reasons for 180 prisoners with incomplete treatment data included: 125 (21%) were released from prison prior to treatment completion, 29 (5%) stopped treatment due to side effects or voluntary cessation, 4 (< 1%) stopped treatment due to lack of virologic response, and 22 (4%) were unknown.

Table 1 Demographics, hepatitis C genotype, and non-invasive fibrosis assessment among Georgian prisoners with chronic hepatitis C infection, December 2013–April 2015

	Among prisoners receiving a full diagnostic evaluation	%
N	880	
Median age (years)	40 (Range: 18–71)	
Male (years)	40 (Range: 18–71)	
Female (years)	43 (Range: 25–54)	
Sex		
Male	858	97.5%
Female	22	2.5%
HCV Genotype		
1	200	22.7%
2	253	28.8%
3	420	47.7%
Mixed 1 & 2	5	0.6%
Mixed 1 & 3	1	0.1%
6	1	0.1%
Non-Invasive Fibrosis Staging		
6.5 kPa – < 8.0 kPa (Metavir F2)	406	46.1%
8.0 kPa – < 10 kPa (Metavir F2-F3)	192	21.8%
10 kPa – < 12.5 kPa (Metavir F3)	127	14.4%
12.5 kPa – < 14 kPa (Metavir F3-F4)	23	2.6%
≥ 14 kPa (Metavir F4)	132	15.0%
FIB-4		
< 1.45	573	65.1%
1.45–3.25	255	29.0%
> 3.25	52	5.9%
APRI		
< 1.0	651	74.0%
1.0–2.0	167	19.0%
> 2.0	62	7.0%

Of 405 treated prisoners with HCV RNA results available, 365 (90%) achieved end of treatment response, and 202 (50%) achieved a SVR12.

Discussion

Georgia's prison population represents 0.3% of the total national population, and the anti-HCV prevalence was 38% in our program. Our findings support the feasibility of HCV treatment in Georgia's penitentiary system. Specifically, the program screened one-third of prisoners for HCV within the first 2 years of its operation, enrolled 21% (585/2730) of those identified with chronic HCV infection in treatment, and achieved a sustained virologic response in at least 50% (202/405) of prisoners treated with interferon-based therapy. This program highlights the high demand for treatment among prisoners, as well as a strong commitment within the MOC and the Georgian government overall to reduce the burden of HCV infection within the prison system. With the introduction of newer, more effective, all-oral direct acting antiviral (DAA) regimens in Georgia starting in April 2015, the program's effectiveness will likely increase and contribute to the government's recent commitment to HCV elimination throughout the country [11].

The 38% anti-HCV prevalence reported in this evaluation is consistent with prevalence estimates reported by studies performed in prisons in the United States, which range from 17 to 41% [8, 9], and in Central Asia where prevalence has been documented at 38% [15]. A recent estimate of the global HCV prevalence among 10.2 million people incarcerated on any given day in 2014 was 15.1%, but authors noted geographic differences and HCV prevalence as high as 30% in Eastern Europe and central Asia [16]. Because of the high prevalence of HCV infection, correctional facilities are ideal locations to conduct screening and treatment programs because a large proportion of persons screened will test positive for chronic HCV infection [17]. High HCV infection prevalence in prisons is likely the result of a concentration of persons who inject drugs (PWID), as drug use is a major cause of incarceration in Georgia, and injection drug use is well recognized as a primary mode of HCV transmission [6, 18]. A meta-analysis estimated the incidence of HCV infection among incarcerated persons in 39 countries at 6.6 per 100,000 detainees with a history of IDU and 0.4 per 100,000 detainees without IDU [15]. In addition, a study in Scotland estimated HCV prevalence to be 49% among injector-inmates, and the HCV prevalence was 53% in those who had injected inside prison [19]. Further, IDU, as well as other risk factors, are prevalent in prisons and contribute to ongoing transmission within the prisons themselves [15]. HCV treatment programs similar to that pioneered by the

Georgian MOC has the potential to reduce the burden of HCV infection within prisons, as well as contribute substantial public health impact by slowing the country's overall HCV epidemic.

Early results from Georgia's HCV prison program also demonstrate its ability to support successful completion of HCV treatment, as more than 70% of prisoners who initiated treatment completed their treatment course. Of the prisoners unable to complete their prescribed regimen, the majority discontinued due to tolerability issues at a rate lower or comparable to non-institutionalized populations [20, 21]. Drop-out rates are likely to decrease with the introduction of newer, all-oral interferon-free DAA regimens. In addition, some prisoners decided to defer interferon-based treatment and wait until the interferon-free regimens were available. We hypothesize that integrating these new regimens would lead to an even higher impact on reducing HCV infection prevalence in Georgia's prison system.

Despite these early successes, there are areas for improvement in Georgia's current HCV prison program. First, due to the opt-in structure of the screening component, less than half of prisoners received anti-HCV testing during the evaluation period. To overcome this challenge, the MOC could adopt an opt-out structure. Second, there were 1335 (26%) anti-HCV positive prisoners who did not receive confirmatory HCV-RNA PCR testing, which may have resulted in an underestimated burden of chronic HCV infection in Georgian prisons. A second blood draw is required to perform HCV RNA testing which may have been a contributory factor. Reflex HCV RNA testing could overcome this barrier. Third, more than half of prisoners with chronic infection did not receive full diagnostic evaluation including non-invasive fibrosis staging. This gap may have led to under treatment of eligible prisoners with chronic HCV infection and could be overcome by performing a comprehensive non-invasive liver fibrosis staging work up in all chronically infected prisoners. In the recently released World Health Organization guidance for HCV, easy to implement non-invasive liver fibrosis scores including FIB-4 and APRI are recommended for liver fibrosis staging [22]. FIB-4 and APRI have been shown to have high sensitivities for identifying persons without cirrhosis [23]. Our data showed moderate agreement for identifying prisoners with advanced fibrosis or cirrhosis using FIB-4/APRI compared with liver elastography. Utilization of other non-invasive liver fibrosis scoring tools could be considered as a screening tool for advanced liver fibrosis in future programs. Fourth, 79% of Georgian prisoners with chronic HCV infection did not enroll in treatment, due to strict eligibility criteria. This barrier could be mitigated by adjusting eligibility criteria to reflect the shorter treatment duration (≤12 weeks) possible with interferon-free regimens recently introduced in Georgia, which will allow prisoners with shorter prison sentences to participate. Further investigation is needed to evaluate interventions to mitigate these gaps in the HCV care cascade [11].

Prevention and education are also necessary components for a successful hepatitis C control program in Georgian prisons. For example, an HCV treatment program in Australian prisons reported that 5 of 57 successfully treated prisoners became re-infected [24], indicating that comprehensive prevention strategies including harm reduction and addiction services are crucial for hepatitis C burden reduction and eventual elimination. The Georgian HCV prison program provides risk reduction education to prisoners, including counseling and methadone therapy if needed, but the effectiveness of these programs was not assessed in this evaluation.

The data from this evaluation show that genotype 3 was the predominant HCV genotype among Georgian prisoners during the evaluation period, consistent with a recent respondent-driven-sampling study of PWID that found that 67% were infected with genotype 3 [18]. A national HCV serosurvey conducted in 2015 found higher prevalence of genotype 1 infection (41% of those with a positive HCV RNA test) compared to 35% with genotype 3 in the general population [5]. These studies indicate that there could be systematic differences in the dynamics of the HCV infection epidemic in the prison system compared to the general population, including risk factors for transmission. The HCV genotype distribution among prisoners impacts choice of treatment regimen and is important to consider when estimating associated costs to payers. Specifically, under the treatment regimens used in Georgian prisons during this evaluation period, treatment duration for genotype 3 infections was half that required for genotype 1 (24 vs. 48 weeks, respectively) and therefore less expensive. The distribution of HCV genotypes among prisoners may have cost considerations in the context of Georgia's HCV elimination strategy.

Our evaluation had several limitations. First, data were abstracted from multiple sources, and some important variables, including prisoners' birth date, individual risk factor data, and treatment committee decisions for those prisoners who were not offered treatment were missing. A single database with a comprehensive set of HCV-related variables would improve monitoring strategies in the future. Second, not all prisoners infected with HCV received a full diagnostic evaluation including non-invasive liver fibrosis staging, potentially resulting in under treatment of eligible prisoners. Third, treatment data were not available for all prisoners completing treatment, thus limiting our evaluation of treatment success.

Fourth, costs for the program were not assessed, and could inform future policy. Finally, since this was a retrospective analysis, we were not able to perform quality assurance and quality control on the data collected.

Conclusions

In conclusion, this evaluation demonstrates that a HCV treatment program within the Georgian prison system is feasible, as the majority of prisoners enrolled in treatment in the first 2 years of this program's operation were able to complete their prescribed treatment course. This evaluation also provided an important opportunity to strengthen the public health capacity of Georgia, and thereby enhance global health security. There are several opportunities to enhance the success of the HCV treatment program in the Georgian prison system in the future. Specifically, an opt-out anti-HCV screening structure would further increase identification of infection, and use of newly introduced interferon-free regimens could improve treatment enrollment, adherence, efficacy, and completion. Offering linkage to community-based care to prisoners with short sentences could improve enrollment and completion rates as well. In addition, improved health information data systems would allow for optimal evaluation of future programs. Because most prisoners are eventually released and reintegrated into the community, HCV treatment and prevention in prisons can reduce the HCV infection burden in the general population, contributing to Georgia's overall goal of HCV elimination and serving as a model for other countries pursuing similar targets.

Abbreviations

ALT: Alanine aminotransferase; Anti-HCV: Antibody to hepatitis C virus; APRI: Aspartate aminotransferase to platelet ratio index; AST: Aspartate aminotransferase; DAA: Direct acting antiviral; FIB-4: Fibrosis-4 score; Fx: Liver fibrosis stage; HCV Genotype: Hepatitis C virus genotype; HCV RNA: Hepatitis C virus ribonucleic acid; HCV: Hepatitis C virus; IDACIR: Infectious Diseases, AIDS and Clinical Immunology Research Center; IDU: Injection drug use; IU/L: International units per liter; MOC: Ministry of corrections; PCR: Polymerase chain reaction; PWID: People who inject drugs; SVR12: Sustained virologic response 12 weeks after completion of treatment

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Availability of data and materials

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Authors' contributions

AMH, JB, FA, and JM conceived of the idea for this evaluation, and AH, OC, JB, KT, TT, LS, AT, MB, JM, and FA contributed to the design. AH, OC, JB, KT, TT, KC, TD, MJ, IB, and MF contributed to data collection, and all authors contributed to interpretation of data. OC, AMH, and JB contributed to statistical analysis. AMH, OC, and JB drafted the manuscript and TT, LS, PS, MF, LH, MB, JM, and FA contributed to critical revision of the manuscript for intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The project determined to be a routine public health activity for disease control, and therefore not to involve human subjects research, by Human Subjects Research Offices at Georgia's NCDC and CDC. All data was de-identified to protect patient confidentiality and was analyzed in Georgia in aggregated format.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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The burden of non-communicable diseases and their related risk factors in the country of Georgia, 2015

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Abstract

Background: Non-communicable diseases (NCDs), mainly cardiovascular diseases, are a substantial cause of mortality in the country of Georgia, accounting for approximately 93% of all deaths (standardized mortality rate 630.7 deaths per 100,000 persons per year) and an important threat to health security. We conducted a nationally representative survey examining the prevalence of NCDs and their risk factors as part of a 2015 Hepatitis C Virus (HCV) and Hepatitis B Virus (HBV) serosurvey.

Methods: We conducted a cross-sectional serosurvey among adults aged ≥18 years using a stratified, multi-stage cluster design ($n = 7000$). We asked participants standardized questions from the Global Adult Tobacco Survey and the WHO STEPwise approach to Surveillance (STEPS) Survey. We also measured blood pressure and Body Mass Index for each participant. Weighted frequencies were computed for NCD and risk factor prevalence and compared to 2010 STEPS results.

Results: Georgians reported high rates of smoking, alcohol use, elevated blood pressure, obesity, diabetes and cardiovascular disease. An estimated 27.1% (95% confidence interval [CI]: 25.3, 28.8%) of adults (51.5% of men and 6.0% of women) reported daily use of tobacco products and 27.5% (95% CI: 25.7, 29.2%) of adults (52.1% of men and 7.0% of women) reported binge drinking within the last 30 days. Physical measurements revealed that 37.5% (95% CI: 35.8, 39.3%) of adults had elevated blood pressure and 33.4% (95% CI: 31.8, 35.0%) had obesity. 5.4% (95% CI: 4.6, 6.2%) of adults had self-reported diagnosed diabetes and 15.3% (95% CI: 14.1, 16.6%) had self-reported diagnosed cardiovascular disease. From 2010 to 2015, the prevalence of obesity increased by 8.3 percentage points (95% CI: 5.9, 10.7%; $p < 0.01$) and the prevalence of elevated blood pressure increased by 4.1 percentage points (95% CI: 1.4, 6.8%; $p < 0.01$).

Conclusions: Georgia has a high NCD burden, and results from the survey showed an increase in obesity and elevated blood pressure since 2010. The prevalence of other major NCDs have remained near levels reported in the 2010 STEPs survey. Comprehensive public health interventions are needed to control the heath security threats of major NCDs and their risk factors in the future.

Keywords: Global Health, Non-communicable disease, Risk factors, Survey, Georgia, Global health security

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Background

Georgia is an Eastern European, middle-income country with 3.7 million residents [1]. Non-communicable diseases (NCDs) are the most substantial causes of mortality and morbidity in Georgia, accounting for an estimated 46,200 deaths in 2015 and resulting in an age-standardized mortality rate of 630.7 deaths per 100,000 persons per year [2]. That rate was 13th highest out of 50 countries in the World Health Organization's (WHO) European Region, up from 16th in 2010, 25th in 2005, and 21st in 2000 [3]. A 2014 report revealed that NCDs accounted for approximately 93% of the country's total mortality. In comparison, NCDs accounted for 90% of total mortality in the European region and 70% of total mortality worldwide [4]. Four main categories of NCDs, namely cardiovascular diseases, cancer, chronic respiratory diseases and diabetes, caused 88% of Georgia's mortality, with 69% of mortality being caused by cardiovascular diseases alone.

A number of risk factors have been indicated in the high prevalence of NCDs, including excessive alcohol use, smoking, obesity, and elevated blood pressure, each of which has been shown to be associated with both NCDs and other negative health outcomes. Excessive alcohol use has been linked to high blood pressure, heart disease, stroke, liver disease, cancer, mental health problems, and alcohol dependence [5]. Smoking has been associated with an increased risk of coronary heart disease, stroke, type 2 diabetes mellitus, rheumatoid arthritis, and various cancers [6, 7]. A higher body mass index (BMI), beyond the normal weight range, is associated with increased morbidity and mortality from coronary heart disease, osteoarthritis, type 2 diabetes mellitus, hypertension, and certain types of cancer [8]. Hypertension is a major risk factor for cardiovascular disease and globally accounts for 54% of all strokes and 47% of all cases of ischemic heart disease [9].

The high mortality from NCDs and the strong association between NCDs and the identified risk factors has highlighted a need to measure national and subnational trends in NCD and NCD risk factor prevalence to inform prevention activities. The most recent NCD risk factor data assessing hypertension, obesity, smoking, and alcohol consumption in Georgia were collected from WHO STEPwise approach to surveillance (STEPS) assessments in 2010 and 2016. STEPs provides a standardized survey tool which includes a manual containing comprehensive guidelines for countries undertaking NCD risk factor surveys. The 2016 STEPs data indicated that 37.7% of the population had elevated blood pressure, with 55.4% of those being untreated [10]. About 64.6% of adults were considered overweight (BMI $\geq$ 25 kg/m^2), with 33.2% being obese (BMI $\geq$ 30 kg/m^2) [10]. Among males, 35.3% reported heavy episodic drinking and 51.5% reported smoking tobacco products daily [10].

In light of the 2010 and 2016 STEPS reports, the Georgian government took several significant steps to decrease the morbidity, disability and mortality caused by NCDs. In particular, the Multi-sectoral Coordination Council of Prevention and Control of NCDs was established under the Minister of Labor, Health and Social Affairs in December 2015. The 2017–2020 Action Plan and the NCD strategy were endorsed in January 2017. A national cancer registry and a birth registry were established (2015, 2016). Additionally, a sentinel surveillance system measuring nutrition and micronutrient deficiency was implemented, several studies on tobacco were conducted (2014, 2014, 2015), state routine surveillance was improved, national cancer screening programs (breast, cervical, colorectal and prostate cancer) were created (2011), and guidelines and protocols for major NCDs were developed.

In an additional effort to monitor Georgia's progress in combating NCDs, a nationally representative, cross-sectional survey examining several NCDs and their risk factors was included as part of the Georgia Hepatitis C Virus (HCV) and Hepatitis B (HBV) Serosurvey in 2015. The objective of the NCD component of the survey was to estimate the prevalence of major NCDs and the major risk factors of NCDs in adults aged 18 years and above in Georgia. The survey built upon previously conducted STEPs surveys and included additional components including geographic estimates of cardiovascular diseases, chronic respiratory diseases, and cancers. This manuscript reports the results of the 2015 survey, including a comparison to the 2010 STEPs survey.

Methods

The National Center for Disease Control and Public Health (NCDC) implemented a stratified, multi-stage cluster survey designed to yield national and subnational prevalence estimates for HCV and HBV, as well as estimates for various NCDs and NCD risk factors [11]. The survey population included all eligible adults aged 18 years and above who were living in a household in Georgia. Temporary household guests, homeless persons, those who were currently incarcerated or institutionalized were not eligible for selection. We calculated a sample size of 7000 people to attain 1% precision in our HCV prevalence estimate, assuming an estimated 6.7% anti-HCV seroprevalence [12], a design effect of 2, and an anticipated 70% response rate.

To select participants, we divided the country into 16 mutually exclusive sampling strata consisting of six major cities and ten regions. We did not include the autonomous regions of Abkhazia and Samachablo (South Ossetia) due to political conflict in the area. We selected 280 clusters, each representing one census sector as

defined by Georgia's National Statistics Office (GeoStat). Within each cluster, we conducted a systematic sample of 25 households. We divided the total number of households in the cluster by 25 and used a random starting point to begin sampling. Within each household, we applied the Kish method to randomly select one adult for participation [13].

We asked participants standardized questions from the Global Adult Tobacco Survey [14] and the WHO STEPwise approach to Surveillance (STEPS) Survey (version 2.1) [15], which was the same version used in Georgia's 2010 STEPs survey. For survey questions concerning other chronic conditions like cancer, cardiovascular disease, and chronic respiratory disease, we developed questions from standard National Health and Nutritional Examination Survey (NHANES) wording [16]. In the analysis below, we report on results for four common NCD risk factors (current daily smoking, heavy episodic drinking, elevated blood pressure, obesity) and four major categories NCDs (chronic respiratory disease, cancer, diabetes, and cardiovascular disease).

We collected data on blood pressure and anthropometric measurements to estimate the proportion of adults that had elevated blood pressure or had obesity. Both measurements were carried out using standard equipment and the recommended WHO STEPS protocol [15]. We calculated BMI by dividing each participant's weight (in kilograms) by their squared height (in meters). If a participant had a BMI $\geq 30\ kg/m^2$, we classified them as having obesity [15]. We used the mean of the 2nd and 3rd of three blood pressure measurements to estimate blood pressure. If a participant's systolic blood pressure was ≥140 mmHg or their diastolic blood pressure was ≥90 mmHg, we classified them as having elevated blood pressure [15]. Current daily smoking, heavy episodic drinking, chronic respiratory disease, cancer, diabetes, and cardiovascular disease were assessed via participants' self-report. The specific wording for each question corresponding to a self-reported indicator is listed in Table 1.

We conducted statistical analysis in SAS (version 9.4, Cary, NC) and accounted for the probability of selection at the cluster, household, and individual levels using survey weights. The weights were calibrated to represent Georgia's national population in terms of sex, age, and geographic distribution based on 2014 census data. We computed descriptive statistics, including weighted prevalence estimates with 95% confidence intervals (CI), to describe the outcomes of interest. Two sample z-tests for proportions ($\alpha = 0.05$) were used to quantify the differences in prevalence over time. Choropleth maps describing the geographic spread of NCDs and NCD risk factors were created in QGIS 2.18.10.

This activity was reviewed in accordance with CDC human subjects review procedures and was determined to be non-research, public health surveillance.

Results

Of the 7000 adults selected for the survey, 6296 (89.9%) consented to participate, with response rates exceeding 70% in all 16 strata. The adults ranged from 18 to 102 years old and the median age was 45. 53.8% were female, and 56.7% lived in urban areas (Table 2). Most (90.8%) had completed education

Table 1 Criteria for inclusion in prevalence calculation

Indicator	Indicator type	Question or criteria
NCDs		
Current daily smoking	self-report	Do you currently smoke tobacco on a daily basis, less than daily, or not at all?
Heavy episodic drinking	self-report	(For men) During the past 30 days, did you had five or more standard alcoholic drinks in a single occasion?
		(For women) During the past 30 days, did you had four or more standard alcoholic drinks in a single occasion?
Elevated Blood Pressure	physical measurement	systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg
Obesity	physical measurement	BMI $\geq 30\ kg/m^2$
NCD risk factors		
Cardiovascular disease	self-report	Have you ever been told by a doctor or other health worker that you have cardiovascular disease?
Cancer	self-report	Have you ever been told by a doctor or other health worker that you have cancer?
Chronic respiratory disease	self-report	Have you ever been told by a doctor or other health worker that you have asthma or lung disease or COPD?
Diabetes	self-report	Have you ever been told by a doctor or other health worker that you have diabetes?

Table 2 Demographic characteristics among Georgian adults, Georgia NCD survey, 2015

Demographic Characteristics	Unweighted sample size n	Population-weighted percentage % (95% CI)
Overall		
Age (years)		
18–29	1115	19.4 (18.1, 20.7)
30–44	1725	29.0 (27.3, 30.7)
45–59	1662	25.5 (24.0, 27.0)
60+	1790	26.1 (24.5, 27.7)
Missing	4	0.05 (< 0.01, 0.1)
Sex		
Males	3868	53.8 (52.0, 55.5)
Females	2428	46.2 (44.5, 48.0)
Missing	0	0
Residency		
Urban	3350	56.7 (52.7, 60.6)
Rural	2946	43.3 (39.4, 47.3)
Missing	0	0
Education		
Completed less than elementary/primary school	43	0.7 (0.5, 1.1)
Completed elementary/primary school	612	8.5 (7.3, 9.8)
Completed secondary school	2567	40.2 (38.1, 42.3)
Completed professional/technical school	1157	16.6 (15.3, 18.0)
Completed university/college or higher	1912	34.0 (31.6, 36.4)
Missing	5	0.09 (< 0.01, 0.2)
Employment Status		
Employed	2120	37.8 (35.6, 39.9)
Student	172	3.6 (2.9, 4.4)
Homemaker	1483	19.1 (17.7, 20.6)
Retired	1405	20.0 (18.7, 21.5)
Unemployed	1110	19.5 (18.0, 21.1)
Missing	6	0.08 (0.02, 0.14)
Household income		
≤ 6000 GEL/year (≤ 4400 USD)	2960	43.7 (41.2, 46.2)
6001–12,000 GEL/year (4400–6800 USD)	953	17.1 (15.5, 18.7)
12,001–24,000 GEL/year (6800–13,600 USD)	724	11.6 (10.4, 12.9)
> 24,000 GEL/year (> 13,600 USD)	1339	21.6 (19.4, 23.9)
Missing	320	5.9 (4.8, 7.0)

through secondary school or higher, and 19.5% were unemployed at the time of the survey. Approximately 60.8% reported an annual household income less than 12,000 Georgian Lari ($6797 USD).

The majority of the individuals surveyed were vulnerable to morbidity from NCDs, with 72.3% (95% CI: 70.7, 73.8%) of adults reporting at least one of four NCD risk factors. Heightened risk existed among the 39.3% (95% CI: 37.3, 41.3%) of people reporting at least two NCD risk factors, and the 12.2% (95% CI: 11.0, 13.4%) of people reporting at least three NCD risk factors (Table 3). The most prevalent risk factor was elevated blood pressure, which was estimated to impact 37.5% (95% CI: 35.8, 39.3%) of the population according to physical measurements conducted during the survey (Table 2). Additionally, an estimated 33.4% (95% CI: 31.8, 35.0%) of adults had obesity, 27.5% (95% CI: 25.7, 29.2%) reported heavy episodic

Table 3 Overall prevalence of NCDs and NCD risk factors

	n	% (95% CI)
NCD risk factors		
Obesity*	2103	33.4 (31.8, 35.0)
Current daily smoking	1707	27.1 (25.3, 28.8)
Heavy episodic drinking†	1731	27.5 (25.7, 29.2)
Elevated Blood Pressure‡	2361	37.5 (35.8, 39.3)
At least one of the above risk factors	4230	72.3 (70.7, 73.8)
At least two of the above risk factors	2188	39.3 (37.3, 41.3)
At least three of the above risk factors	613	12.2 (11.0, 13.4)
At least four of the above risk factors	114	2.3 (1.7, 3.0)
NCDs		
Cardiovascular Disease	964	15.3 (14.1, 16.6)
Cancer	57	0.9 (0.6, 1.2)
Chronic Respiratory Disease	246	3.9 (3.2, 4.7)
Diabetes	340	5.4 (4.6, 6.2)
At least one of the above NCDs	1465	22.1 (20.5, 23.6)
At least two of the above NCDs	207	3.0 (2.4, 3.5)
At least three of the above NCDs	17	0.4 (0.1, 0.7)
At least four of the above NCDs	0	0

*Obesity is defined as BMI ≥30 kg/m^2
†For men, heavy episodic drinking is defined as consuming 5 or more standard alcoholic drinks in a single occasion in the last 30 days
†For women, a heavy episodic drinking is defined as consuming 4 or more standard alcoholic drinks in a single occasion in the last 30 days
‡Elevated blood pressure is systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg

drinking in the last 30 days, and 27.1% (95% CI: 25.3, 28.8%) reported currently smoking tobacco products on a daily basis.

A high prevalence of NCDs was also observed in this survey. An estimated 22.1% of adults reported at least one of the four main categories of NCDs (cardiovascular diseases, cancers, chronic respiratory diseases, and diabetes), 3.0% of reported at least two and 0.4% reported at least three. The most prevalent NCD was cardiovascular disease, which was reported among 15.3% (95% CI: 14.1, 16.6%) of the population. In decreasing order of prevalence, respondents also reported diabetes, 5.4% (95% CI: 4.6, 6.2%), chronic respiratory diseases, 3.9% (95% CI: 3.2, 4.7%), cancer, 0.9% (95% CI: 0.6, 1.2%).

A comparison between our 2015 dataset and the 2010 STEPS survey data revealed mixed results in Georgia's effort to reduce the prevalence of NCD risk factors (Table 4). Over the five year period between surveys, the prevalence of obesity increased by 8.3 percentage points (95% CI: 5.9, 10.7%; z = 6.8, $p < 0.01$). The prevalence of elevated blood pressure for females increased by 3.2 percentage points (95% CI: 0.4, 6.0%; z = 2.2, $p < 0.05$). The prevalence of heavy episodic drinking among males increased by 2.3 percentage points (95% CI: -2.8, 7.4%; z = 0.9, $p = 0.37$), although the apparent increase was not statistically significant and may have been due to sampling error. Among females, reported heavy episodic drinking actually decreased by 3.3 percentage points (95% CI: 1.1, 5.5%; z = – 2.9, p < 0.01). Current daily tobacco use also decreased by 0.6% (95% CI: -2.0, 3.2%; z = 0.2, $p = 0.64$), although again, the apparent decrease was not significant.

Table 4 Change in non-communicable disease risk factor prevalence, 2010–2015

Disease	2010 STEPS survey % (95% CI)	2015 HCV survey % (95% CI)	Change % (95% CI)	z	*p*-value
Obesity*	25.1 (23.3, 26.8)	33.4 (31.8, 35.0)	8.3 (5.9, 10.7)	6.84	< 0.01
Male	21.8 (19.3, 24.3)	29.0 (26.6, 31.4)	7.2 (3.7, 10.7)	4.06	< 0.01
Female	28.5 (26.6, 30.3)	37.1 (35.1, 39.2)	8.6 (5.8, 11.4)	6.12	< 0.01
Current daily smoking	27.7 (25.8, 29.5)	27.1 (25.3, 28.8)	−0.6 (−3.2, 2.0)	0.46	0.64
Male	51.1 (48.1, 54.0)	51.5 (48.5, 54.6)	0.4 (−3.8, 4.6)	0.17	0.85
Female	4.0 (2.9, 5.0)	6.0 (4.7, 7.3)	2.0 (0.3, 3.7)	2.36	0.02
Heavy episodic drinking†	NR	27.5 (25.7, 29.2)	NA	NA	NA
Male	49.8 (45.7, 53.9)	52.1 (49.2, 55.0)	2.3 (−2.8, 7.4)	0.89	0.37
Female	10.3 (8.5, 12.0)	7.0 (5.7, 8.3)	−3.3 (−5.5, −1.1)	2.94	< 0.01
Elevated Blood Pressure (measured)‡	33.4 (31.4, 35.5)	37.5 (35.8, 39.3)	4.1 (1.4, 6.8)	2.97	< 0.01
Male	37.1 (34.0, 40.3)	42.7 (39.9, 45.5)	5.6 (1.4, 9.8)	2.59	< 0.01
Female	29.8 (27.9, 31.8)	33.0 (31.0, 35.1)	3.2 (0.4, 6.0)	2.21	0.03

*Obesity is defined as BMI ≥30 kg/m^2
†For men, heavy episodic drinking is defined as consuming 5 or more standard alcoholic drinks in a single occasion in the last 30 days
†For women, a heavy episodic drinking is defined as consuming 4 or more standard alcoholic drinks in a single occasion in the last 30 days
‡Elevated blood pressure is systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg

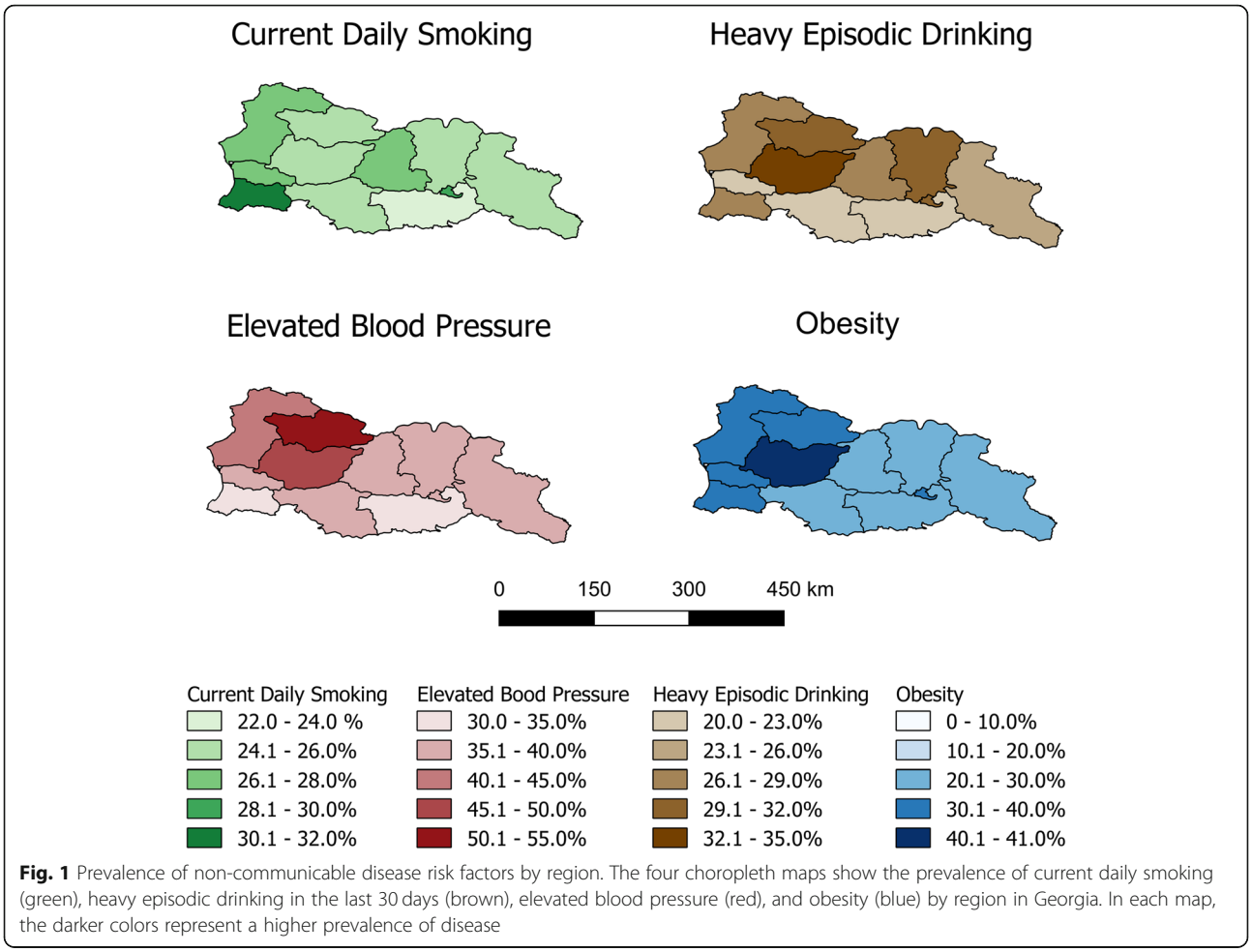

Fig. 1 Prevalence of non-communicable disease risk factors by region. The four choropleth maps show the prevalence of current daily smoking (green), heavy episodic drinking in the last 30 days (brown), elevated blood pressure (red), and obesity (blue) by region in Georgia. In each map, the darker colors represent a higher prevalence of disease

An analysis of the geographical variation in NCDs and NCD risk factors (Figs. 1 and 2) found that the region of Imereti had the highest prevalence of obesity (40.1, 95% CI: 35.9, 44.2%), the highest reported prevalence of heavy episodic drinking (32.1, 95% CI: 28.3, 35.8%), and the second highest prevalence of elevated blood pressure (45.5, 95% CI: 42.3, 48.6%). The only region with higher elevated blood pressure (50.9, 95% CI: 44.8, 57.1%) was Racha-Lechkumi, which also reported the highest prevalence of cardiovascular disease (36.2, 95% CI: 30.4, 42.0%) and diabetes (6.7, 95% CI: < 0.1, 15.2%). The proportion of people who reported daily tobacco use was highest in Tbilisi (30.0, 95% CI: 25.7, 34.2%) and Ajaria (30.5, 95% CI: 26.9, 34.1%), the regions containing the first second largest cities in Georgia, respectively. Tbilisi also reported the highest prevalence of chronic respiratory disease (6.4, 95% CI: 4.3, 8.4%), perhaps partially because of the aforementioned high smoking rate. The highest reported prevalence of cancer occurred in the region of Guria (1.9, 95% CI: < 0.1, 4.3%). A full analysis of geographical variation is provided (Additional file 1: Table S1).

Wide disparities in the prevalence of NCD and NCD risk factors between gender and age groups were also apparent. Men engaged in much higher rates of unhealthy behaviors, most notably smoking and heavy episodic drinking. 51.5% (95% CI: 48.5, 54.6%) of men reported smoking tobacco products daily, compared to 6.0% (95% CI: 4.7, 7.3%) of females. 52.1% (95% CI: 49.2, 55.0%) of men reported heavy episodic drinking in the last 30 days compared to 7.0% (5.7, 8.3%) of women. Women were more likely to have obesity, with 37.1% (95% CI: 35.1, 39.2%) of women having a BMI $\geq$ 30 kg/m^2, compared to 29.0% (95% CI: 26.6, 31.4%) of men. Compared to those under 45 years of age, older adults (45+) were more likely to have elevated blood pressure and obesity, and were more likely to report cardiovascular disease, cancer, chronic respiratory disease, and diabetes. A full analysis of NCD and NCD risk factor prevalence by age group and gender is provided (Additional file 2: Table S2).

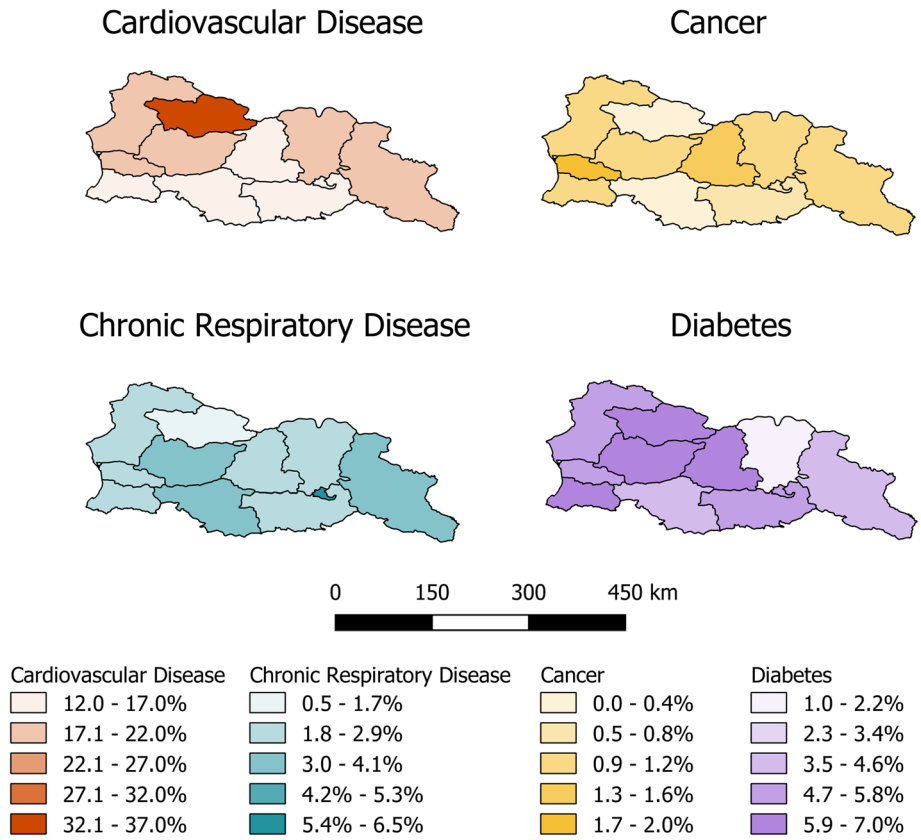

Fig. 2 Prevalence of non-communicable diseases by district. The four choropleth maps show the prevalence of cardiovascular disease (orange), cancer (gold), chronic respiratory disease (aqua) and diabetes (purple) by region in Georgia. In each map, the darker colors represent a higher prevalence of disease

Discussion

The results of this nationally representative survey highlight the high burden of common NCDs and their major risk factors in Georgian adults. Compared to many of its European peers, Georgia has not yet been successful in limiting tobacco use, obesity, diabetes, or cardiovascular disease. While significant steps have been made to improve NCD surveillance and care in Georgia, measurable decreases in risk factors and disease have not yet been observed. Modest victories, including a decrease in daily tobacco use and heavy episodic drinking (among women) since 2010, provide a reason for optimism and offer a blueprint for future action. Setbacks, including the increase in obesity and hypertension, reiterate the importance of prevention efforts and underscore the need to bolster existing interventions.

While the overall, nationwide burden of NCDs is high, it is not equally distributed across the population. Regional and demographic differences in NCD prevalence underlie differences in lifestyle, socioeconomic status, and access to healthcare. Older residents tend to report diminished outcomes compared to their younger counterparts. Wide gender disparities were evident, with men reporting higher levels of tobacco use and heavy episodic drinking, but women reporting higher prevalence of cardiovascular diseases and cancers. With such differences in mind, a concerted effort to focus potential health interventions on specific high-risk populations may be warranted. Targeted interventions can provide a dual benefit; they are likely to be more cost efficient while also serving to promote health equity.

Georgia's increasing obesity prevalence is consistent with global and regional trends, and could be attributed to a number of potential factors, including an aging population and continued high rates of alcohol consumption [17]. Adults who were 45 years or older, especially women, had a much higher obesity prevalence than those in the younger age groups. Interventions aimed at improving physical activity and healthy dietary intake, particularly those focused among high-risk demographic groups, may help to ease the obesity burden in Georgia.

The observed increase in elevated blood pressure was also notable, and may have been even greater than

estimated. In the 2010 STEPS survey, an individual was labeled hypertensive if their measured blood pressure was elevated (≥140 SBP or ≥ 90 DBP) or if they were on blood pressure medications. This study did not collect information on blood pressure medication usage so it did not include those with normal pressure (< 140 SBP and < 90 DBP) who were taking blood pressure medications as the 2010 STEPS rates did. This difference in methodology would underestimate the rate of hypertension found in 2015 compared with 2010, assuming persons on anti-hypertensive therapy would have good blood pressure control. Efforts to control hypertension with medical care and education regarding nutrition, staying active, and moderating alcohol use may help reduce hypertension [18] in the population.

There were several limitations of this study. First, we used self-reported data to estimate the prevalence of NCDs, which could potentially be subject to inaccuracies due to recall bias. Second, social desirability bias may have occurred due to the potential stigmatization of certain behaviors and conditions, including questions about behaviors such as smoking and alcohol consumption. Third, we collected data on broadly defined disease categories, such as diabetes, cancer, and cardiovascular disease. Thus, we are unable to make inferences on specific subtypes of those diseases, for example comparisons between type 1 and type 2 diabetes, or comparisons between heart disease and stroke. Fourth, while we used sampling weights designed to adjust for non-response, the moderate response rate may have still resulted in some degree of non-response bias. Finally, the estimated prevalence of hypertension was not directly comparable to the 2010 STEPS survey, due to the methodological differences described above. Despite these limitations, this study adds updated information on the NCD burden and identifies the trends of major NCD risk factors in Georgian adults. The NCD risk factor prevalence estimates generated by the 2015 survey have since been corroborated by similar 2016 STEPs survey estimates (when direct comparisons were possible).

Conclusions

The NCD risk factors listed in this study are each associated with multiple NCDs. Thus, improving the prevention of a single risk factor could result in a decreased prevalence of multiple NCDs. Conversely, an increase in a single risk factor could lead to multiple negative health outcomes. Continued investment in comprehensive prevention and control interventions could be considered to combat these negative outcomes. A concerted national effort to enact prudent, evidence-based interventions could improve quality of life, reduce mortality, strengthen global health security, and counteract the economic costs associated with the high burden of NCDs.

Additional files

Additional file 1: Table S1. NCD and NCD risk factor prevalence by region (DOCX 15 kb)

Additional file 2: Table S2. NCD and NCD risk factor prevalence by gender and age group (DOCX 16 kb)

Abbreviations

BMI: Body mass index; CDC: Centers for Disease Control and Prevention; CI: Confidence interval; DBP: Diastolic blood pressure; GeoStat: Georgia's National Statistics Office; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HIV/AIDS: Human immunodeficiency virus infection and acquired immune deficiency syndrome; NCD: Non-communicable disease; NCDC: National Center for Disease Control and Public Health; NHANES: National Health and Nutritional Examination Survey; QGIS: Quantum Geographic Information System; SAS: Statistical analysis system; STD: Sexually transmitted disease; STEPS: STEPwise approach to surveillance; WHO: World Health Organization

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Availability of data and materials

The raw data will be not publicly available but the de-identified raw data can be requested from the corresponding author after providing the necessary justification for request.

About this supplement

This article has been published as part of *BMC Public Health Volume 19 Supplement 3, 2019: 10th anniversary of the Centers for Disease Control and Prevention - Global Disease Detection program.* The full contents of the supplement are available online at https://bmcpublichealth.biomedcentral.com/articles/supplements/volume-19-supplement-3.

Authors' contributions

SR was the primary author and data analyst. SS and LH were responsible for the conception, implementation, and supervision of the serosurvey. LS, CL, JM, MT, CB, LH, and SS contributed to the study design, collection and interpretation of the data, writing and editing the manuscript. SR prepared the first and second drafts. All authors were involved in subsequent editing and agreed on the final version.

Ethics approval and consent to participate

This activity was reviewed in accordance with CDC human subjects review procedures and was determined to be non-research, public health surveillance. Written consent was obtained from all subjects participating in the survey.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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July 26, 2019

World Hepatitis Day — July 28, 2019

World Hepatitis Day, observed each year on July 28, was established to raise awareness and promote understanding of viral hepatitis around the world. The theme of this year's World Hepatitis Day is "Invest in Eliminating Hepatitis," underscoring the need to increase commitment for hepatitis response. In 2015, an estimated 257 million persons were living with hepatitis B and 71 million with hepatitis C worldwide (*1*).

Persons who inject drugs are at highest risk for hepatitis C virus (HCV) infection. Globally, an estimated 15.6 million persons aged 15–64 years inject drugs, 52% of whom are HCV-antibody positive (*2*). This issue of *MMWR* features a report on the progress in the country of Georgia toward prevention and detection of HCV infection, and linkage to treatment, of persons with HCV infection who inject drugs (*3*). Georgia's hepatitis C elimination program, launched in 2015, was recently named the world's first Centre of Excellence in Viral Hepatitis Elimination by the European Association for the Study of the Liver International Liver Foundation. Access to hepatitis C testing and treatment for persons who inject drugs is critical to achieving elimination in countries where persons who inject drugs account for a significant proportion of HCV infection. Additional information and resources about viral hepatitis are available at https://www.cdc.gov/hepatitis.

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Progress in Testing for and Treatment of Hepatitis C Virus Infection Among Persons Who Inject Drugs — Georgia, 2018

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In April 2015, the country of Georgia, with a high prevalence of hepatitis C virus (HCV) infection (5.4% of the adult population, approximately 150,000 persons), embarked on the world's first national elimination program (*1*,*2*). Nearly 40% of these infections are attributed to injection drug use, and an estimated 2% of the adult population currently inject drugs, among the highest prevalence of injection drug use in the world (*3*,*4*). Since 2006, needle and syringe programs (NSPs) have been offering HCV antibody testing to persons who inject drugs and, since 2015, referring clients with positive test results to the national treatment program. This report summarizes the results of these efforts. Following implementation of the elimination program, the number of HCV antibody

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tests conducted at NSPs increased from an average of 3,638 per year during 2006–2014 to an average of 21,551 during 2015–2018. In 2017, to enable tracking of clinical outcomes among persons who inject drugs, NSPs began encouraging clients to voluntarily provide their national identification number (NIN), which all citizens must use to access health care treatment services. During 2017–2018, a total of 2,780 NSP clients with positive test results for HCV antibody were identified in the treatment database by their NIN. Of 494 who completed treatment and were tested for HCV RNA ≥12 weeks after completing treatment, 482 (97.6%) were cured of HCV infection. Following the launch of the elimination program, Georgia has made much progress in hepatitis C screening among persons who inject drugs; recent data demonstrate high cure rates achieved in this population. Testing at NSPs is an effective strategy for identifying persons with HCV infection. Tracking clients referred from NSPs through treatment completion allows for monitoring the effectiveness of linkage to care and treatment outcomes in this population at high risk, a key to achieving hepatitis C elimination in Georgia. The program in Georgia might serve as a model for other countries.

The Georgian Harm Reduction Network began operating and receiving hepatitis C testing data from NSPs in 2006. As of 2016, 16 NSPs were operating in 13 cities across Georgia. During 2017–2018, with additional resources provided by the Global Fund to Fight AIDS, Tuberculosis and Malaria, two additional NSP centers and eight mobile NSP units became operational, increasing coverage to approximately 50 of 79 municipalities countrywide. The Georgian Harm Reduction Network also provides diverse services* to persons who inject drugs to improve their health outcomes (*5*).

Persons who inject drugs and who test positive with a rapid HCV antibody test at NSPs are offered case management support and referred to authorized treatment sites for testing to confirm active HCV infection.† Since 2017, those persons who agree to treatment referral are asked to provide their 11-digit NIN to the NSP so that further clinical management can be confirmed and documented in the national program treatment database. Once at the treatment center, those patients with confirmed infection are enrolled in the treatment program and, if eligible for treatment, prescribed a direct-acting antiviral regimen according to national treatment guidelines (*6*). Within 12–24 weeks of completing treatment, patients are instructed to return to the treatment site for HCV RNA testing to determine whether sustained viral response (i.e., virologic cure) was achieved. Demographics, diagnostics, and treatment outcomes are recorded in real-time in the national program treatment database.

For this analysis, program records from the Georgian Harm Reduction Network were reviewed to ascertain annual HCV

* Services provided though the Georgian Harm Reduction Network include distribution of sterile injecting equipment, condoms, and naloxone; voluntary counselling and testing for hepatitis C, human immunodeficiency virus, hepatitis B, and syphilis; peer-to-peer education; raising prevention awareness among persons who inject drugs; and advocacy for increased access to NSPs.
† Positive for HCV RNA or HCV core antigen.

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antibody screening and positivity frequencies at NSPs during January 2006–December 2018 among persons who inject drugs; age group and sex distribution data were available from NSPs for 2015–2018. NSPs entered testing and service provision data into a database, which were validated by data management specialists at the Georgian Harm Reduction Network. Deduplication of test results was not conducted during 2006–2013 because of insufficient resources; during 2014–2018, deduplication of results was performed for each calendar year. Data for HCV antibody-positive persons who inject drugs who provided their NIN to NSPs during January 1, 2017–December 31, 2018, were linked to the national program treatment database to ascertain the hepatitis C care cascade, which summarizes the sequential steps in care. Because this analysis constituted a program evaluation, institutional review board oversight was not indicated.

During 2006–2018, NSPs provided 118,943 HCV antibody tests to persons who inject drugs, 48,228 (40.5%) of which were positive (Figure 1). During the years preceding program implementation (2006–2014), 32,738 (average 3,638 per year) tests were conducted; nearly half (49.6%; 16,247) were positive. Following implementation of the elimination program (2015–2018), the average number of antibody tests performed each year among persons who inject drugs increased approximately 500%, to 21,551. Among the 86,205 HCV antibody tests provided during this period, 31,981 (37.1%) were positive. Males accounted for 96.1% of tests, and persons aged 30–39 years were the most frequently tested age group (33.7%). In 2018, the HCV antibody prevalence among persons aged 18–29 years was 5.5%, the lowest among all age groups during 2015–2018. HCV antibody positivity was 37.8% among males and 24.0% among females tested at NSPs during 2015–2018.

During 2017–2018, among 12,163 HCV antibody-positive test results from 11,424 clients at NSPs, 2,780 (24.3%) persons were identified by their NIN in the national treatment database, 1,626 (58.5%) of whom received a follow-up diagnostic test for active HCV infection (Figure 2). Among those tested, 1,370 (84.3%) had active HCV infection. Of those with active infection, 1,029 (75.1%) initiated treatment, 892 (86.7%) of whom completed treatment and were eligible for sustained viral response testing. Of these, 494 (55.4%) returned for sustained viral response testing, 482 (97.6%) of whom achieved cure.

Discussion

Hepatitis C testing at NSPs in Georgia is an effective strategy for identifying persons with HCV infection. During the 3 years following the launch of the elimination program in Georgia in 2015, the number of HCV antibody tests performed at NSPs increased nearly fivefold, and the number of persons with positive test results doubled, compared with the number with positive test results during 2006–2014. Further, voluntary

FIGURE 1. Number of tests for hepatitis C virus (HCV) antibody conducted and positive test results among persons who inject drugs — Georgian Harm Reduction Network, Georgia, 2006–2018

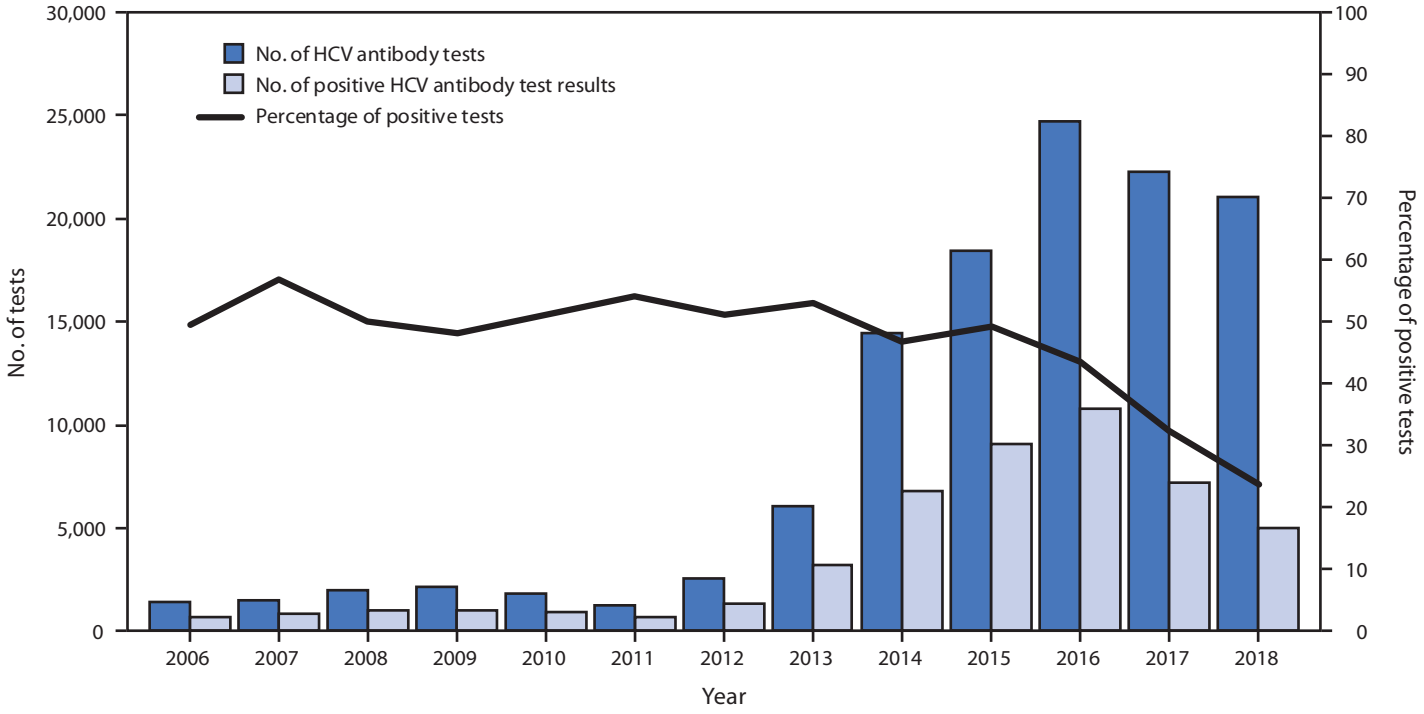
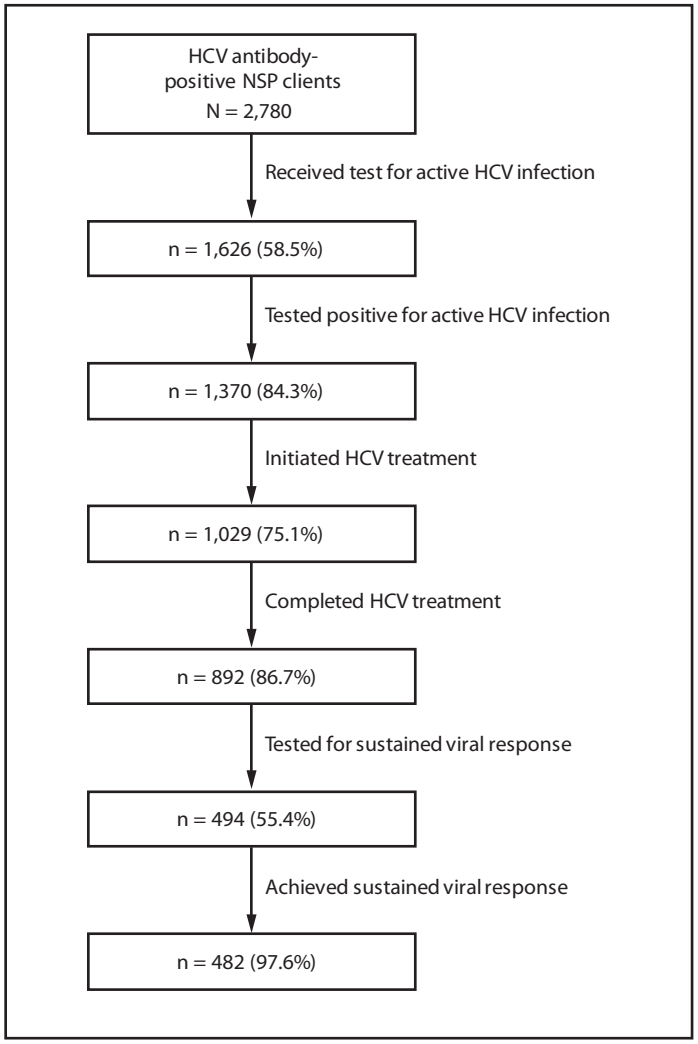


FIGURE 2. Hepatitis C virus (HCV) testing* and treatment outcomes among persons who inject drugs referred by needle and syringe programs (NSPs) to the national hepatitis C treatment program, as identified by their national identification numbers — Georgia, 2017–2018



* HCV RNA or HCV core antigen.

use of the NIN among persons who inject drugs and receive services at NSPs permitted monitoring the linkage to care and treatment, as well as treatment outcomes, among this population at high risk. The number of tests performed annually at NSPs peaked in 2016, and the percentage of positive test results has been trending down since the launch of the elimination program in 2015. The reasons for the decrease in testing after 2016 are unclear but might represent a decreasing pool of persons who inject drugs and remain unaware of their HCV infection status. The decrease in the proportion of positive test results at NSPs during 2016–2018 suggests that a higher proportion of persons who inject drugs screened in recent years have not yet had exposure to HCV. This interpretation is supported by the finding that among all age groups, those aged 18–29 years had the lowest HCV antibody positivity prevalence in 2018 and might attest to the effectiveness of the prevention measures provided by NSPs. Given the estimate of approximately 50,000 persons who inject drugs in Georgia and that nearly 120,000 HCV antibody tests have been conducted at NSPs (with approximately 50,000 positive HCV antibody test results) since 2006, it is likely that the majority of persons who inject drugs in Georgia have been tested at least once for HCV antibody.

Fewer than one fourth of persons who inject drugs agreed to provide their NIN to NSPs for the purpose of tracking clinical outcomes. Stigma related to drug use and fear of adverse legal, social, and economic consequences might discourage persons from disclosing their NIN to NSPs before accessing hepatitis C care and treatment (*6*). To avoid revealing their injection drug use status in the national registry and treatment database, persons could opt to visit treatment sites without divulging their affiliation with NSP services. At present, no incentives are offered by NSPs to motivate persons to provide their NIN. Without the NIN, persons who inject drugs cannot be tracked throughout the cascade of hepatitis C care, and the degree to which elimination efforts are proceeding in this population is hard to ascertain. A study is currently underway to examine the feasibility and effectiveness of providing screening, care, and treatment services at NSPs.

The findings in this report are subject to at least three limitations. First, data from NSP screening and the treatment programs could not be independently verified and could be subject to data entry errors. Second, resources were unavailable to deduplicate NSP test records before 2014; thus, it is not known whether each HCV antibody test during 2006–2013 represented a single person screened. Finally, because only a small proportion of screening data from NSPs were linked to

Summary

What is already known about this topic?

Georgia, with a high prevalence of hepatitis C virus (HCV) infection and a high prevalence of injection drug use, launched a hepatitis C elimination program in 2015. Since 2006, needle and syringe programs (NSPs) have offered HCV antibody testing for persons who inject drugs.

What is added by this report?

Following the launch of the hepatitis C elimination program, the number of HCV antibody tests performed at NSPs has increased fivefold, and the number of persons with positive test results has doubled.

What are the implications for public health practice?

Hepatitis C testing at NSPs is an effective strategy for identifying persons with HCV infection. The program in Georgia might serve as a model for other countries.

treatment data, this analysis could not fully assess the effectiveness of linkage from NSP screening to the national care and treatment program.

Strategies to engage persons who inject drugs in hepatitis C prevention, care, and treatment are needed to ensure elimination in Georgia. Lessons from Georgia could inform other countries with a high prevalence and similar epidemiology of hepatitis C.

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All authors have completed and submitted the ICMJE form for disclosure of potential conflicts of interest. No potential conflicts of interest were disclosed.

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Editorial

JOURNAL OF HEPATOLOGY

Excellence in viral hepatitis elimination – Lessons from Georgia

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Globally, there are more than 70 million people living with chronic hepatitis C virus (HCV) infection, and an estimated 257 million people are living with hepatitis B virus (HBV) infection, both of which cause significant morbidity and mortality primarily as consequences of chronic infection, including hepatocellular carcinoma and liver failure.[1] Georgia, a small country in the South Caucasus, has a high prevalence of HCV infection with an estimated 150,000 adults living with hepatitis C, representing 5.4% of the adult population.[2] Georgia was the first country in the world to undertake the challenge of hepatitis C elimination. A serosurvey in 2015 laid the foundation for the elimination program; the survey not only defined the burden of hepatitis C in the country, but also identified the major risk factors for transmission (injection drug use and receipt of blood products) and the demographic profile of those infected, thus allowing for clear characterization of the epidemic including identifying the most at-risk populations.[2] The cost of treatment in 2015 was prohibitive, so a key partnership was established with Gilead Sciences, who agreed to support the elimination program by providing free-of-charge treatment directly to the country because of the government's commitment to hepatitis C elimination nationwide.

Georgia launched the hepatitis C elimination program in April, 2015[3] and set an ambitious goal of 90% reduction in hepatitis C prevalence by 2020.[4,5] The initial program focus was on treatment, and through April 2019, nearly 60,000 persons had initiated treatment (Fig. 1). However, because of an appreciation of the importance of prevention, the program embraced a comprehensive approach, developing a strategy that addresses prevention, surveillance, advocacy, education, quality diagnostics, screening, and linkage to care, in addition to treatment.[6] Further, Georgia has invested in and developed an advanced hepatitis C information system,[7] which links screening, laboratory diagnostics, and treatment data allowing for near real-time monitoring of the care cascade (Fig. 1) and feedback on the effectiveness of programs and interventions, providing policymakers with the ability to quickly identify deficiencies and make evidence-based adjustments.

Another critical element of the success of the program has been the country's commitment to scientific excellence. To accomplish this, Georgia has assembled an international group of experts in all aspects of hepatitis C elimination that come together annually as the Technical Advisory Group (TAG)[7] to review progress and make recommendations to the program. Georgia has also developed a Scientific Committee[7] that oversees and coordinates the research agenda for the elimination program. The Scientific Committee is also charged with documenting progress, assessing program effectiveness through the monitoring of key performance indicators, developing and testing innovations, and ensuring scientific integrity.

A further key to success has been the country's openness to working with partners and community. One group of key partners are without a doubt the clinicians and patients in Georgia that were early on aggressively advocating for ways to obtain treatment with the new life-saving direct acting antivirals (DAAs). Among the clinicians, providers from the four major infectious diseases hospitals provided critical leadership. The dedicated infectious disease specialists from these four centers were the first to offer treatment in the country, and have been instrumental in the scale-up of the program. The United States Centers for Disease Control and Prevention (CDC), another key partner, has been providing technical assistance to the program since 2013. The program has over time gained additional external partners, ranging from non-governmental organizations, to industry, to academic institutions, to patient advocacy groups (see acknowledgements); each of these partners bring key expertise and perspectives.

Despite the significant progress of the Georgia hepatitis C elimination program since its launch, challenges remain. A substantial portion of the estimated 150,000 HCV infected people still need to be identified and linked to care (Fig. 1). The number of patients entering the program has slowed after peaking at more than 4,000 patients per month in late 2016.

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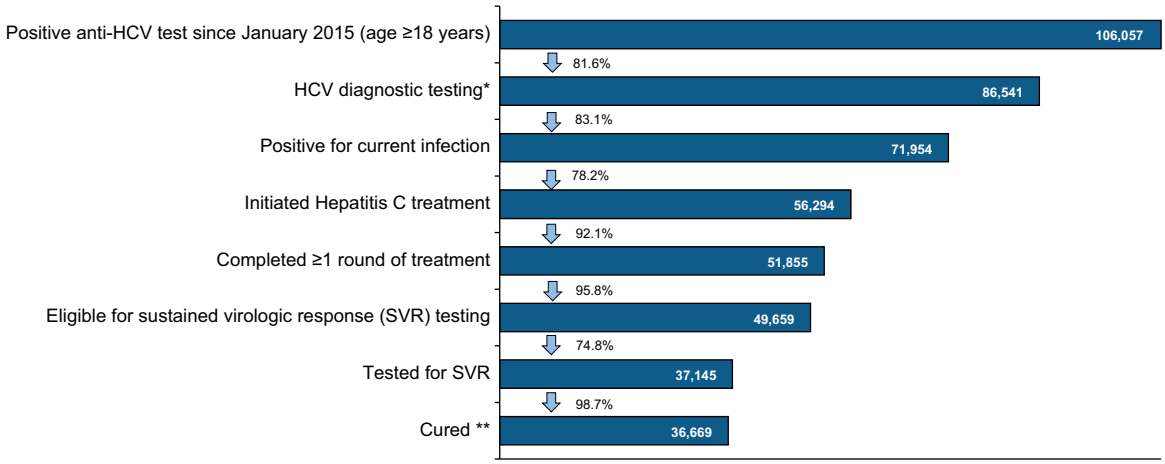

Fig. 1. Georgia hepatitis C elimination program care cascade, April 28, 2015 – April 30, 2019. *Either hepatitis C virus RNA or core antigen testing, **Includes retreatments. Among 37,582 persons tested after their 1st round of treatment, 36,098 (96.1%) achieved SVR. 1,327 persons initiated a 2nd round of treatment, with 94.2% (615/653) of those tested achieving SVR. HCV, hepatitis C virus; SVR, sustained virologic response.

In response, the government took additional steps to decrease barriers by lowering the cost of diagnostics and by integrating screening, care and treatment services into primary healthcare settings and harm-reduction centers throughout the country. Integration of these services allows infected individuals to receive hepatitis C care and treatment services in familiar and convenient locations, a strategy that has proven effective.[8,9] Georgia plans to expand services to every district in the country, doubling the number of hepatitis C provider sites. In addition, the program provides services to the most marginalized and at-risk populations including people who inject drugs and incarcerated populations.

In line with the World Health Organization's (WHO's) targets to eliminate viral hepatitis B and C as a public health threat by 2030,[1,10] many countries have developed and adopted viral hepatitis elimination strategies. However, despite the tremendous progress that has been made in recent years, only 12 of the 194 countries that endorsed the WHO global health sector strategy are on track to reach the WHO elimination targets.[11] Georgia was the world's first country to formally launch a national hepatitis C elimination program, although a few other countries, like Australia and Iceland, are now embarking on elimination as well.[12,13] Georgia embraced a comprehensive hepatitis C elimination program[6] that includes strategies in place to not only identify those infected with HCV and link them to care and treatment services, but also to safeguard the nation's blood supply, improve access to quality affordable diagnostics, and reduce infection among people who inject drugs and in the healthcare setting.[4,7,14,15] Georgia's efforts are all the more remarkable as it is not a high-income country.[16] The leadership exhibited by Georgia in hepatitis C elimination is the result of several factors including: the highest levels of political commitment, the allocation of significant resources, and the comprehensive nature of the program.[6] This has culminated in the great success attained to date, and has led to the country being named as the World's first European Association for the Study of the Liver (EASL)-International Liver Foundation Center of Excellence in HCV Elimination,[17] meeting all established criteria (Box 1).

The introduction of the Center of Excellence designation allows the EASL-International Liver Foundation to support viral hepatitis elimination efforts around the world. The EASL-International Liver Foundation is seeking to expand the Center of Excellence concept in viral hepatitis elimination to other regions of the world. For governments (*e.g.* a country or a region) which already fulfill the criteria, the designation provides a standardized framework and process to affirm their commitment towards viral hepatitis elimination. The designation may help elimination programs maintain their momentum during challenging times, such as changes in government or economic downturns that may jeopardize the government's commitment to elimination. For governments which are not meeting the Center of Excellence criteria, but

Box 1. European Association for the Study of the Liver-International Liver Foundation Criteria for Center of Excellence in Viral Hepatitis Elimination Designation.

CRITERIA:

A government department, ministry division, unit, or partner etc., prominent within a country's national/state viral hepatitis elimination program can be designated as an EASL-International Liver Foundation Centre of Excellence in Viral Hepatitis Elimination on behalf of the national/state viral hepatitis elimination program based on the fulfilment of the following criteria, as approved by EASL-International Liver Foundation

- A valid estimate of national/state viral hepatitis burden
- A funded comprehensive strategic plan for the national/state elimination of viral hepatitis as a public health threat
- A valid, time-bound, measurable targets for the national/state elimination of viral hepatitis as a public health threat
- Demonstrable progress towards national/state elimination of viral hepatitis through valid indicators
- High quality research outputs in relation to national/state elimination of viral hepatitis
- Demonstrable state of the art viral hepatitis training and educational programming
- Demonstrable partnership between state and non-state actors (academia, private providers, civil society groups, key affected groups and patients advocates) in hepatitis C elimination program planning and implementation
- Clear ability, capacity and readiness to contribute to the achievement of viral hepatitis elimination in other countries/states through technical assistance

wish to obtain the designation, the EASL-International Liver Foundation may assist by providing technical assistance in support of fulfilling the benchmarks (Box 1). Such a community of designated Centers can serve as a global network of shared best practices and information exchange. Centers can support neighboring countries in launching comprehensive viral hepatitis elimination activities. As a Center of Excellence, Georgia has committed to sharing their experiences with the world, has hosted other countries, including delegations from Egypt and Afghanistan, and is available to provide technical assistance to neighboring countries. As a Center of Excellence, Georgia is working with the EASL-International Liver Foundation to ensure access to information and lessons learned, including their strategic plan, annual progress reports, TAG recommendations, and publications through the development of a website. The Foundation is fully committed to welcoming additional Centers of Excellence throughout the world; a network of viral hepatitis centers of excellence have the potential to contribute tangibly towards the goal of global viral hepatitis elimination by 2030.

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The other authors declare no conflict of interest.

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RESEARCH ARTICLE

On the way to Hepatitis C elimination in the Republic of Georgia—Barriers and facilitators for people who inject drugs for engaging in the treatment program: A formative qualitative study

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Abstract

Hepatitis C virus (HCV) infection is a significant public health concern worldwide. Georgia is among the countries with a high burden of HCV infection. People who inject drugs (PWID) have the highest burden of infection in Georgia. In 2015, the Government of Georgia, with partners' support, initiated one of the world's first Hepatitis C Elimination Programs. Despite notable progress, challenges to achieving targets persist. This qualitative study is aimed to better understand some of the barriers and facilitators to HCV testing and treatment services for PWID to inform HCV treatment policies and practices. The study instrument examined social, structural, and individual factors influencing HCV testing and treatment practices. We started with key informant interviews to guide the study instrument development and compare the study findings against health care planners' and health care providers' views. Forty PWID with various HCV testing and treatment experiences were recruited through the snowball method. The study found that along with structural factors such as political commitment, co-financing of diagnostic and monitoring tests, and friendly clinic environments, knowledge about HCV infection and elimination program benefits, and support from family and peers also play facilitating roles in accessing testing and treatment services. On the other hand, inability to co-pay for diagnostic tests, fear of side effects associated with treatment, poor knowledge about HCV infection, and lack of social support hampered testing and treatment practices among PWID. Findings from this study are important for increasing the effectiveness of this unique program that targets a population at high risk of HCV infection.

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Introduction

Hepatitis C virus (HCV) infection is a significant public health concern worldwide. An estimated 13 million people are infected with HCV in the European region [1]. People who inject drugs (PWID) are the main drivers of the HCV epidemic. It has been estimated that 64.7% (56.6% -72%) of PWID are exposed to HCV in Eastern Europe, which has the highest prevalence across the regions [2]. Georgia is among the countries with a high burden of HCV infection. A national population based survey conducted in 2015 found that 7.7% of the general population is anti-HCV positive and 5.4% are HCV RNA positive [3]. The study also revealed that use of injection drugs accounted for more than one third of cases among the general population [4]. Similar to other countries, PWID in Georgia are particularly vulnerable to HCV infection due to risky behaviors and exposure to structural and environmental risk factors. Approximately 65%-75% of PWID in Georgia are HCV antibody positive [5].

HCV treatment was first introduced to Georgia in 2011 through a program supported by the Global Fund to Fight AIDS, Tuberculosis and Malaria ("The Global Fund") [6]. Initially, a combination therapy with pegylated interferon and ribavirin was available to HIV/HCV co-infected individuals at no cost [7]. In 2013, the Government of Georgia introduced free HCV treatment for prisoners and offered reduced price HCV treatment to the general population at a 60% discount rate [6,7].

In April 2015, the Government of Georgia and partners (i.e., the U.S. Centers for Disease Control and Prevention, World Health Organization, Gilead Sciences, The Global Fund, Emory University [USA], and Bristol University [UK]) initiated one of the world's first Hepatitis C Elimination Programs with the goal of 90% reduction in HCV prevalence by 2020 [3,8]. Gilead Sciences, the pharmaceutical company that produces direct acting antiviral (DAA) HCV treatments, agreed to provide initial 5,000 courses of the antiviral medication sofosbuvir (Sovaldi) free-of-charge to support the program [3,7]. Patients with severe liver disease (i.e., METAVIR score F3 or F4) were prioritized to receive treatment during the first year of the program. The initial treatment regimens consisted of sofosbuvir in combination with pegylated interferon and ribavirin [8]. By February 2016, Gilead Sciences again agreed to provide 20,000 treatment courses of ledipasvir-sofosbuvir (Harvoni) annually at no cost [3] and the patients began receiving the new DAA regimen. The national program still uses interferon/ribavirin containing regimens in certain circumstances with the goal of eliminating interferon containing regimens and using of all-oral DAAs. In the second phase of the program, the severe liver disease criterion was abolished and as of today the program is accessible to all citizens of Georgia with chronic HCV infection [8].

By way of process, after screening for HCV infection, individuals positive for anti-HCV antibodies undergo confirmatory testing to determine active HCV infection by quantitative HCV nucleic acid test (NAT) or HCV core antigen test. If the diagnosis is confirmed further tests are required to determine liver fibrosis status and HCV genotyping. Number of tests are conducted during the course of treatment to monitor treatment progress and at the end to determine the treatment outcome.

Pre-treatment diagnostics, treatment monitoring, and post-treatment laboratory tests were covered by the program and local governments with some co-financing required from patients. Since the beginning of the program implementation socially vulnerable patients and war veterans have been co-financed up to 70% by the program and up to 30% by local municipalities so they receive completely free testing services. As for the rest of the population, cost sharing for diagnostics, monitoring, and post-treatment tests across the years is presented in Table 1 below.

Table 1. HCV diagnostics, treatment monitoring and post-treatment tests cost sharing.

Tests	Total costs (GEL)	2015	2016	2017	From Sept 2018
Screening					
Anti-HCV antibody testing		Patient– 0% Program -100%	Patient– 0% Program -100%	Patient– 0% Program -100%	Patient– 0% Program -100%
Confirmation					
HCV NAT	110	Patient—70% Program– 30%	Patient– 10%-60% Municipality 60%-10% Program– 30%	*From 1 Dec 2017*: Patient—0% Program– 100%	Patient -0% Program– 100%
HCV core antigen test	60 –from Dec 2017				
Tests for inclusion: Liver fibrosis status	375	Patient—70% Program– 30%	Patient– 10%-60% Municipality 60%-10% Program– 30%	Patient– 70% Program– 30%	Patient– 70% (max 160 GEL) Program– 30%
Further examination including HCV Genotyping	140	Patient—70% Program– 30%	Patient– 10%-60% Municipality 60%-10% Program– 30%	Patient– 70% Program– 30%	Patient– 0% Program– 100%
Treatment monitoring tests	300–500	Patient—70% Program– 30%	Patient– 10%-60% Municipality 60%-10% Program– 30%	Patient– 70% Program– 30%	Patient– 70% Program– 30%
Post treatment test and consultation	130	Patient—70% Program– 30%	*From mid 2016*: Patient– 0% Program -100%	Patient– 0% Program -100%	Patient– 0% Program -100%
All tests for socially vulnerable population and war veterans		Program– 70% Municipality– 30%			

GEL = Georgian Lari

NAT = Nucleic Acid Test

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Drugs for HCV treatment were, and continue to be, fully covered by the program. With the goal of achieving 90% reduction in HCV prevalence by 2020, Georgia's Hepatitis C Elimination Strategic Plan outlines the following elimination goals: (1) testing 90% of HCV-infected people for their infection, 2) treating 95% of the patients with chronic HCV infection, and 3) curing 95% of the patients treated of their HCV infection [8].

Georgia made substantial progress in the first year of the Elimination Program. Between April 2015 and April 2016, 27,392 people with HCV were enrolled in the program and 8,448 initiated treatment [3]. This translates to a more than 400% increase over the number of patients treated in the previous four years [3]. Yet, as is the case with any new larger-scale program, implementation can be challenging, especially with PWID. Despite evidence that this population can be successfully treated for HCV, the literature also describes low HCV treatment uptake among PWID and challenges associated with engaging them in HCV treatment [9,10].

This qualitative study aims to better understand the barriers and facilitators to HCV testing and treatment services for PWID in order to inform HCV treatment policies and practices in Georgia. Specifically, the research objectives were to (1) identify the societal, structural, and individual barriers and facilitators to HCV screening, completing diagnostic testing, and initiating HCV treatment services among PWID and (2) examine the perceived risk of HCV re-infection and its consequences among PWID.

Methods

Conceptual framework

A conceptual framework based on the health service utilization framework developed by Anderson & Newman (2005) was used to inform the PWID in-depth interview guide development. The health service utilization framework posits that health service utilization is influenced by characteristics of the health services, societal norms, and individual factors [11].

We modified the framework and identified social, structural, and individual factors that may act as barriers or facilitators to using testing and treatment services (Fig 1). Social factors include family and community support, stigma, and peer influence as well as other social norms or attitudes that may influence a PWID's decision to seek treatment, such as national pride in the Hepatitis C Elimination Program. Structural factors were defined as those over which a person has little control such as political will, policies, program resources, financial and geographical access barriers to service use, quality of care, and civil society organizations CSO activities. Individual factors include knowledge, attitudes, and beliefs regarding HCV infection, the Elimination Program in general, and HCV treatment specifically. Individual factors also include patient motivation and willingness, general lifestyle and drug use behavior, ability to pay, and satisfaction with services. Social and structural factors interact with each other and together influence individual factors.

Sample and recruitment

Prior to the recruitment of PWID we conducted key informant interviews with the individuals who had first-hand knowledge about the Hepatitis C Elimination Program implementation, successes, and challenges. The purpose of these interviews was to guide the PWID data collection tool development and complement the study findings by examining the views of health care planners and health care providers on policies, elimination program resources, and other structural factors. The key informants were identified through a snow-ball method. We interviewed representatives from the Ministry of Labour, Health and Social Affairs (MoLHSA), HCV testing and treatment services, and Civil Society Organizations (CSOs) involved in harm reduction activities, who had particularly informed perspectives on the research topic. In total, seven key informants were interviewed face-to face by lead researchers in April 2016. This number was sufficient to gain a broad perspective of a situation from the representatives of divergent groups involved in the Hepatitis C program development and implementation.

PWID were recruited from six cities of Georgia (i.e., Tbilisi, Kutaisi, Batumi, Zugdidi, Telavi, and Gori). The target sample size was 40 PWID. We note that sample sizes in the 10s of participants are par for the course with qualitative studies [12]. Indeed, 40 is robust for a qualitative study. The concept of "saturation"–i.e., interview to redundancy–is often mentioned when discussing sample sizes in qualitative studies [13]. After 40 PWIDs had been recruited and their interviews reviewed, coded, and analyzed, the team discuss whether there was a need for additional interviews. Given the breadth and depth of the information collected through those 40 interviews as well as redundancy in perspectives on the processes of interest, we concluded that our sample reached saturation with respect to our research questions.

Eligibility criteria required that participants be 18 years of age or older, able to communicate in Georgian, and have injected drugs at least once during the six months prior to the study. PWID were recruited through harm reduction services using snowball sampling. In each harm reduction center, initial seeds were recruited and were asked to bring their peers to the study. The participants were especially encouraged to invite female injecting drug users. The selection criteria also required participants to represent the following subgroups: 1)

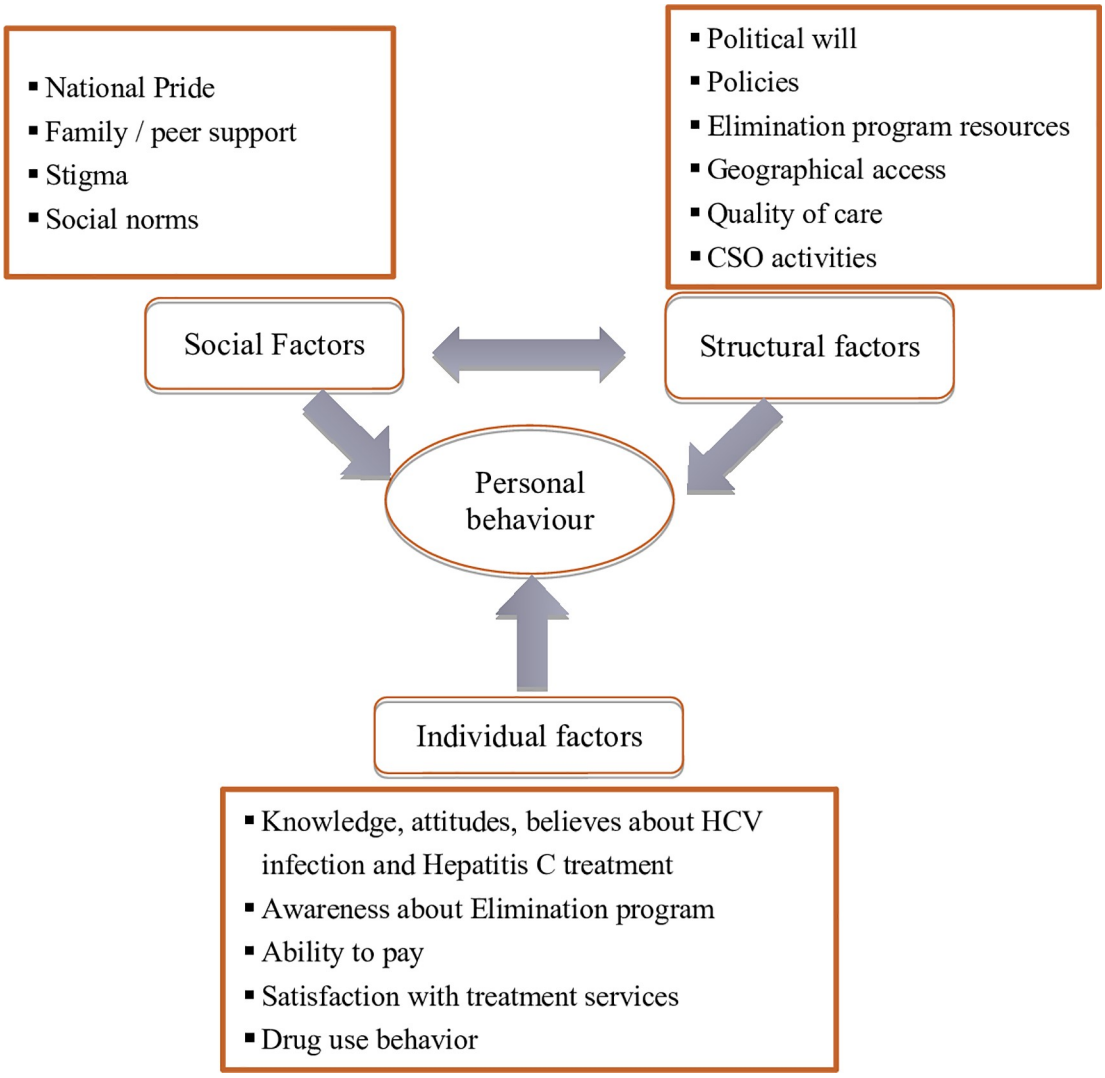

Fig 1. Health service utilization conceptual framework (modified Anderson and Newman, 2005).

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PWID that have completed HCV treatment; 2) PWID undergoing a course of treatment; 3) PWID who were aware of their HCV status but were not receiving treatment; 4) PWID who were not aware of their status (i.e., have not been tested for the past 5 years); and 5) PWID who initiated treatment but interrupted before completion.

The study protocol was approved by the Institutional Review Board of the Infectious Diseases, AIDS and Clinical Immunology Research Center of Georgia (OHPR # IRB00006106).

Data collection

The field work took place in June and July, 2016 during the second phase of the Hepatitis C Elimination Program. Experienced interviewers carried out face-to-face in-depth interviews with PWID in a private setting. Participants provided written informed consent for participation in the study. Semi-structured interview guides included open-ended questions and follow-up questions with probes relevant to the PWID experience. Demographic information was collected at the beginning of the interview. Interviews were audio recorded if the

respondents granted their permission. Only one respondent refused to be audio-recorded. In this case detailed notes were taken by another data collector. Remuneration of 25 Georgian Lari (11 USD) was given to PWID respondents for their participation in the study.

Data analysis

Interviews were audio-taped with participants' permission, transcribed verbatim, and translated into English for analysis. Three members of the research team conducted an initial reading of all the transcripts to identify patterns and initial themes emerging from the data and themes that relate to the conceptual framework. After the initial reading, the research team utilized constant comparison to further develop a coding structure and a detailed code book. Two researchers coded all transcripts using a qualitative software QSR-Nvivo 11.4. Additional codes that emerged were discussed as they came up and were added to the codebook upon agreement. The complete set of coded transcripts was reviewed by one researcher for discrepancies and inconsistencies. Any differences in the coding were resolved through group discussions, review of the transcripts, and re-coding. Thematic analysis was conducted according to the conceptual framework.

Results

In total, 40 current PWID participated in the study. Eight respondents had already completed HCV treatment, ten respondents were currently being treated for HCV, eighteen respondents were not involved in the program of which seven were not aware of their HCV status, and four respondents were on the waiting list for HCV treatment. The study failed to recruit any respondent who initiated and interrupted treatment. Demographic characteristics of the sample are presented in Table 2.

The results are structured as follows: we first present facilitators and barriers of the decision to seek treatment and then adherence to treatment. Facilitators and barriers are further categorized by social, structural and individual factors. Finally, we present HCV re-infection risks among PWID. Findings from the key informants are presented along with those from the PWID.

Facilitators of the decision to seek HCV treatment

Political support and media campaign (structural). The Hepatitis C Elimination Program received strong political support from its early stages. As mentioned by the key informants, the Program became one of the most frequently cited topics by high government

Table 2. Demographic characteristics of the sample.

Characteristic	N
Gender	
Male	39
Female	1
Age	
45 years and older	23
26–44 years	14
25 years and younger	3
Injecting drugs	
10 years and more	35
less than 10 years	5

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officials in their media appearances. The Program has been considered as one of the successes of Georgia health care system in 2015–2016. Key informants and PWID participants all mentioned the crucial role of media in advertising the Hepatitis C Elimination program.

Hepatitis C elimination program as a national pride (social). Availability of such an expensive program (in the range of 60,000 to 120,000 USD per patient) at almost no cost to the patients was acknowledged as one of the leading factors that influenced PWIDs' decisions to seek and complete treatment. Respondents admitted that they are "fortunate" that such program is available in the country.

> "This is a huge thing done by the state to me, an ordinary person having an infectious disease. This is the same as having a new chance to live because it is a rather expensive program. I am fully aware of how much it costs, what is the price of the flacon of the medicine. I could not afford it. I had already gotten used to the fact that I had an incurable disease before the program was launched." (Male PWID from Zugdidi)

> "To us, to the patients this was so unimaginable that we were ready to tolerate everything. We tolerate everything to bring the treatment course to an end." (Male PWID from Tbilisi)

Key stakeholders, treatment service providers, harm reduction network representatives also prized the program and consider it to be "unique" and not only valuable for Georgia but globally.

> "Hepatitis C elimination program is an excellent opportunity for the population of our country to receive treatment using new generation, effective, and very expensive drugs. Many years ago, even during our advocacy efforts, we could not imagine such universal access to expensive medications, which are vitally important and grant patients a higher chance of being cured." (Key informant)

> "This program is important from the global perspective, and will set a precedent by eradicating the disease" (Key informant)

All key informants cited that the current treatment regimen has fewer side effects and better treatment outcomes. They also mentioned that news of successfully treated cases rapidly disseminated among patients' networks, increasing the credibility of the program.

Knowledge about the HCV infection (individual). PWID described HCV disease as a "liver disease leading to a cirrhosis," and "silent death." They were well aware of how HCV was transmitted as well as risk behaviors associated with spreading the virus such as sharing of needles and syringes. PWID described other modes of transmission including dental procedures and sexual contact. Participants mostly associated the disease with symptoms such as "fatigue, weight loss, jaundice;" however, very few mentioned that the disease could be asymptomatic. The participants, including those who were not involved in the program, believed that the disease could be cured, only one PWID thought that the disease is incurable.

Referral to the program and Public Financial support (structural). According to the key informants, CSOs played a significant role in facilitating PWID referral to the HCV elimination program services. Harm reduction networks were actively involved in directing patients to treatment sites. The information was also widely spread by peer educators:

> "The network of peer educators works very well. The information is transmitted rather quickly by word of mouth, sometimes I say something to a patient and couple of days later

some other person comes and repeats my words. They spread this information rather quickly." (Key informant)

Respondents from the capital city frequently mentioned the contributions of CSOs in covering diagnostic test expenses. Tbilisi patients appeared to be in a better position due to significant contributions from the Mayor's office that, at the time of the study since 2016 have been covering 60% of diagnostic and monitoring test costs in addition to the program co-financing of 30%. Respondents also admitted that even though they needed to pay some amount for clinical diagnostics and laboratory tests to monitor treatment outcomes, compared to the complete cost of HCV treatment, theirs was a small share.

"Yes, you will find dissatisfied people everywhere but first they should look at the program, the quality and the price of the medicines they get, the amount the state pays for them. Compared to that, we pay a small portion. It is a minor share we pay, so let nobody say that this is a big amount for the tests." (Male PWID from Zugdidi)

Social support from family and friends (social). The support of family members, relatives and friends was considered to be a very important factor influencing patients' decision to seek treatment. All patients, regardless of their desire and current involvement in HCV Elimination Program, admitted that such support is crucial.

"I would not have joined the program had my mother and family not insisted on it." (Male PWID from Kutaisi)

"It is rather important. For example, my mother visited the Mayor's Office as well as other places for the documents. I would not have been able to do that alone" (Male PWID from Kutaisi)

One participant who is no longer involved in treatment reported that if his family members had more information on the program and insisted on his treatment, he would probably have sought it. Another participant not currently involved in the program said that he "needs someone to take him to treatment," and his family members have a difficulty providing such support.

Barriers for decision to seek HCV treatment

Exemption from the program (structural). Of the eighteen respondents who were not enrolled in the program, eleven reported that they did not qualify for the program based on the initial enrolment criteria. The patients regrettably admitted, "This is sad, because the treatment has been provided for free." During the period when the interviews were conducted, severe liver damage (i.e., Metavir score F3 or F4) as a precondition for treatment had already been abolished. However, some of the patients did not know about these changes while some of those who knew were still planning to apply for treatment.

Ability to pay (individual). As mentioned above, expenses for HCV screening were fully covered by the program, while confirmatory tests and tests needed for inclusion into the program were partially covered by the program (up to 30%) with co-sharing from the patients and local governments for the patients living in their municipalities. Additional tests are needed during treatment monitoring which also require patient contributions. As the respondents did not make clear distinctions between financial barriers associated with diagnostic, pre-

treatment, and monitoring tests, we present these findings all together in the ability to pay section under the barriers to HCV treatment adherence.

The share of co-financing from local governments varied by municipality, resulting in some degree of inequality between residents of different geographic areas. During interviewing period in 2016, patients in the regions had to pay higher amounts than Tbilisi residents due to smaller contributions in the provinces from local authorities compared to the Tbilisi Mayor's office. The patient's co-payment ranged from 350 to 600 GEL (145–250 USD) for pre-treatment and monitoring laboratory diagnostics. To overcome this barrier, some PWID were trying to find ways to be registered as Tbilisi residents.

> "We know about cases when patients registered in Tbilisi to receive more affordable treatment." (Key informant)

Several cases were identified where patients who did not seek HCV testing stated that they could not afford the costs associated with treatment:

> "I also think that I may need money for treatment but I have rather serious problems. It is not possible for me to start the treatment course now."(Male PWID from Rustavi, not enrolled in the program)

Geographical access (structural). Geographic barriers were mentioned as an obstacle for the patients living in the Kakheti region, where at the time of data collection, treatment facilities did not exist. This lack of facilities created an additional financial burden to PWID in that region because of associated travel costs to Tbilisi.

Knowledge about HCV, risk perception, and difficulty initiating treatment (individual). Among the entire sample, only six respondents (15%) have never been tested for HCV in their lifetime. Inadequate knowledge about the disease and lack of awareness that HCV infection could be asymptomatic discouraged PWID from seeking HCV testing. Others thought that HCV testing is unnecessary because they considered themselves to be at low risk of contracting HCV due to safe injecting practices. At the same time, some admitted that if they were infected then they would seek treatment.

> "I think: Why should I go if nothing bothers me? I do not have to hurry. I will go there tomorrow; I will go there the day after tomorrow. Then you forget about it". (Male PWID from Tbilisi, not enrolled in the program)

> "If I had C hepatitis I would feel something, would not I? I think so . . . I cannot be 100% sure but I still think that I do not have it" (Male PWID from Tbilisi, not enrolled in the program)

Some patients expressed low interest in their health and the possibility of treatment. They were more preoccupied with other problems, even though they did not rule out the disease. Some expressed nihilism about the disease and its consequence:

> "Maybe I am afraid but at that moment I do not think about that, I think about injecting drugs. . . .. I say to myself 'let it kill me whenever it decides to do so'" (Male PWID from Rustavi, not enrolled in the program)

Some patients found it difficult to initiate treatment: "I just need to begin it," and "I need someone to push me."

Interestingly, these PWID were in contact with their peers who were under treatment and were aware of the program. Some of them had heard about unsuccessful cases, and were discouraged from initiating treatment.

Fear of test results and treatment (individual). Few PWID reported fear of learning that they are HCV positive as a barrier from getting tested:

> "I may be afraid of that most. If I go there and they tell me that I have a terrible condition, when I know that I have no health problems, this will cause depression of course." (Male PWID from Tbilisi, not enrolled in the program)

Some participants not yet enrolled in HCV treatment believed that treatment may harm more than cure. Fear of side effects and damage to their liver discouraged them from initiating treatment. Treatment with Interferon was not attractive to some of those who were not looking for treatment; however, some were exploring the possibility of treatment abroad where "interferon-free" treatment is available.

> "I am afraid to start treatment. I saw some people feeling bad because of Interferon. I used to think I could die because of the treatment. This is fear, fear of death probably." (Male PWID from Batumi, not enrolled in the program)

> "I am afraid of the medicines they use here. I saw people who were on Interferon. They could hardly stand on their feet, they had fever." (Male PWID from Tbilisi, not enrolled in the program)

Service providers also indicated that there are misconceptions about the side effects of interferon treatment that hamper treatment initiation. Providers describe several cases where patients were reluctant to initiate interferon treatment out of fear of its side effects. These misconceptions are rooted by negative experiences with interferon side effects that are shared among peers. Successful treatment outcomes with the interferon regimen play an important role in reducing these misconceptions.

> "There are many rumors here about interferon and other drugs. They say it causes falling of hair and teeth. I explain to everyone that this is not the case, and I am an example of this." (male PWID from Kutaisi)

PWID not currently involved in the program are curious about whether a new generation drugs has been introduced and what will happen to their health if they resume using drugs after HCV treatment; they are eager to learn about treatment outcomes from their peers.

Stigma (social). All the participants, with the exception of one, did not feel stigmatized as a result of their positive HCV status. Among the participants currently not under treatment, none reported social stigma as a factor preventing them from treatment. Nevertheless, there are cases where participants do not wish to disclose their status and chose to hide it, because HCV is associated with drug injection.

> "I do not want many people to know that I have Hepatitis C, this is what makes me uncomfortable." (Male PWID from Kutaisi)

> "I know many people who do not tell their families and receive treatment in secret. . ." (Male PWID from Tbilisi)

The study managed to enroll only one female PWID and she addressed her experience of being a female with HCV infection. Although she did not report any stigmatized attitudes from treatment service providers during the treatment process, making a decision to start treatment was difficult nonetheless.

> "There is a tendency to stigmatize woman with Hepatitis C which causes them to feel discomfort to get treatment. Unless the organization (CSO) had offered I would not have been able to do that myself." (Female PWID from Rustavi)

Skepticism about effectiveness of the program (individual). In two cases the participants expressed a lack of confidence in the program:

> "There are the following speculations: "Why would they (the government) do that to you?", "they are helping us die," "maybe this is some experiment?" (Male Batumi PWID, not enrolled in the program)

> "But is the medicine reliable? Does it treat patients? Which other side effects does it have? . . . I do not even know the name of the medicine." (Male Batumi PWID, not enrolled in the program)

According to the key informants, at the initial stages of the program implementation enrolment of individuals with severe liver damage did not deliver the desired results. Some patients with severe liver disease were not cured or died soon after treatment; news of such cases spread quickly through PWID networks. Moreover, patients and even health workers did not immediately understand why such an expensive program was offered to the Georgian population free of charge and were skeptical about it.

Stakeholders believed that the Government needs to spend more time explaining the advantages of the HCV elimination program to the country as well as what motives the pharmaceutical company might have. Clarifying that donating the drug is in the pharmaceutical company's business interest would resolve the skepticism.

Programmatic challenges (structural). Key informants identified several challenges that were encountered at the beginning of the program. The program start-up was preceded by an intensive preparatory stage, but doctors were informed that the program was to begin only one week prior to initiation of activities. Training was provided only after the program launched; however, since then doctors have received continuous technical support.

Key informants mentioned that, at some point, the program's public relations campaign was so aggressive and mismatched with the program's phases that it created problems with the patient flow and waiting lists. Due to very intensive advertisement in media, patients rushed to get treatment and it was difficult to manage the processes.

PWID respondents also indicated that such problems were gradually resolved in the process of the program implementation. The MoLHSA was responsive and eager to fix the problems in a timely manner to allow a smooth implementation of the program.

Facilitators of HCV treatment adherence

Clinical environment (structural). *Attitude of staff*. Eight out of the ten PWID respondents who completed treatment or were in the process of being treated described treatment sites to be safe environments with friendly and responsive staff. They mentioned that health professionals acknowledge the patients' needs and are flexible in scheduling appointment times to ensure that the patient is seen. Participants pointed out that positive patient-provider

relationships promote adherence to treatment. They described how health professionals are an important support in this process.

"The doctor greets you and talks to you in such a manner that you are pleased to visit the clinic." (Male PWID from Tbilisi)

"The doctor also encouraged me and gave me hope. This was a big incentive to me." (Male PWID from Kutaisi)

Waiting times. The patients recalled waiting times at the beginning of the program, with fewer lines now. They would describe 10–15 minutes waiting time in queues. The MoLHSA took steps to reduce the influx of patients to the facilities and started to manage the lines at the central level. They introduced a new mechanism by which a front office would schedule patients based on the clinics' availability. Very few participants still mentioned lengthy waiting times during the treatment process; however, this was not considered as a barrier to receive treatment among patients.

Pill taking in front of camera. The program protocol requires taking pills in front of a camera in certain cases when there is suspicion that the treatment regime was violated.

In most of the cases, patients did not feel concerned about this. There was a threat of incarceration associated with injection drug use; however, participants were confident that the recordings would not be disclosed to the police or the public. Those who were involved in the methadone substitution program felt more relaxed about this feature, as methadone dosing in Georgia is also conducted in front of a camera. Similarly, the service providers confirmed that the patients did not object to taking pills in front of camera.

Quality of care (structural). PWID talked about caring and responsive health professionals who were always ready to provide detailed answers to their questions. Doctors provided advice about taking care of themselves during the treatment process and warned about harmful behaviors. Respondents were confident that they were in the hands of qualified professionals and received appropriate care.

At the same time, patients (who had experience with interferon treatment) wished that they had a qualified provider to deal with mental health symptoms (e.g., irritability, depression, sleep disturbances) which were perceived to be quite frequent side effects of interferon treatment. HCV treatment service does not include consultations with mental health specialists qualified to provide such care.

Social support from family and friends (social). For many patients, family members and friends provide invaluable emotional and practical support during the treatment process. Family members encouraged patients, reminding them to take their prescribed drugs and accompanying them to medical appointments.

"They provide incentives for living. When you have people who stand by your side you have hope." (Male PWID from Batumi)

"Family support is important, very important. Not only in this regard. A family member, a spouse, may tell you something that will make you give up treatment, or the opposite, support you and make you think that it is worth to live." (Male PWID from Batumi)

Barriers to HCV treatment adherence

Ability to pay (individual). Among the barriers to seek and remain in treatment, participants reported financial challenges in covering costs for tests. Apart from the HCV screening

test, which is free under the program, a number of additional tests are required for confirmation testing, inclusion in the program, and treatment monitoring. At the time of data collection, the national program covered 30% of these costs and the rest were co-shared between the local authorities and patients. The patient's co-payment ranged from 350 to 600 GEL (145–250 USD) for pre-treatment and treatment monitoring laboratory diagnostics. During the interviewing period in 2016, Tbilisi patients had to pay 10% of these costs due to higher contribution from the Tbilisi Mayor's office compared to other municipalities. To overcome the financial barriers, some PWID were trying to find ways to be registered as Tbilisi residents.

> "We know about cases when patients registered in Tbilisi to receive more affordable treatment." (Key informant)

The co-payment was not affordable for some households. Several cases were identified where patients who did not seek HCV testing stated that they could not afford the costs associated with treatment.

The problem was more profound for those living far from the cities where treatment sites are located, due to additional transportation costs.

> "I do not have anything to complain about myself but people are not able to pay for the tests. I basically mean people from provinces. . . I came across the cases when some patients could not afford tests and were not able to continue treatment." (Male PWID from Rustavi)

For some patients, extra expenses before treatment appeared to be much bigger than anticipated. This was mainly for cases when the three months duration of HCV treatment was not sufficient to achieve cure.

At the beginning of the elimination program implementation, patients had to co-finance the final HCV NAT test needed to confirm the treatment outcome, which along with the consultation, costs 130 GEL (54 USD). As reported by key informants, due to financial difficulties, patients did not show up for this final test. This ultimately affected the treatment outcome data and the overall program performance statistics. After acknowledging this problem, the MoLHSA made a decision to fully reimburse the final HCV NAT test. This came into force at the beginning of the second phase of the elimination program, in mid-2016.

From January 2017, the Tbilisi Mayor's office and other municipalities stopped co-financing HCV confirmatory and monitoring tests. This was partly due to a budget deficit and partly aimed to reduce inequality between Tbilisi and residents in other cities. One key informant viewed this as a positive, rather than a negative step towards creating motivation to adhere to treatment:

> "When patients have some obligation to pay they feel more responsible during treatment. Moreover there was a significant difference between Tbilisi and other city residents which created a lot of complaints." (Key informant)

Side effects (individual). Patients who were treated with interferon experienced the side effects associated with this drug, mainly with the first injections. Common side effects include fever, fatigue, depression, anxiety, panic attacks, and insomnia. Patients were informed in advance by service providers about possible side effects and how to reduce them. However, in some cases, the side effects were more severe than expected, and patients indicated that only receiving information about side effects was not sufficient. Patients expressed fear that they

could not tolerate taking this drug again if needed. Some patients refused to initiate treatment with interferon, opting to wait for new drugs before resuming treatment.

The MoLHSA representative mentioned that in the few months prior to the interview they encountered cases where patients interrupted treatment and resumed it later. To reduce the likelihood of such cases, the program added a policy to restrict re-enrolment into the program for one year for patients who stopped their treatment before completion of the regimen.

Prevention of re-infection

Patients were well aware of HCV re-infection risks. They were advised by treatment service providers not to use drugs or to share injecting equipment. Some participants were firm in their decision not to engage in risk behaviors, to adopt a healthy lifestyle, and even to abandon drug injection following completion of treatment. Some drug users tried to shift to non-injection drugs, however about 60% thought that abandoning the use of injection drug was far from reality, ". . .if someone offers (drugs), this is a great temptation," ". . .if I say 'definitely no,' that would be a lie."

As they continue to inject drugs, respondents admitted to being at risk for reinfection with HCV. PWID articulated that such "failure" would be their fault. They were well aware of the risks associated with non-sterile injecting equipment use; however, in certain circumstances they may still use unsafe injection practices.

> "We always have syringes from here (harm reduction program). But generally, of course there is a risk. . . ..If it happens again it will be because of our carelessness. More or less all of us know that we should not do that but. . ." (Male PWID from Zugdidi)

> "It could happen maybe, when a person tells you that "yes, the syringe is new." Moreover, not to offend them we do not ask whether the syringe is new and raise doubts . . . If I have the slightest doubt I will refuse–but who knows, he could be mistaken." (male PWID from Tbilisi)

Some blamed dental clinics for transmitting HCV, which is "difficult to control" and poses risk for re-infection.

Discussion

Georgia is poised to provide treatment to more than 120,000 individuals with chronic HCV infection, with the ultimate goal of reducing prevalence of HCV infection by 90% [8]. This is an unprecedented approach to implementing HCV treatment on such a large scale. From April 2015 through March 2018, Georgia's HCV Elimination Program has managed to enroll 45,000 chronic HCV patients in treatment, of whom 29,000 achieved cure (i.e., sustained virologic response) [14].

Despite notable progress, challenges to achieving targets remain. A major challenge is that Georgia has a high a prevalence of injection drug use; according to a 2017 study about 52,000 adults or 1.41% of the general population injects drugs [15]. Moreover, PWID have the highest burden of infection in Georgia; more than 60% were HCV antibody positive as per a 2017 bio-behavioral study across seven major cities of Georgia [5]. A 2012 study among 216 active PWID in Tbilisi reported 92% were anti-HCV antibody positive and 82% were positive by HCV NAT [16]. Undiagnosed and untreated PWID may transmit HCV to other PWID as well as their sexual partners. Georgia's National Strategy for Hepatitis C Elimination recognizes PWID as a key target group. To reach the Elimination Program goal, the national strategy

outlines activities such as supporting access HCV treatment for PWID as well as promoting harm reduction to reduce disease incidence [8].

Our study provides a better understanding of PWID in the context of seeking and adhering to HCV treatment, which is critical to improving treatment uptake and retention. Factors influencing treatment seeking and adherence include structural, social, and individual factors. In terms of structural factors, political commitment, co-financing of diagnostic and monitoring tests, and friendly clinic environments were key facilitators for the Hepatitis C Elimination Program in Georgia. The study identified some programmatic gaps; however, they were profound largely at the beginning of the program and mostly created operational challenges for service providers, rather than influenced treatment seeking and adherence among patients.

The program received substantial political support starting from its launch and remains among the top health sector priorities in the country [8]. The study findings support the suggestion that strong political commitment plays a key role in smooth implementation of the program and its success so far. Other structural factors positively influencing treatment uptake were the roles of TV and harm reduction networks in advertising the program and referring patients to the treatment sites. The success of the campaign at initial stages even created problems due to rapid influx of new patients seeking treatment; however, the program quickly adapted to manage the situation.

Many participants described the relatively low cost for medical testing to monitor treatment response. Availability of co-financing from the program's side for diagnostic and monitoring tests was critical to facilitating access to treatment services. However, the share to be paid by patients created a burden for some individuals, particularly in the provinces. At the time of data collection, local municipalities additionally co-financed monitoring tests for those seeking such financial support. Some of the key informants raised valid concerns that offering no-cost treatment might undermine the patients' commitment to complete treatment. In addition, different co-financing offered by various municipalities created inequities in patients' financial contributions. As a result, municipality co-financing was suspended starting in January 2017. Further policy changes in 2017 and 2018 included covering costs for the confirmatory test along with the final testing and HCV genotyping from the program budget. Current patients who are not under the poverty line need to pay about 125–155 USD (320–400 GEL) for pre-treatment, treatment monitoring and post-treatment tests. Whether this structural change has any influence on treatment seeking behavior or on treatment adherence is difficult to judge without further research. However, considering that average monthly income among PWID is within 40–120 USD (100–300 GEL) in Georgia the test costs may act as a barrier in access to treatment [5].

Additional financial barriers existed for those who were living in the regions where treatment services were not available. During 2017 and 2018, the number sites providing HCV treatment services more than doubled thereby reducing some existing geographical and financial barriers to treatment entry. Individuals who fall under the poverty line and war veterans were totally exempted from co-payments from the beginning of the program. Few of our respondents who qualified for the financial exemptions confirmed that treatment was completely free for them.

Our research identified social factors that affected access and adherence to treatment. Under this domain we included family and peer support, stigma, social norms, and other cultural factors. Social support was found to be essential in encouraging PWID to seek treatment and engaging them in treatment until completion, which is in line with the literature that examined the role of social context in treatment uptake and adherence [17]. Family and peer support could help PWID overcome structural barriers and positively influence personal behavior. Peer-to-peer support has been shown to increase treatment adherence [18]. Local

experiences have also highlighted the important role of peers in maximizing treatment adherence: more than 200 PWID enrolled in HCV treatment during the first phase of the elimination program were followed by specially trained peer workers that resulted in 98% completion of the treatment course [19].

Stigma associated with injection drug use and HCV as a barrier to seek treatment has been documented in the literature [20]. Participants in our study did not mention experiencing stigmatized attitudes from health professionals at HCV treatment sites; however, more generalized stigma due to the association of HCV with injection drug use has been reported. This, along with lower prevalence of injecting drug use among females could be reasons for poor recruitment of female PWID in our study, as well as in other studies related to PWID in Georgia [5,15,19].

The majority of PWID respondents, as well as key informants and service providers, highly valued the program and admit that the country has received an extraordinary opportunity to benefit from it. The program represents a point of national pride and respondents expressed concern that failure of the program will show the country in a negative light. We speculate that such representation of the program could stimulate the service providers' performance that, in turn, will positively affect patients' behavior.

In general, a wide range of individual, patient-related factors influence the decision to seek treatment and [17,20]. study demonstrated that PWID in Georgia had a high degree of awareness of HCV treatment possibilities. At the same time, underscoring of the consequences of the disease, lack of knowledge that HCV can be asymptomatic, false perceptions that they are at low risk to contract the disease once they practice safe injection (i.e., use of sterile needle and syringe), and fear of being tested represented barriers at the stage of decision to get tested for HCV and enter treatment. The recent PWID bio-behavioral study in Georgia found that HCV testing remains inadequate–a serious impediment for the elimination program. The study showed that 26.5% of current PWID have never been tested for HCV. Among those who have never been tested, one third thought that they "do not need it," another one third "do not think about it," and 12% were afraid of the test results [5].

HCV drugs side effects may hamper the decision to start and stay in treatment; fear of side effects were mentioned by a few respondents as barriers to seeking treatment and this finding is also corroborated by the bio-behavioral study indicating that about 5.6% of those who were not on treatment refrained from it because of possible side-effects [5]. Inadequate management of mental health symptoms associated with HCV treatment was mentioned in our study and may be an obstacle in treatment continuation [21]. However, it is expected that the DAA, already in place in Georgia, will reduce this issue as fewer and less side effects are associated with these medications [22]. The study did not look at other mental health issues.

Once the patients are enrolled in treatment, they comply with the treatment regimen for the most part. This is largely supported by a friendly environment in the clinics as well as a responsive and caring staff that is critical to maintain the patients in treatment. The study is in line with the other research indicating that a friendly environment in the clinics, flexible service hours, and professionalism of the staff are important facilitators to treatment adherence [18].

Reinfection after cure could be another threat to the Hepatitis C Elimination Program. Enrollment into the Program does not require active PWID to quit injecting drugs. A majority of the study participants admitted that they will continue injecting drugs; therefore, the risk to of reinfection is real. The literature suggests that risk of reinfection among PWID was considerably lower than estimates of the risk of primary HCV infection among the same group [23]. Advice on reducing the risk of re-infection will be critical to minimize reinfection rates. This could be effectively delivered by harm reduction programs and peer educators [19]; however,

another drawback is the poor uptake of harm reduction services by PWID in Georgia. According to the latest research reports only 26.8% of PWID have benefited from the needle and syringe exchange program [5].

Study limitations

Our study is subject to several limitations. Although the study attempted to recruit female PWID, we were only able to enroll one female participant. In general recruitment of female PWID is challenging in Georgia due to lower prevalence of drug injection among females compared to males and high levels of stigma towards women who inject drugs leading them to be one of the most hidden subgroups [15,19]. The study also failed to enroll the PWID with a history of treatment interruption therefore our sample excludes views of this subset.

The respondents in the study were a convenience sample recruited through harm reduction service centers, therefore the findings should not be generalized to the PWID community in the country and other geographic areas. The views of the participants who agreed to participate in the qualitative study might be different from those who were unwilling to participate. Finally, PWID interviews were conducted during a limited time period, while some policy changes took place afterwards and therefore their effects were not captured by the study.

Despite these limitations, findings from this study are important for increasing the effectiveness of this unique program that is reaching a critical population at risk infected by HCV.

Conclusion

This study provides important insights into the implementation of the Hepatitis C Elimination Program in Georgia and also highlights barriers and facilitators to HCV treatment initiation and completion. The Georgian program should enhance its outreach to PWID communities to encourage HCV testing and use of harm reduction services as well as to provide education about HCV and HCV treatment. This can be accomplished by continuing to leveraging PWID relationships with CSOs.

Co-financing for clinical diagnostics and laboratory tests is an essential element of the program, particularly for impoverished PWID. Ensuring that this program element is sustained at adequate levels across the country will be an important facilitator of treatment initiation and completion.

Despite some challenges the Georgian program is an example for other countries wishing to initiate HCV elimination programs.

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REVIEW ARTICLE

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Innovative strategies for the elimination of viral hepatitis at a national level: A country case series

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Abbreviations: DAAs, direct-acting antivirals; DBS, dried blood spot; GHSSH, Global Health Sector Strategy on Viral Hepatitis; HBIg, hepatitis B immunoglobulin; HBsAg, hepatitis B surface antigen; HIV, human immunodeficiency virus; MTCT, mother-to-child transmission; NSP, needle and syringe program; OAT, opioid antagonist treatment; PWID, people who inject drugs; RNA, ribonucleic acid; SDG, Sustainable Development Goals; TRIPS, Trade Related Aspects of Intellectual Property Rights; WHO, World Health Organization.

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Abstract

Viral hepatitis is a leading cause of morbidity and mortality worldwide, but has long been neglected by national and international policymakers. Recent modelling studies suggest that investing in the global elimination of viral hepatitis is feasible and cost-effective. In 2016, all 194 member states of the World Health Organization endorsed the goal to eliminate viral hepatitis as a public health threat by 2030, but complex systemic and social realities hamper implementation efforts. This paper presents eight case studies from a diverse range of countries that have invested in responses to viral hepatitis and adopted innovative approaches to tackle their respective epidemics. Based on an investment framework developed to build a global investment case for the elimination of viral hepatitis by 2030, national activities and key enablers are highlighted that showcase the feasibility and impact of concerted hepatitis responses across a range of settings, with different levels of available resources and infrastructural development. These case studies demonstrate the utility of taking a multipronged, public health approach to: (a) evidence-gathering and planning; (b) implementation; and (c) integration of viral hepatitis services into the Agenda for Sustainable Development. They provide models for planning, investment and implementation strategies for other countries facing similar challenges and resource constraints.

KEYWORDS
developing countries, disease elimination, hepatitis B, hepatitis C, investment case, organizational case studies

1 | INTRODUCTION

Viral hepatitis contributes substantially to the global burden of disease, with 248 million people infected with hepatitis B and 71 million infected with hepatitis C worldwide.[1] If left untreated, chronic viral hepatitis can cause life-threatening complications, such as cirrhosis and hepatocellular carcinoma.[2] Despite this, the public health consequences of viral hepatitis have long been neglected.[1] In contrast to the progress in combating many other communicable diseases in recent years, viral hepatitis-related morbidity and mortality continue to rise.[1,3] In 2010 viral hepatitis was the 10th leading cause of death, but by 2015, with 1.2 million deaths, it had overtaken HIV, malaria and tuberculosis to rise to sixth.[4] Most viral hepatitis deaths are avertable through increased access to prevention, diagnosis and treatment.

In areas of high hepatitis B endemicity (eg Southeast Asia and sub-Saharan Africa), perinatal mother-to-child transmission (MTCT) and horizontal transmission during childhood are the most common routes of infection, while sexual contacts, unsafe injecting practices, and unhygienic medical or cosmetic procedures

Key points

- Viral hepatitis is the 6th leading cause of death globally, surpassing all other chronic infectious diseases including HIV, tuberculosis and malaria
- Elimination of viral hepatitis as a public health threat is achievable; all WHO member countries endorsed this goal formally in 2016
- Planning, implementation and integration of national responses to viral hepatitis is ongoing, and many countries have adopted innovative approaches to address the diverse challenges of this endeavour in their local contexts
- Existing approaches demonstrate that investing in viral hepatitis is affordable and cost-effective, provides multisectoral cost-benefits, and alleviates the human burden of the epidemic

drive transmission elsewhere.[5-7] Risk of developing chronic hepatitis B infection is inversely related to age at infection: around 90% of infants infected perinatally develop chronic infection, unless vaccinated at birth. This risk decreases to around 30% among children infected before the age of six years and to less than 5% of persons infected as adults.[8-10]

The hepatitis C epidemic is similarly geographically diverse and mode of transmission differs substantially between regions.[11-14] Globally, an estimated 52% of people who inject drugs (PWID) are hepatitis C antibody positive.[15] Lack of access to needle and syringe programmes (NSPs) and opioid antagonist treatment (OAT) result in unsafe injecting practices, which are the major route of transmission in high-income countries.[15,16] In low- and middle-income countries, additional transmission occurs in healthcare settings through substandard infection control practices.[17]

In 2016, the 69th World Health Assembly adopted the Global Health Sector Strategy on Viral Hepatitis (GHSSH) 2016-2021. The strategy outlines five synergistic prevention and treatment service coverage targets to achieve the elimination of viral hepatitis as a public health threat by 2030 (defined as 90% reduction in incidence and 65% in mortality, see Table 1).[18] Implementation of the strategy is expected to strengthen health systems while enabling progress toward the United Nations' Sustainable Development Goal (SDG) 3 target of universal health coverage.[19,20] Modelling studies suggest that rapid investment in diagnostic, prevention, and treatment services could achieve the World Health Organization (WHO) targets by 2030.[21,22]

1.1 | How can viral hepatitis be eliminated by 2030?

Eliminating viral hepatitis requires substantial investments in health systems strengthening and the full continuum of hepatitis services.[18] Investing in the prevention and treatment of viral hepatitis provides many direct, indirect and cross-sectoral economic benefits through saving lives and alleviating the cost burden of disease to the individual, their families and the state.[23-26] To achieve elimination at a national level, the country-specific context and its unique challenges must be considered. A multipronged approach comprising three main pillars is most effective in addressing the local context; comprising (a) evidence-gathering and planning the response; (b) implementation of disease-specific activities, including investments in the delivery of care; and (c) integration of the viral hepatitis response into SDG 3 by adopting a public health approach and embedding services into universal health coverage.[27]

The necessary tools for viral hepatitis elimination are already available, but worldwide implementation of a concerted viral hepatitis response is slow and faces many challenges. These include low levels of investments in health overall; inadequate data and weak surveillance systems; poor infrastructure; low awareness among policymakers, at-risk populations and primary care practitioners; high prices of some diagnostics and treatments; and a lack of prioritisation of viral hepatitis.[28,29] While most countries are on track to meet the WHO's 2030 target of < 0.1% Hepatitis B surface antigen (HBsAg) prevalence among 5-year-olds, without substantial further investments this target is currently unachievable for 20 countries, mainly in Africa and the Western Pacific. Moreover, only 12 countries are currently on track to achieve the hepatitis C elimination goal that all WHO member states adopted in 2016.[30]

We have developed a Viral Hepatitis Investment Framework outlining the resourcing required to achieve elimination, the cost of the elimination of viral hepatitis globally, and methods for countries to address existing challenges.[31] The Viral Hepatitis Investment Framework highlights key enablers to support a comprehensive viral hepatitis response and outlines priority national and international activities to maximise return on investment (Figure 1). Using the structure of the Investment Framework, this paper presents case studies from diverse countries (Table 2) that are successfully implementing innovative strategies to eliminate viral hepatitis (see Table 3). Additional case studies listed in Table 3 are summarised in the Appendix S1 (Figures 2-4).

1.2 | Evidence-gathering and planning

Low-quality surveillance systems and a lack of reliable cause-specific mortality data limit countries' capacity to guide, implement and monitor effective viral hepatitis responses.[32,33] To advocate for an adequate allocation of domestic resources and to mobilise external funding support, countries should develop a national plan that sets ambitious but achievable targets, informed by a robust local investment case for viral hepatitis. Gathering accurate data to inform a targeted approach can improve the cost-effectiveness of specific interventions.[34-36] Since the launch of the GHSSH 2016-2021, more countries have developed national hepatitis plans[1] and both local and global investment cases for the elimination of viral hepatitis have been built.[31,35,37] Many countries have begun collecting epidemiological data through national seroprevalence surveys or by adding key hepatitis indicators into existing surveillance systems. Below, we give examples of countries that have gathered evidence and are developing a national plan (Georgia), produced an investment case for elimination (South Africa) and obtained accurate data to inform the response (Scotland).

1.3 | Georgia: the development of a national plan

Georgia was the first country in the WHO European region to set a hepatitis C elimination goal and develop a national plan for viral hepatitis tailored to the local context. Georgia's significant experience with HIV prevention and control programmes and the existing human and technical capacities to implement large-scale health programmes facilitated the implementation of their national hepatitis C elimination programme.[38] An international Technical Advisory Group assisted with describing the local hepatitis C epidemiology and proposing strategies, objectives and actions to address gaps in advocacy and awareness, surveillance, harm reduction, blood safety, infection control, and evidence-based screening and linkage to care. Gilead Science provided direct-acting antiviral (DAA) w to Georgia at

TABLE 1 Viral hepatitis service coverage and impact targets

Target area	Baseline 2015	2020 Target	2030 Target
Service coverage targets			
Hepatitis B virus vaccination: childhood vaccine coverage (third dose coverage)	82% of infants	90%	90%
Prevention of hepatitis B virus mother-to-child transmission: hepatitis B virus birth-dose coverage or other approach to prevent mother-to-child transmission	38%	50%	90%
Blood safety: donations screened with quality assurance	89%	95%	100%
Injection safety: use of engineered devices	5%	50%	90%
Sterile needle/syringe set distributed per person per year for people who inject drugs	20	200	300
Viral hepatitis B and C diagnosis (coverage %)	<5% of chronic hepatitis infections diagnosed	30%	90%
Viral hepatitis B and C treatment (coverage %)	<1% receiving treatment	3 million	80% eligible treated
Impact targets			
Incidence: new cases of viral hepatitis B and C infections	Between 6 and 10 million infections are reduced to 0.9 million infections by 2030 (95% declined in hepatitis B virus infections, 80% decline in hepatitis C virus infections)	30% reduction (equivalent to 1% prevalence of HBsAg among children)	90% reduction (equivalent to 0.1% prevalence of HBsAg among children)
Mortality: viral hepatitis B and C deaths	1.4 million deaths reduced to less than 500 000 by 2030 (65% for both viral hepatitis B and C)	10% reduction	65% reduction

Source: Global Health Sector Strategy on Viral Hepatitis, 2016-2021.[18]

no cost after the elimination programme commenced; reportedly, a key reason for their decision was the Georgian Government's commitment to an elimination response.

The programme initially focused on increasing access to affordable diagnostics; providing free DAA treatment to persons with severe liver disease at highest-risk of hepatitis C-related mortality; and building capacity to achieve programme goals of preventing transmission and eliminating the disease.[39] Initial obstacles included suboptimal alignment of programme development and implementation, leading to bottlenecks in patient flow and wait lists.[40] Training for healthcare workers was only provided after the programme launched; however, doctors have subsequently received continuous technical support.

The programme has now expanded its scope to treat every person chronically infected with hepatitis C, as outlined in the "Strategic plan for the Elimination of Hepatitis C Virus in Georgia, 2016-2020". Hepatitis C treatment services are provided at treatment centres located throughout the country and treatment decentralisation in harm reduction centres and primary care is ongoing. Patient out-of-pocket fees for diagnostics and clinical monitoring are based on ability to pay. Georgia is working to integrate its hepatitis C elimination programme into the overall health system, because this will benefit the management of other health problems such as HIV and tuberculosis.[41] This is primarily being achieved via treatment decentralisation into primary care and harm reduction services.

The implementation of the national action plan increased access to hepatitis C testing and linkage to care while driving improvements in monitoring and surveillance, infection control and prevention.[38,41] The evaluation of harm reduction-based peer-supported hepatitis C treatment demonstrated excellent treatment uptake and retention in care among PWID based in Tbilisi.[42] By January 2019, 53 000 people had initiated treatment with the new DAAs, of whom almost 34 800 had already achieved hepatitis C cure (Figure 5A). Remaining challenges relate to the marginalised status of PWID, with stigma and discrimination preventing PWID from accessing hepatitis C services. Punitive drug laws (such as criminal responsibility for personal drug use) challenge the effectiveness of harm reduction programmes and lead to high rates of incarceration and hepatitis C transmission in prisons, where access to OST is limited. As well, as in other countries aiming for hepatitis C elimination, treatment numbers declined after the first two years of the programme, with many people being unaware of their hepatitis C status or not commencing treatment.

1.4 | South Africa: The development of an investment case

South Africa's National Action Plan 2017-2021 is one of the first examples of an investment case that combines tools for costing, impact modelling, cost-effectiveness analysis, and fiscal space analysis for scaled-up hepatitis B and hepatitis C disease control scenarios.[35] The action plan was developed in collaboration with leading South African experts, Ministry of Health officials, and external specialists in global health policy and economics, who

FIGURE 1 Investment framework for viral hepatitis elimination

assessed cost and affordability, health impact and cost-effectiveness for four priority interventions: hepatitis B birth dose vaccination, prevention of MTCT and treatment for hepatitis B and C.

The model suggests expanded hepatitis B prevention and treatment for hepatitis B and C (using DAAs for the latter) is cost-effective and affordable in the South African context,[35] noting that hepatitis B

TABLE 2 Country characteristics

	Georgia	South Africa	Scotland	Brazil	China	Egypt	Rwanda	Australia
Population total (million, 2017)	3.72	56.72	5.3 (2011)	208.49	1.386 billion	97.55	12.21	24.6
Life expectancy at birth (years)	73	63	79	76	76	71	67	83
GNI per capita (US$)	3780	5430	42 370 (UK total)	8840	8690	3010	720	51 360
HBsAg positive population (%)	115 948 (2.64%)[2]	3.5 million (6.7%)[2]	8700 (0.2%)[2,100]	1.28 million (0.65%)[2]	74.6 million (5.49%)[2]	1.34 million (1.7%)[2]	722 449 (6.7%)[2]	83 121 (0.37%)[2]
HCV-RNA positive population (%)	150 000 (5.4%)[101]	356 000 (0.7%)[102]	37 000 (0.8%)[103]	700 000 (0.71%)[104]	9.8 million (0.7%)[105]	3.81 million (7%)[76]	175 000 (3.1%)[11]	230 000 (1%)

birth dose vaccination should be prioritised if funds are insufficient for the full implementation. The five-year Action Plan was estimated to cost US$270 million, with the "testing, care, and treatment" component being the most costly. Whilst this is a significant amount of money, seen against 5-year HIV expenditure, the cost of the Hepatitis Action Plan is estimated to be less than 4% of the projected HIV spend in South Africa.[43] Integrating the action plan into the existing health system, particularly maternal and child health and HIV/AIDS services, was estimated to improve implementation feasibility.

The modelling data suggest the initial five-year investment could avert an estimated 13 000 hepatitis B-related deaths and 7000 hepatitis C-related deaths. Moreover, a continued expansion of the treatment programme beyond 2021 has the potential to avert 672 000 hepatitis B-infections and 60 000 deaths averted from hepatitis C-related liver disease, which would put South Africa firmly on the path to achieve elimination by 2030 (Figure 5B).[35]

The multi-stakeholder approach used to develop an investment case for the cost-effectiveness and affordability of hepatitis control and elimination for South Africa provides a template for other countries.[44] Implementation of the investment case-informed Viral Hepatitis Action Plan is expected to commence on 1st April 2019, with five priority interventions during the first year: (a) hepatitis B birth dose vaccination; (b) healthcare worker hepatitis screening, vaccination and training in viral hepatitis (c) increasing awareness, diagnosis and management of Hepatitis B virus (Tenofovir is on the Essential Medicine list); (d) registration of DAAs and price negotiations; (e) a comprehensive package of viral hepatitis services for key populations – men who have sex with men and people who use/inject drugs.

Key obstacles to the response are a lack of funding being allocated to the Programme due to fiscal constraints; a shortage of trained health workers; lack of knowledge about viral hepatitis in the general public; viral hepatitis-related stigma; limited access to harm reduction services; and punitive drug laws. There is a need to improve viral hepatitis services in other key populations, including prisoners, sex workers and men who have sex with men. Moreover, DAAs are yet to be registered in South Africa due to administrative delays at the South African Health Products Regulatory Authority, preventing broader hepatitis C treatment scale-up.

In order to address these obstacles, the South African Viral Hepatitis Working Group has established three subcommittees to oversee implementation of the hepatitis B birth dose vaccine, training of healthcare workers in conjunction with training on new HIV treatment regimens, and hepatitis C micro-elimination programmes.

1.5 | Scotland: accurate data to inform the response

In Scotland, advocates used political pressure and scientific evidence to raise awareness of the human impact of hepatitis C and its links to inequalities, which generated political consensus to support significant funding and evidence-based policy initiatives.[45] Social and political recognition of the scale of the problem galvanised policymakers into action. Innovative strategies such as the introduction

TABLE 3 National activities and country examples aimed at elimination of viral hepatitis

	National activities	Country examples presented in this paper
Evidence-gathering and planning	National hepatitis plan (addressing hepatitis B, hepatitis C or both)	Georgia, Australia, Brazil, China, Egypt, Iceland, Malaysia, Portugal, Scotland, South Africa
	Accurate data to inform the response (Surveillance and Monitoring)	Scotland, Portugal, Brazil, Egypt, Georgia, Iceland, Pakistan, South Africa
	Local investment case	South Africa, Rwanda
Implementation	Raising awareness and stigma reduction	Brazil, Australia,, China, Egypt, Iceland, Malaysia, Portugal, Pakistan
	Investment in prevention	China, Fiji, Pakistan, Australia, Brazil, Iceland, Georgia, Malaysia, Portugal, Scotland
	Testing, linkage to care and treatment	Egypt, Australia, China, Georgia, Iceland, Malaysia, Portugal, Scotland, South Africa
Integration	Investment and financing for sustainability	Australia, China, Iceland, Malaysia, Rwanda
	Health Systems Strengthening	Rwanda, Brazil, Fiji, Georgia, Malaysia, South Africa

Source: Global Policy Report on the prevention and control of viral hepatitis.[106]

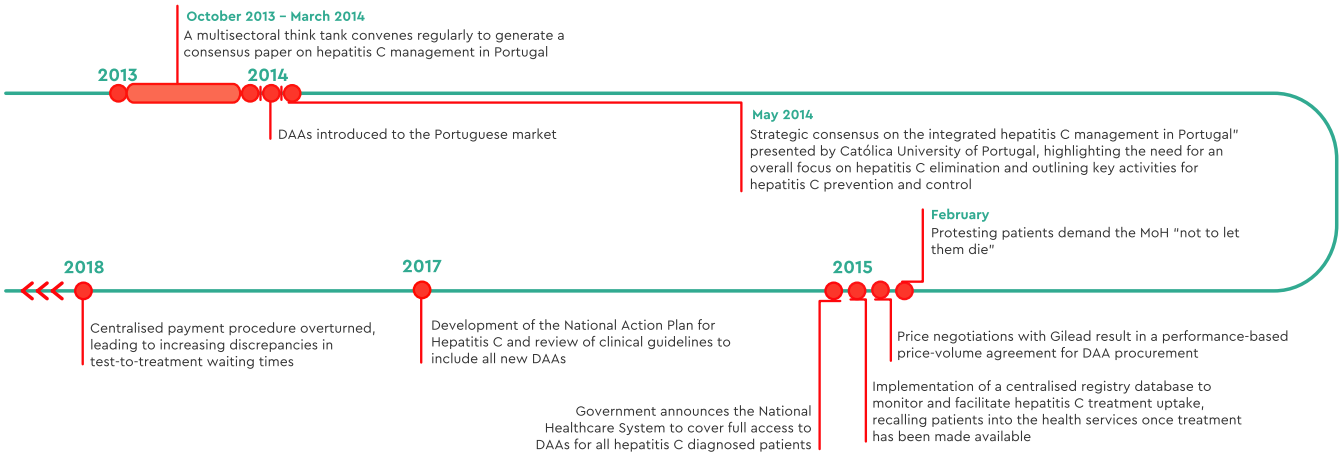

FIGURE 2 Timeline of national activities, Portugal

of dried blood spot (DBS) sampling in community drug services made the model of viral hepatitis care more acceptable to affected communities and helped overcome barriers to testing.[46] Adopting a project management approach ensured achievable goal-setting and controlled ongoing cost. Substantial investment in a robust monitoring and surveillance system – combined with ambitious treatment targets – facilitated progress and demonstrated immediate impact, which helped to sustain momentum.[47] Scotland's response – the National Hepatitis C Action Plan – has been a phased one. Launched in 2006, Phase I focused on gathering evidence to inform and generate proposals for the development of hepatitis C services and identify the additional investment required. Subsequently, in Phase II the Scottish Government committed funds to substantially improve prevention (including increasing coverage of harm reduction services), diagnosis and treatment services and deliver evidence-based actions throughout the country for improved hepatitis C prevention and control (Figure 5C). Since 2011, the Hepatitis C Action Plan has been integrated with other national policies within the Scottish Government's Framework on Sexual Health and Blood Borne Viruses, which adopts a multi-agency outcomes-based approach with a strong focus on challenging inequalities.[48,49]

The national strategy to improve prevention, diagnosis and treatment services led to a significant decline in hepatitis C incidence, more new diagnoses, more people undergoing hepatitis C treatment and achieving cure, reductions in liver-related morbidity and mortality, and a decreased population prevalence of chronic hepatitis C.[47,50-52] Scotland's example showcases the utility of evidence-based national hepatitis C strategies in reducing the financial and societal burden of the epidemic[52,53] and provides a working model for other countries to follow.

Despite the progress made in improving harm reduction services in Scotland during the era of interferon-based treatment, the prevalence of hepatitis C infection had remained stubbornly high. The recent scale-up of DAA therapy to PWID is hoped to bring a treatment-as-prevention benefit.[54] While the roll-out of DBS testing was effective at diagnosing infection, a substantial minority of the infected population remains undiagnosed. It has proven difficult to fully engage general practitioners in case-finding initiatives, with awareness-raising campaigns having limited success.[55,56] However, it is hoped that the availability of DAAs within primary care and other community settings will increase treatment uptake as the utility of the new therapies is recognised.

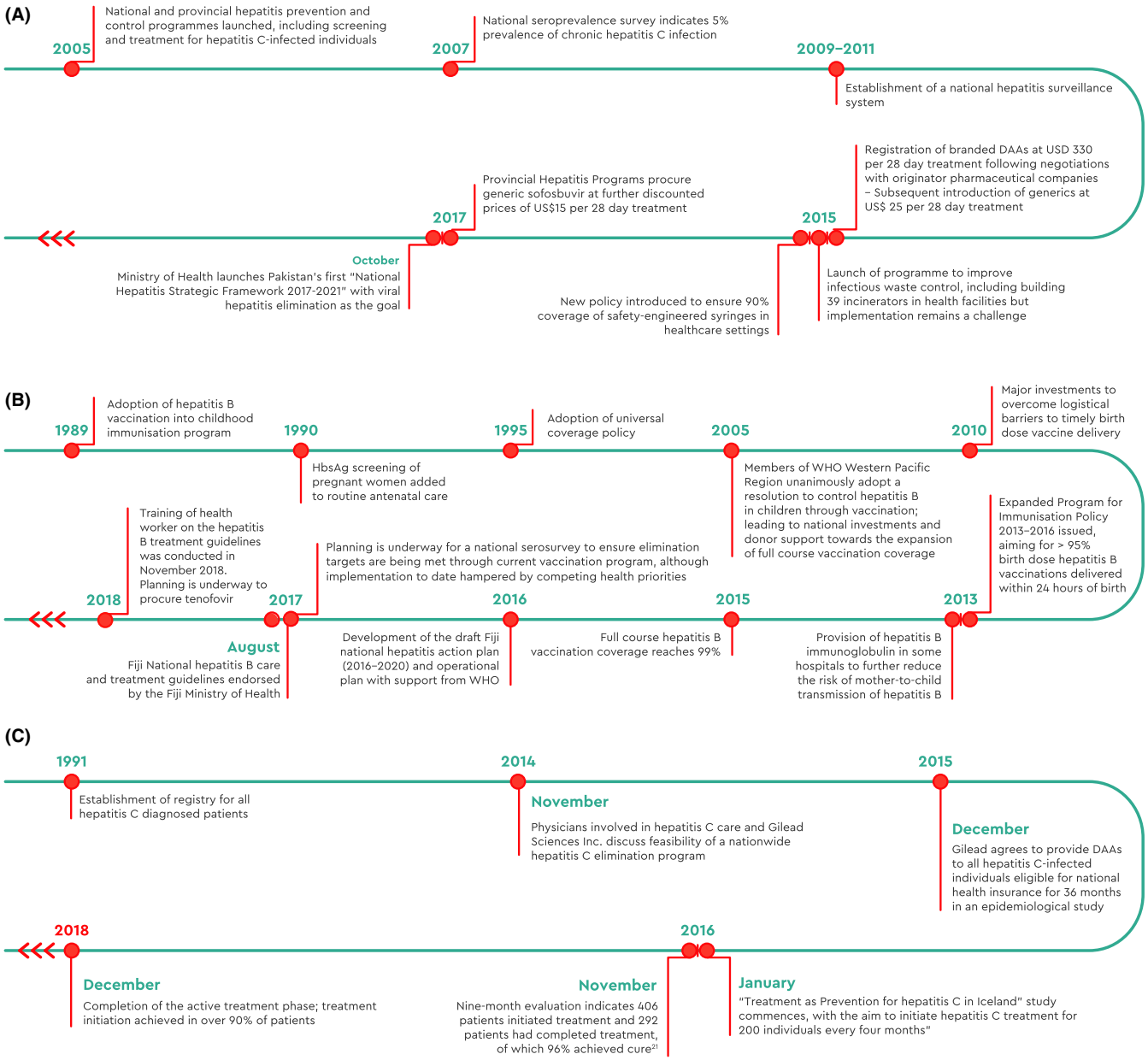

FIGURE 3 Timeline of national activities, Pakistan (A), Fiji (B), and Iceland (C)

1.6 | Implementation

Globally, nine of the 10 people living with viral hepatitis are unaware of their infection,[33] and lack of public knowledge is often compounded by viral hepatitis-related stigma and discrimination. Implementation of a viral hepatitis strategy should therefore include awareness-raising activities to generate demand for viral hepatitis care (eg through social media campaigns, such as in Brazil[57]) in conjunction with supportive laws, policy and guidelines that aim to reduce stigma and enable the establishment of community-focused responses.[46]

Prevention activities should be implemented and scaled up to effectively eliminate viral hepatitis transmission. A highly effective hepatitis B vaccine has been available since the 1980s, and early immunisation plus the distribution of hepatitis B immunoglobulin (HBIg) to at-risk infants prevents perinatal transmission, as China has demonstrated.[58] Harm reduction interventions, including NSPs and provision of OAT, cost-effectively reduce primary and reinfection incidence among PWID.[59-61] Iatrogenic transmission can be eliminated through routine screening of blood supply[62] and implementation of safe infection practices (including reducing unnecessary injections, staff training and effective waste management),[63] while simultaneously contributing to health systems strengthening.[4,64]

Finally, implementation of a viral hepatitis response must aim to optimise the viral hepatitis care cascade by substantially improving testing rates, linkage to care and treatment numbers. The case of Egypt (and Iceland, see Appendix S1) demonstrates that concerted

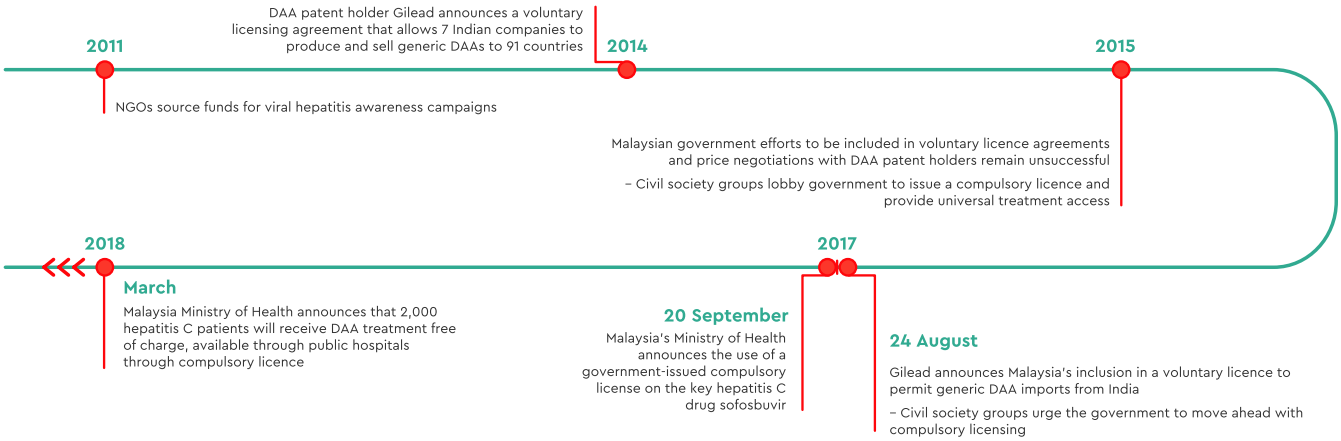

FIGURE 4 Timeline of national activities, Malaysia

efforts enable substantial advances towards the WHO targets of 90% of people diagnosed and 80% of eligible people treated.[30,65,66]

Below are examples of implementation: raising awareness and stigma reduction (Brazil), investment in prevention (China), and investment in testing, linkage to care and treatment (Egypt).

1.7 | Brazil: raising awareness and stigma reduction

Brazil, a middle-income country, has been providing universal access to antiretroviral therapy for HIV since 1996, driven by strong political will, multisectoral mobilisation and use of Trade Related Aspects of Intellectual Property Rights (TRIPS) flexibilities, and civil society engagement.[67] It has championed the cause of viral hepatitis and advocated for an intensified global response for many years. Learning from its successes in reversing the trend of the HIV epidemic, Brazil established a national hepatitis programme informed by up-to-date estimates of disease prevalence, international guidelines and cost-effectiveness in the Brazilian Unified Health System.[57] Brazil invested in universal hepatitis B vaccination, increased capacity for hepatitis C testing in HIV services, expanded its laboratory network and set up a referral system for hepatitis patients. To reach the target population, the Ministry of Health conducted new public awareness and diagnosis campaigns using a variety of media with endorsement from civil society and the scientific community.[57]

Brazil was able to obtain an unprecedented discount for an upper-middle-income country through price negotiations with originator pharmaceutical companies. Between 2015 and 2018 it provided treatment to nearly 90 000 people, and is expected to treat another 50 000 patients in 2019, largely thanks to the strong advocacy of civil society.

The remarkable process applied in Brazil was based on epidemiological data and scientific evidence, and motivated by its engagement with the SDGs, which may inspire other countries to identify ways to achieve these goals by 2030.[57] Brazil has pledged to provide free hepatitis C treatment to everyone infected and is one of 12 countries on track to achieve hepatitis C elimination by 2030 (Figure 6A).[30]

Despite this progress, geographical, social and economic disparities in Brazil challenge the provision of equitable service access across varied geographical regions. Brazil is working to improve diagnosis rates and mitigate losses to follow-up, resulting from the long delays between diagnosis and treatment initiation arising from small numbers of specialists who can provide DAA treatment.[68]

1.8 | China: investment in prevention

China is home to nearly one third of all people living with hepatitis B infection globally. HBsAg prevalence is estimated at 5.5%[2] and hepatitis B causes over 300 000 deaths annually due to liver diseases.[69] The implementation of a universal hepatitis B vaccination programme for infants has reduced chronic hepatitis B incidence dramatically during the past two decades. The full implementation of a national programme for the prevention of MTCT guarantees adequate supply of HBIg for at-risk newborns. Domestic procurement of the hepatitis B vaccine and auto-disable syringes ensures sustainable supply chains and stimulates regional industry and technology markets.[70]

Driven by strong political commitment and with support from the Global Alliance on Vaccine and Immunization, including an investment of ~ USD76 million to subsidise the hepatitis B catch-up vaccination programme for 15 million children through public-private partnerships such as with Rotary and the ZeShan Foundation,[71] multiple strategies were developed and implemented collaboratively (Figure 6B). As a result, >95% of infants receive the hepatitis B vaccine within 24 hours of birth.[72-75] This programme led to a nationwide catch-up vaccination drive for children up to the age of 15, reaching 68 million people over a 3-year period (2008-2011) (private communication). Between 1992 and 2013, China's efforts have prevented 90 million cases of chronic hepatitis B infection and 24 million fewer people are carriers of the virus –a massive reduction in the global burden of viral hepatitis.[70]

Although China has made considerable progress with hepatitis B, systemic obstacles to the elimination of MTCT remain. The physician-centred approach of the medical service infrastructure discourages affected pregnant women from seeking timely treatment, because

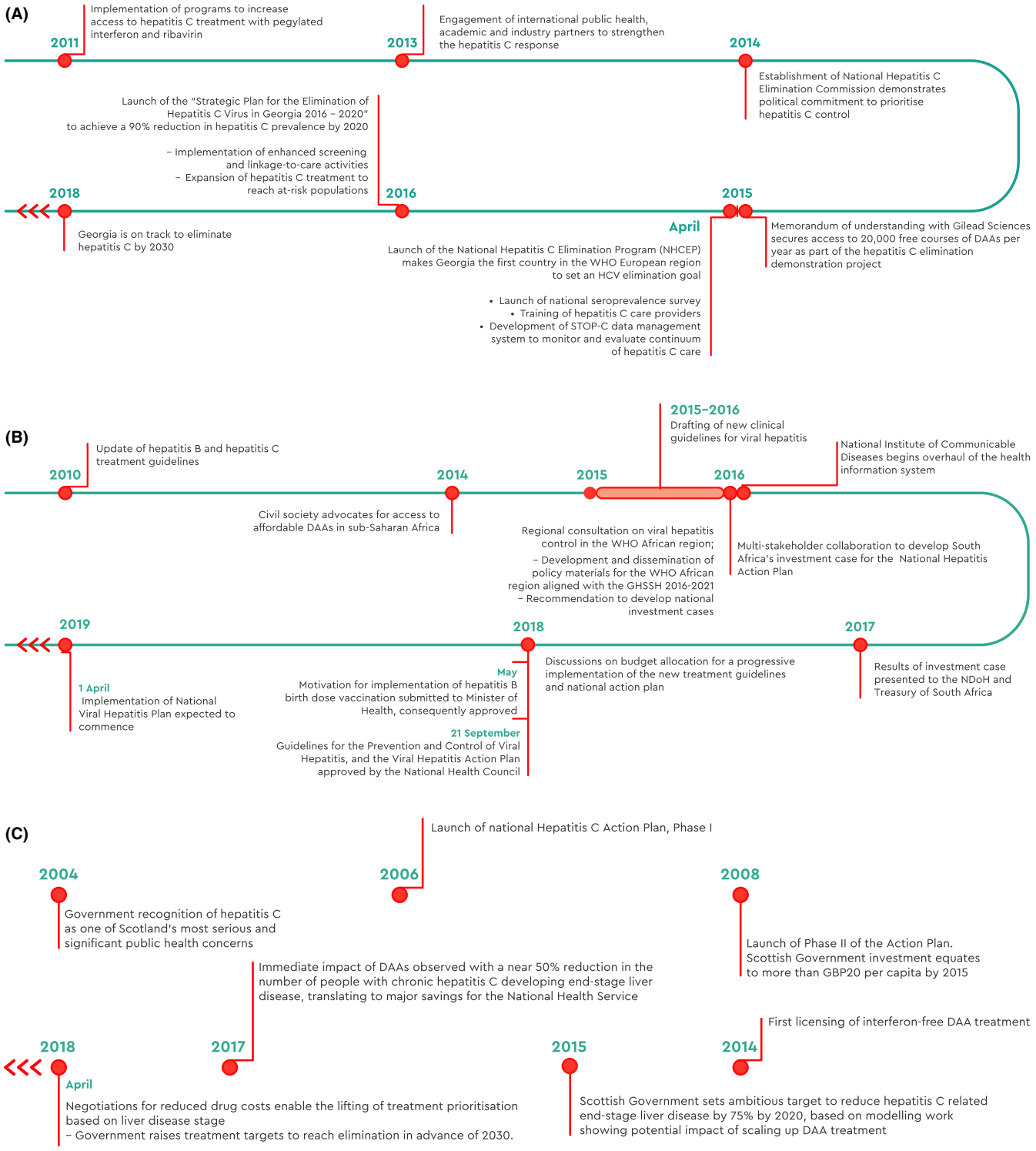

FIGURE 5 Timeline of national activities, Georgia (A), South Africa (B), and Scotland (C)

physicians trained to provide treatment (ie obstetricians, gynaecologists, gastroenterologists and infectious disease specialists working in central hospitals) are often reluctant to do so. Moreover, China is yet to implement a comprehensive national strategy addressing its hepatitis C epidemic. Few DAAs have been approved and their high cost restricts inclusion in basic health insurance programmes; consequently, DAA treatment is not universally available. Policy changes and education campaigns are needed to overcome stigma and discrimination and improve diagnosis rates, and linkage to care needs improvement.

1.9 | Egypt: testing, linkage to care and treatment

Egypt has a very high burden of hepatitis C infection and disease, with approximately 7% of Egyptians aged 18-59 living with chronic hepatitis

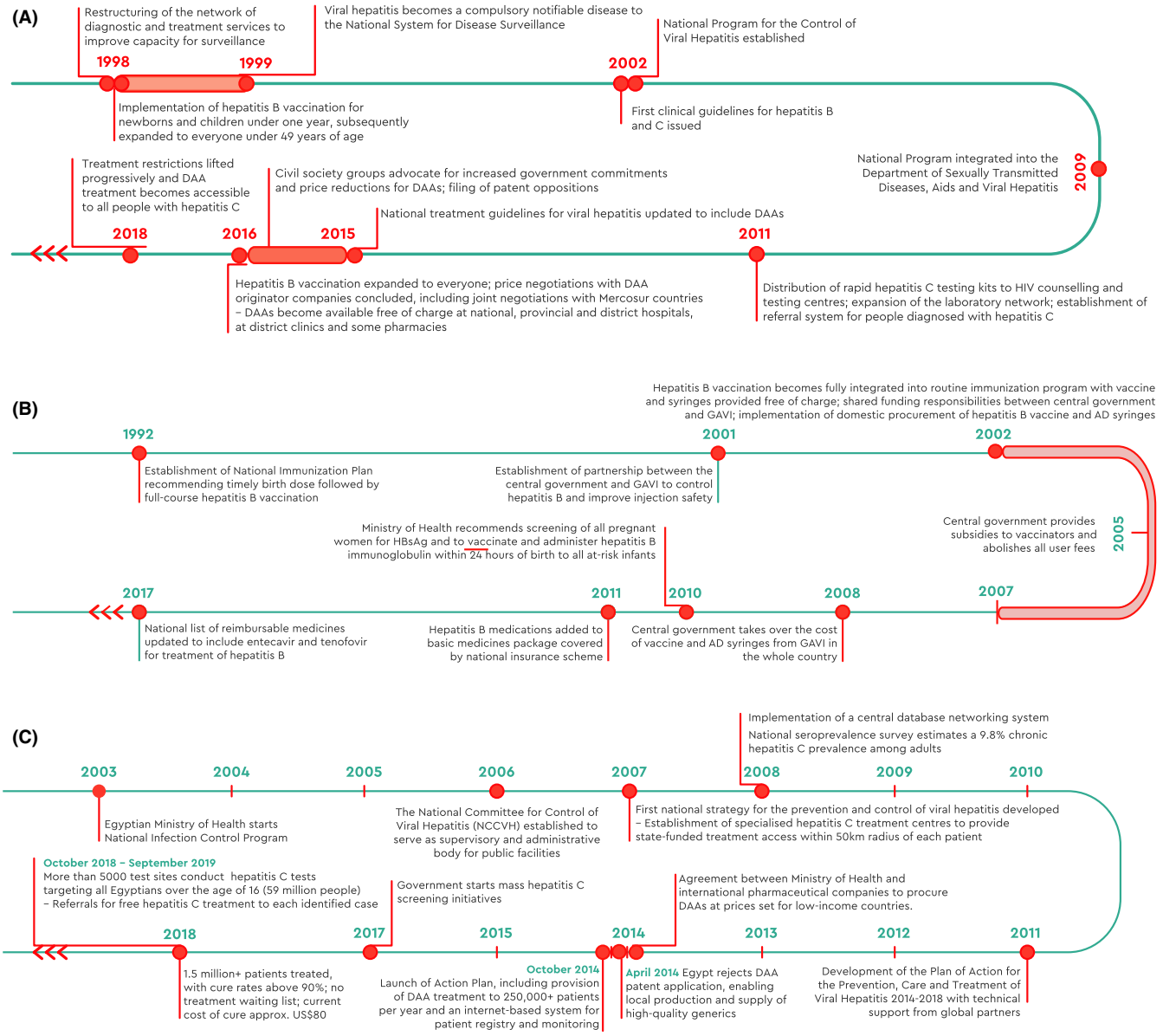

FIGURE 6 Timeline of national activities, Brazil (A), China (B), and Egypt (C)

C infection in 2015.[76] This large reservoir of active infection and continued unsafe medical practices contribute to ongoing transmission; in 2016, an estimated 150 000 Egyptians were newly infected.[77]

Egypt is committed to ending its generalised hepatitis C epidemic. It has developed one of the largest national programmes for hepatitis C treatment.[78] Egypt provides free and universal access to locally produced DAA treatment, as part of a national action plan for the prevention and control of viral hepatitis. To maximise efficiencies, the country has rolled out mass screening since October 2018, providing direct linkage to hepatitis C care. Over six months, more than 49 million people were reached, of whom over 2 million were diagnosed as hepatitis C-antibody positive (in addition, >2.5 million possible cases of diabetes and > 10 million possible cases of hypertension were identified and referred for further assessment and management). Of hepatitis C patients linked to care and confirmed as ribonucleic acid (RNA) positive, 750 000 started treatment.

By 2019, over 2.4 million Egyptians had been treated, and the country is on track to achieve WHO elimination targets in spite of its high hepatitis C prevalence (Figure 6C).[78,79] Egypt's response was facilitated by strong political will and government advocacy, effective price negotiations, removal of patent barriers on DAAs and ability to produce DAAs locally.[66,80]

Despite great progress Egypt's response is challenged by difficulties in capturing non-responders to treatment and lack of appropriate medications to initiate retreatment. Moreover, children under 12 years old cannot be treated because the medications have not yet been approved for this age group. Finally, plans and strategies for surveillance to reliably capture whether hepatitis C elimination targets have been met are not fully developed.

1.10 | Integration

The cost burden of viral hepatitis diagnostic tests and treatment – in particular the new DAA treatment for hepatitis C – challenges the feasibility and sustainability of effective viral hepatitis elimination activities. Unlike for other major communicable diseases such as HIV, tuberculosis and malaria, there is little funding available for viral hepatitis at an international level and most countries lack dedicated hepatitis budgets or programmes.[18] Although the private sector (such as pharmaceutical companies) and international funders and organisations are important actors in global elimination efforts, most funding will have to be mobilised from public, domestic sources to ensure the sustainability of viral hepatitis services as part of a broader effort to increase overall investments in health.[29,81,82] Increasing investment in infrastructure and health service delivery (ie health systems strengthening) is not only a key enabler for viral hepatitis elimination but a requirement to reach the overarching SDG 3 for health and its target of universal health coverage.[19] Ensuring that hepatitis services are integrated within these systems can reduce costs, compared to an isolated, non-strategic approach,[31] exemplified here in the case of Rwanda.

Integrating the viral response into the health system by utilising existing structures and trained workforces can save costs and generate efficiencies, as well as maximising access to services for key risk populations.[83] For example conducting viral hepatitis testing at HIV services is likely to yield high diagnosis rates because people living with HIV have a higher risk of hepatitis B or hepatitis C co-infection, and may improve their engagement in care.[84] However, it is important to look beyond integrating the response into HIV programmes, because further opportunities exist to broaden the viral hepatitis response by integrating it within tuberculosis, maternal and child health, and diabetes programmes. Also such an approach may not be useful in countries with generalised epidemics (such as China and Egypt) that require population-based approaches to testing and treatment.

Even when the response is integrated within the broader health system, there will be extra costs due to the need to expand services and to increase staffing levels to accommodate the increased activity. For example, additional time is needed to administer a hepatitis B vaccine or to provide post-test counselling for positive test results.[82] Due to concerns about extra costs and workload, efforts to integrate viral hepatitis responses into existing systems and platforms may receive substantial pushback, particularly initially. However, there is no evidence to support the notion that introducing viral hepatitis care into these systems causes existing structures to collapse.[85]

Moreover, multiple countries have been able to make treatment accessible to the broader population by successfully negotiating with patent holders (eg Australia), making use of patent licenses either available directly from the patent owner or those held by the Medicines Patent Pool (eg Rwanda),[86] or using TRIPS flexibilities to circumvent patent barriers to accessing lower priced generic DAAs (eg Malaysia, see Table 4 and Appendix S1).[87]

Below are examples of integration: health systems strengthening (Rwanda) and investment and financing for sustainability (Australia). Importantly, the health systems in both countries have coped with this considerable scale-up of treatment and care.

1.11 | Rwanda: expanding on universal health coverage

Rwanda is a low-income country that is using a public health framework for hepatitis control and care to progress on its aim to achieve universal health coverage.

The country has made tremendous gains in maternal and child health, malaria, tuberculosis and HIV outcomes. The Rwandan Government now invests major resources in viral hepatitis, using programmatic steps that form a blueprint for other low-income countries in the region.[88] Key elements of Rwanda's programme for viral hepatitis prevention and treatment include:

- Simplified treatment algorithms not requiring hepatitis C genotype or hepatitis B viral load and largely able to be delivered by nurses at health centre level
- Selective partnerships and preferred suppliers to drive down price, consolidate the supply chain and streamline diagnostic platforms to avoid siloed approaches to healthcare[89]
- Study of necessary resources for efficient implementation
- Development of a training programme for health staff
- Development, funding and implementation of birth dose vaccination for hepatitis B.

To ascertain feasibility and ensure financing for sustainability, a national operational plan was developed to demonstrate priority-setting of key activities and provide costing estimates for different levels of coverage of screening, diagnosis, and treatment of both hepatitis B and C.[88] Several initiatives were used to secure funding, including support from international donors, in particular the Clinton Health Access Initiative. Rwanda has a voluntary licensing agreement for DAAs and is therefore able to produce medication at reduced cost (approx. US$ 560 in 2017).[66,88] Rwanda's Essential Medicines List includes generic hepatitis B medicines treatment; this is subsidised by government for people with HIV coinfection. All major private health insurance companies (as well as military medical insurance) reimburse for the cost of DAAs, and the Rwanda social security board covers 85% of the cost. Ultimately, the aim is to provide reimbursement for hepatitis C diagnostics and treatment by the community-based health insurance scheme.[88] As of June 2017, 2500 patients had been treated with DAAs and treatment for 9000 additional patients had been procured (Figure 7A). Rwanda aims to establish treatment capacity at all 48 district hospitals countrywide by 2020.

Major ongoing barriers to addressing viral hepatitis in Rwanda include the lower awareness of, and priority given to, viral hepatitis compared to other infectious diseases (eg malaria and HIV) and the competing priorities for limited public-sector health funding. A prior strategy (from 2011) that failed and has since been abandoned was to develop local viral hepatitis treatment guidelines based upon international consensus guidelines, without sufficient attention to the resources required for implementation (including particularly

TABLE 4 Hepatitis B vaccination coverage and procurement status of hepatitis C medicines

Country	Hepatitis B vaccination coverage (2019)[75]		Hepatitis C treatment procurement (2017)[107]			
	Three-dose vaccination <1 y	Timely birth dose	DAAs registered in country	Voluntary license (VL) or Compulsory/ government-use license (CL)	Generic local production	Support from originator company
Australia	94%	91%	Yes	—	No	No
Brazil	86%	76%	Yes	No	No	No
China	99%	96%	Yes	No	No	No
Egypt	95%	13%	Yes	VL	Yes	Yes
Fiji	93%	95%	No	VL	No	No
Georgia	92%	94%	Yes	VL	No	Yes
Iceland	[a]	[a]	Yes	—	No	Yes
Malaysia	98%	88%	Yes	CL and VL	No	No
Pakistan	86%	<1%	Yes	VL	Yes	Yes
Portugal	98%	97%	Yes	—	No	No
Rwanda	98%	0%	Yes	VL	No	Yes
Scotland	<1% (UK)	<1% (UK)	Yes	—	No	No
South Africa	74%[2]	n/a	Yes	VL	No	No

[a]Estimates of hepatitis B vaccination coverage were produced only for countries with universal birth dose policy.[75]

laboratory testing and availability of medications) or the skills and experience required of clinicians. These guidelines thus lacked local contextualisation and recommended unavailable or unaffordable management; consequently, they were impractical and did not influence daily clinical practice greatly.

1.12 | Australia: a multipronged approach to elimination

In 1999, Australia was one of the first countries to implement and subsequently refine their national hepatitis C strategies and has since then become a best practice model for hepatitis C elimination. Key to Australia's response, including achieving universal treatment access (described below), has been strong community advocacy, health research, health sector and political leadership that foster continued commitment to the WHO 2030 elimination targets, including a timely response to new challenges.[90] Australia has had a long and sustained harm reduction approach to injecting drug use, with engagement of civil society, the health sector and government. This is beneficial in reducing bloodborne virus transmission and cultivates a point of engagement with PWID in providing health and social services.[59-61,91] Strong engagement with PWID is crucial to Australia's response.

By negotiating a volume-based, risk-sharing agreement with originator pharmaceutical companies and committing over AUD1 billion to the purchase of DAAs between March 2016 and February 2021, Australia obtained major discounts on drug list prices and as a consequence limited its expenditure. With no cap on treatment numbers,[92] there is an incentive to diagnose and treat as many people as possible to maximise Australia's investment and its public health benefits. This provides an enabling environment to prioritise high-prevalence groups with ongoing risks for treatment, such as PWID and prisoners, necessary to achieve hepatitis C elimination. In addition, all registered medical practitioners are able to prescribe DAA therapy, enabling more convenient, patient-centred care. In Australia, close collaboration between people living with hepatitis C, community organisations, clinicians and policymakers facilitated improved access to diagnosis and treatment scale-up (Figure 7B).

Australia aims to treat around 15 000 to 20 000 hepatitis C patients per year, to reach the WHO target to eliminate viral hepatitis as a major public health threat by 2030. This early commitment to achieving elimination and provide unrestricted treatment access enabled rapid treatment uptake during the first two years of DAA availability.[90] Between March 2016 and late 2018, over 70 000 patients (around 30% of all infected Australians) were treated. The proportion of individuals prescribed DAA treatment by general practitioners increased from 8% in March 2016 to 39% in June 2017.[93] With the successful implementation of its hepatitis C strategy – a global benchmark for best practice[94] – Australia is on track to achieve elimination by 2030.[95]

Of concern in Australia is the continuing drop off in the number of patients undergoing screening and confirmatory testing and treatment since March 2016.[93] While treatment numbers have been sufficient to maintain the elimination targets, further decline could

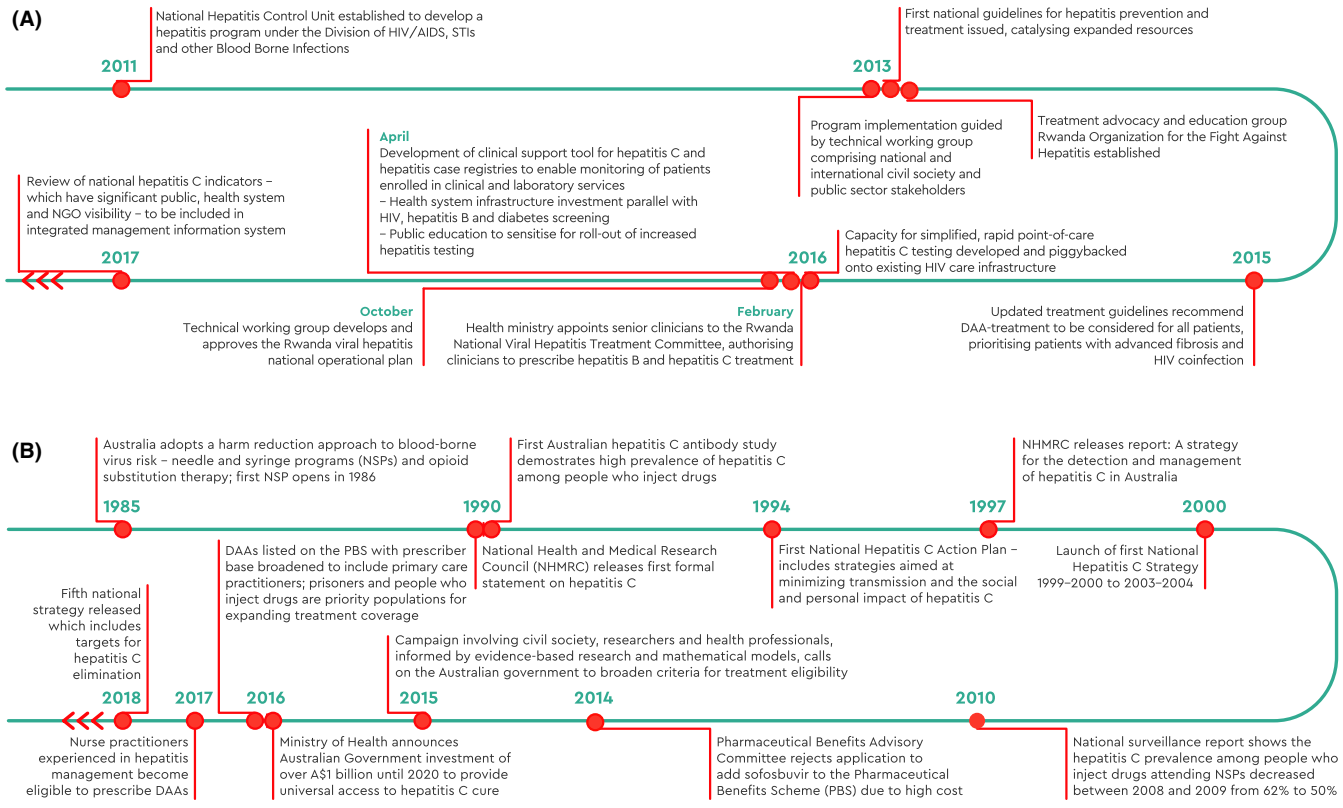

FIGURE 7 Timeline of national activities, Rwanda (A) and Australia (B)

put the elimination effort at risk. The decline in treatment numbers demonstrates that universal availability of DAA treatment alone is not enough to improve access to diagnosis and retention in care. Continued political commitment and policy and health system interventions are needed to facilitate treatment access for key populations to sustain momentum and overcome ongoing programme challenges to treatment scale-up.

2 | DISCUSSION

The broader benefits of investing in the elimination of viral hepatitis – including progressing on the SDGs - are increasingly being recognised. Countries with different income levels, public health infrastructures and policy environments are effectively responding to their respective epidemics.

Attaining the viral hepatitis elimination targets set by the global community in 2016 is achievable but also highly ambitious and comes with considerable challenges (see Appendix S1). These should not be ignored, but instead considered and addressed both at a global level and within the local context to invigorate and maintain national elimination efforts. Gathering sufficient funds to finance viral hepatitis programmes continues to be difficult among competing health priorities and budget constraints. Not all countries currently benefit from generic competition, with heavily burdened middle-income countries (eg China, Malaysia, Thailand) struggling to afford higher drug prices. A further obstacle is the increasing cost of diagnostics; for example, in Egypt expenditure on diagnostics now exceeds that on hepatitis C treatment.[68] There are few WHO prequalified point-of-care viral hepatitis tests and little production of low-cost high-quality generic tests. In many low-income countries, strengthening primary health care systems for maternal and child health, developing laboratory capacity, and improving weak registration and procurement systems for essential medicines is an ongoing challenge. For hepatitis B, cold chain barriers to vaccination including birth dose delivery exist, and while the controlled temperature chain presents a cost-effective alternative that could vastly improve coverage[96] it is yet to be broadly adopted.

Even in countries such as Australia, where there is close collaboration between community, government and health practitioners to guide implementation, elimination cannot be guaranteed because many patients remain undiagnosed and/or do not access treatment.[93,97,98] Identification of sufficient numbers of infected patients needing treatment remains a challenge globally; meanwhile, in countries where scale-up of a viral hepatitis response is pending, demand for viral hepatitis testing and treatment can outstrip available testing and treatment facilities,[85] creating bottlenecks within the care cascade leading to losses to follow-up. High levels of stigma, discrimination, social marginalisation and legal impediments imposed on key populations at risk or infected with viral hepatitis (eg PWID, prisoners, men who have sex with men, sex workers) is a major issue preventing engagement in care and service access[84] and in many countries legal protections remain insufficient.[68] The impact of regressive policies and laws on the elimination response cannot be underestimated.

The country case studies presented here demonstrate that major gains are possible in spite of these challenges – across various epidemic profiles, within a diverse range of resource constraints and within relatively short-time frames. The case studies illustrate that political will and commitment, civil society advocacy, donor support and community acceptance are crucial and can make a difference. From concerted screening efforts in Egypt and using innovative approaches to increase hepatitis C testing in Scotland, to building local investment cases in South Africa, to integrating viral hepatitis services into existing health infrastructure in Brazil and Rwanda, these pioneers provide important models for other countries to follow. In all countries multi-stakeholder engagement of national and international experts, civil society organisations and affected communities form critical components across the three pillars of evidence-gathering and planning, implementation and integration.

On a global level, civil society bodies such as the World Hepatitis Alliance are instrumental in generating pressure on governments and international organisations, providing an evidence-based approach to the response.[82] Locally, robust evidence and civil society advocacy helped to achieve political commitment and facilitated the development of national plans. Collaboration and cooperation between civil society, the pharmaceutical industry and government smoothed the introduction of prevention and control programmes. Such unified, evidence-informed strategies at the political and technical levels are crucial to attract and sustain commitment and financing. Learnings from these country examples and other local projects demonstrating the feasibility of elimination (eg micro-elimination projects[36,99]) can help persuade policymakers in other countries to support viral hepatitis prevention and control plans. In-country and global advocacy must be maintained to keep viral hepatitis high on the political agenda.[82]

3 | CONCLUSION

At the 2016 World Health Assembly, the global community uniformly endorsed the unique opportunity to eliminate viral hepatitis as a public health threat. Although an ambitious goal, technological advancements have made it scientifically feasible and increasing recognition of the public health threat posed by viral hepatitis provides the grounds for substantial political and societal support. The broader benefits of investing in the elimination of viral hepatitis – including progress on the Agenda for Sustainable Development – are now well recognised. Sustaining political momentum will be critical if elimination efforts are to be successful and more countries will need to take action if global elimination of viral hepatitis is to be achieved. Looking to existing approaches that address viral hepatitis can facilitate political support, because they demonstrate that investing in viral hepatitis is cost-effective and can be made affordable, provide multiple economic benefits, and above all alleviate the human burden of the epidemic. The case studies presented in this paper provide clear and feasible examples of successful approaches taken by

low-, middle- and high-income countries with diverse epidemics of hepatitis B and C to achieve the WHO 2030 viral hepatitis elimination targets.

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CONFLICT OF INTEREST

AHS reports grants and travel funding to her institution from ViiV Healthcare. ETH is the former director of the Medicines Patent Pool. NS has received investigator-initiated research funding from Gilead Sciences. JVL reports grants and personal fees from AbbVie, Gilead Sciences and MSD, personal fees from CEPHEID and Janssen outside the submitted work. MES is principal investigator in an investigator-initiated trial sponsored by Gilead Sciences (received no PI fees, trial closed April 17th 2019) and reports an educational grant to travel to EASL 2019 (Gilead Sciences). SJH received honoraria from Gilead, unrelated to submitted work. MH's institute receives investigator-initiated research funding from Gilead Sciences, Abbvie and BMS. JH received the Gilead Sciences Australia fellowship (2017). DW, CK, RA, RBL, MB, LA, AG, SH, RH, WL, RBM, SO, RP, MS, CWS, TS, MT, TW and ESS have nothing to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Interim effect evaluation of the hepatitis C elimination programme in Georgia: a modelling study

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Summary

Background Georgia has a high prevalence of hepatitis C, with 5·4% of adults chronically infected. On April 28, 2015, Georgia launched a national programme to eliminate hepatitis C by 2020 (90% reduction in prevalence) through scaled-up treatment and prevention interventions. We evaluated the interim effect of the programme and feasibility of achieving the elimination goal.

Methods We developed a transmission model to capture the hepatitis C epidemic in Georgia, calibrated to data from biobehavioural surveys of people who inject drugs (PWID; 1998–2015) and a national survey (2015). We projected the effect of the administration of direct-acting antiviral treatments until Feb 28, 2019, and the effect of continuing current treatment rates until the end of 2020. Effect was estimated in terms of the relative decrease in hepatitis C incidence, prevalence, and mortality relative to 2015 and of the deaths and infections averted compared with a counterfactual of no treatment over the study period. We also estimated treatment rates needed to reach Georgia's elimination target.

Findings From May 1, 2015, to Feb 28, 2019, 54 313 patients were treated, with approximately 1000 patients treated per month since mid 2017. Compared with 2015, our model projects that these treatments have reduced the prevalence of adult chronic hepatitis C by a median 37% (95% credible interval 30–44), the incidence of chronic hepatitis C by 37% (29–44), and chronic hepatitis C mortality by 14% (3–30) and have prevented 3516 (1842–6250) new infections and averted 252 (134–389) deaths related to chronic hepatitis C. Continuing treatment of 1000 patients per month is predicted to reduce prevalence by 51% (42–61) and incidence by 51% (40–62), by the end of 2020. To reach a 90% reduction by 2020, treatment rates must increase to 4144 (2963–5322) patients initiating treatment per month.

Interpretation Georgia's hepatitis C elimination programme has achieved substantial treatment scale-up, which has reduced the burden of chronic hepatitis C. However, the country is unlikely to meet its 2020 elimination target unless treatment scales up considerably.

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Introduction

Hepatitis C virus (HCV) infection causes liver disease,[1,2] with 71 million people being infected globally in 2015 and 80% of them living in low-income and middle-income countries.[3] HCV is primarily transmitted by injection drug use and unsafe medical procedures.[4–6] The development of highly curative direct-acting antiviral treatments for HCV contributed to WHO's 2016 global strategy to eliminate hepatitis C.[7]

Hepatitis C prevalence is high in Georgia, with 150 000 adults (5·4% of the adult population) infected in 2015.[8] Georgia launched the first national hepatitis C elimination programme in 2015, with donated treatments from Gilead Sciences and technical assistance from the US Centers for Disease Control and Prevention.[9] This programme aims to reduce the prevalence of chronic hepatitis C infection by 90% through diagnosing 90% of infections, treating 95% of diagnosed infections, and curing 95% of treated individuals (90-95-95 target) by 2020.

A national survey done in 2015[8] found considerable variation in prevalence of chronic hepatitis C by gender and age. The highest prevalence of infection (15·7%) was among men aged 30–49 years, with much lower prevalence in adult women (2·2%). The high prevalence of chronic hepatitis C in men in this age bracket is thought to have resulted from extensive transmission after the collapse of the Soviet Union in 1991, when civil war and economic collapse[10] resulted in considerable drug trafficking and injection drug use in Georgia.[11] Although injection drug use has decreased since then, Georgia still has a high rate of injection drug use (2% of adults)[12] compared with the global average (0·33%).[4] Iatrogenic HCV transmission also occurred because of insufficient infection control practices and inadequately screened blood supply, which were not addressed until

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Research in context

Evidence before this study

We identified mathematical models of hepatitis C elimination by searching PubMed from database inception to May 1, 2019, using the terms "("HCV" OR "Hepatitis C") AND "elimination" AND ("model" OR "projection")" in title and abstract fields. We identified several studies that project the scale-up of treatment of hepatitis C virus (HCV) infection required to eliminate hepatitis C within high-risk populations, such as people who inject drugs (PWID) or people living with HIV in subnational regions of the UK, Greece, Australia, and the USA, or nationally in Iceland, the USA, and Australia. We also identified models of hepatitis C elimination among the general population for subnational regions of the USA and Austria; at the national level for Switzerland, Australia, Italy, Greece, Belgium, Egypt, and Pakistan; regionally for the EU; and one global model. Of the national-level studies, only the general population models for Egypt and Pakistan, and the PWID-focused models in Iceland, Australia, and USA were based on dynamic HCV transmission models that account for the prevention impact of treatment on HCV incidence. No studies evaluated the interim effect of an ongoing HCV elimination programme.

Added value of this study

This study uses a dynamic model of HCV transmission among PWID and the general population to assess the interim effect of the first national-level HCV elimination programme in Georgia, a country with high HCV prevalence (5·4% in 2015). This study illustrates the importance of using modelling to assess the progress of ongoing elimination programmes. It suggests that a substantial effect (37% decrease in incidence and prevalence) has already been achieved by the Georgian HCV elimination programme, but that treatment rates either need to be increased dramatically (by four times) or the duration of the programme needs lengthening (from 2020 to 2026), to ensure it reaches its primary endpoint of a 90% reduction in HCV prevalence compared with the prevalence in 2015.

Implications of all the available evidence

Published data highlight that rapid and substantial treatment scale-up is required to reach HCV elimination targets set by WHO by 2030. This study shows that countries can achieve large increases in treatment, which should achieve substantial decreases in prevalence and incidence, but highlights the challenges of implementing sufficient scale-up to achieve elimination over a short timeframe even with a high level of government commitment.

after 2009.[8,13] Prevention of these modes of transmission and improvements in harm-reduction interventions for people who inject drugs (PWID) are goals of the elimination programme, alongside HCV case-finding and treatment.[14]

We estimated the interim effect of the Georgian hepatitis C elimination programme using HCV transmission modelling with empirical treatment data and evaluated whether treatment needs scaling up to achieve the elimination target.

Methods

Model description

We developed a compartmental model of HCV transmission related to injection drug use and in the general population (iatrogenic and other risk factors) incorporating the changing demographics of PWID in Georgia (appendix pp 2–6). The model assumes susceptible (ie, uninfected) individuals can become infected, with some spontaneously clearing their infection and the remainder developing life-long chronic infection unless treated. Successful treatment leads to a sustained virologic response (ie, effective cure), which results in individuals becoming susceptible to re-infection. The model is stratified by HCV infection status (figure 1A), gender, age (figure 1C), liver disease progression (figure 1B), and injection drug use status (ie, PWID, people who have never injected drugs [non-PWID], and people who used to inject drugs; figure 1C).

See Online for appendix

Individuals enter the model at birth as susceptible non-PWID and transition through age categories, with some starting injection drug use at age-specific and gender-specific rates to match self-reported ages of initiation of injection drug use and proportion of female PWID (appendix p 4). Vertical HCV transmission is not included because few young women are infected (1%). Mortality of PWID is increased, compared with the general population, because of drug-related causes and this population ceases injecting at age-specific rates.

Susceptible individuals become infected at a rate proportional to Georgia's chronic hepatitis C prevalence, with a general transmission rate that applies to the whole population and an additional injection drug use-related transmission rate. Both transmission rates vary over time to account for changes in risk and harm-reduction intervention coverage. The model also allows for assortative mixing between younger (<30 years) and older (≥30 years) PWID.

Individuals with chronic infection progress through stages of liver disease (figure 1B). Individuals with decompensated cirrhosis and hepatocellular carcinoma have a heightened liver-related mortality. Treatment rates (ie, the number of individuals that initiate treatment per month) vary over time and by liver disease stage to match data from the elimination programme. Sustained virologic response halts disease progression for mild or moderate liver disease, whereas it continues at a decreased rate for more progressed

disease.[15] Individuals with hepatocellular carcinoma are not treated.

Model parameterisation and calibration

The model was parameterised and calibrated to the current HCV epidemic in Georgia, as described herein. We simulated a stable population approximating current demographic trends, within which we initiated injection drug use and HCV transmission in 1960. This time threshold was selected because individuals infected with HCV before this time are unlikely to be alive now and it enabled modelled HCV prevalences to reach equilibrium before changes in injection drug use were introduced. We modelled changes in injection drug use and associated HCV over time because evidence suggests it has shaped the Georgian HCV epidemic.[11]

Calibration and validation data

The model was calibrated to data on the prevalence of chronic hepatitis C from the 2015 national prevalence survey[8] and seven biobehavioral surveys of PWID done during 1998–2015 (table 1; appendix pp 11).[17,18,20–23] The model was also calibrated to an observed ageing of PWID between 1998 and 2015, thought to be due to reductions in initiation of injection drug use (appendix p 14). Model projections were validated against empirical unpublished data for HCV incidence among PWID in 1997–2001 (appendix pp 7, 8), chronic hepatitis C prevalence data for PWID from five surveys (2001–12), and age-specific chronic hepatitis C prevalence data from the 2015 national prevalence survey not used for calibration.[8,17,18,20–23]

Model parameterisation

Disease progression and HCV-related and injection drug use-related mortality were obtained from published literature,[15,24–26] whereas gender-specific and age-specific mortality were derived from life tables for Georgia[27] (table 2; appendix pp 9–11). PWID recruitment and cessation parameters were estimated by fitting the model to the proportion of PWID that were aged 18–29 years and 30–49 years in 1998 and 2015, the estimated number of PWID in 2014, and their gender distribution (table 1; appendix p 11). The number of PWID in Georgia is thought to have increased dramatically after the fall of the Soviet Union, as suggested by an eight-fold increase in police records for people who used drugs over 1990–2004.[10,11] However, no PWID population size estimates exist over this time period,[10] so we assumed a transient peak in the initiation of injection drug use, allowing uncertainty in its timing and magnitude (table 2; appendix pp 9, 10). The effect of assuming a peak in initiation of injecting was tested in our sensitivity analyses.

Needle and syringe programmes were initiated in Georgia in 2001 and opioid substitution therapy in 2005,[29] with 4·5 million syringe kits distributed and 30 330 PWID reached by needle and syringe programmes in 2016, and 4775 PWID on opioid substitution therapy in the same year.[20] The efficacy of opioid substitution therapy for reducing the risk of HCV acquisition (37–60) among

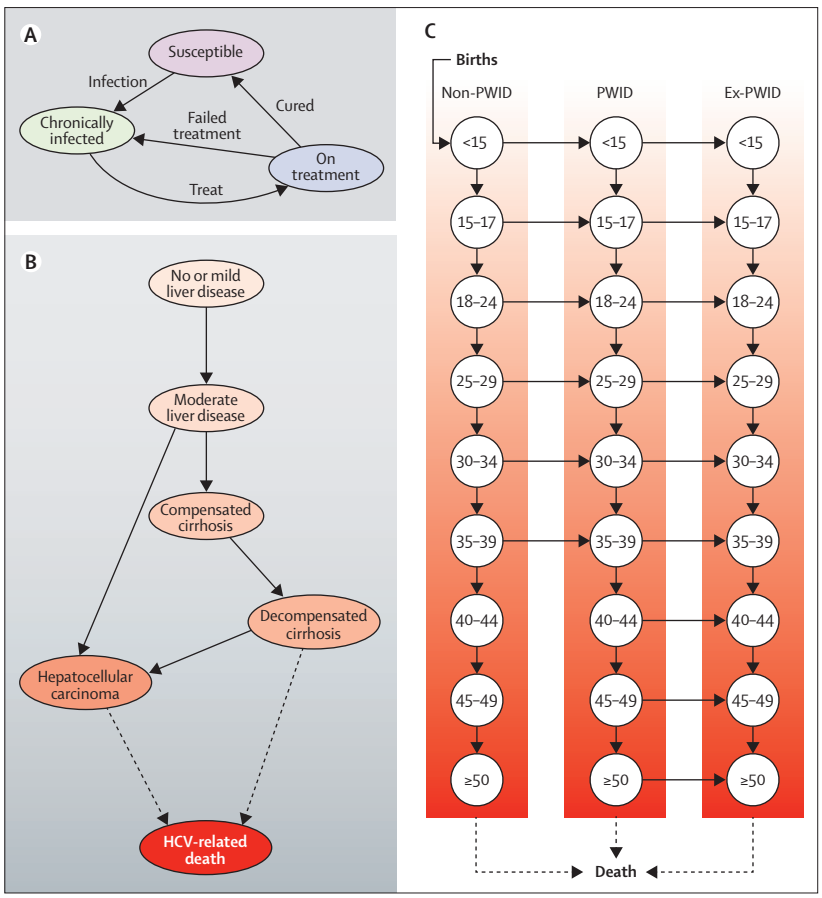

Figure 1: **Schematics of state transitions in the model**
(A) Infection compartments, (B) liver disease state compartments, (C) PWID and age compartments. Gender compartments are not shown. Dotted lines indicate transition to death. ex-PWID=people who used to inject drugs. Non-PWID=people who have never injected drugs. PWID=people who inject drugs.

	Target value	Mean and range across baseline model fits
Population of Georgia[16]	3·72 million	3·73 million (3·35–4·10)
Hepatitis C prevalence in adult population[8]	5·4%	5·4% (4·5–6·3)
Hepatitis C prevalence in adult women[8]	2·2%	2·2% (1·6–2·9)
Hepatitis C prevalence in adult men[8]	9·0%	9·7% (6·7–12·6)
Hepatitis C prevalence among PWID[17]	51·0%	50·8% (45·4–66·3)
Hepatitis C prevalence in PWID aged 18–24 years[17]	15·5%	36·1% (14·6–46·7)
Ratio of hepatitis C prevalence in PWID younger than 30 years in 1997 vs 2015[17,18]	0·5	0·81 (0·40–1·0)
PWID population size in Georgia,[19] in 2014	49 700	83 999 (23 932–190 501)
Proportion of PWID that are female[17]	2·0%	3·1% (0·1–8·0)
Proportion of PWID <30 years old,[18] in 1998	63·2%	62·4% (51·5–72·6)
Proportion of PWID <30 years old[17]	19·4%	34·6% (20·7–46·0)

Data refer to 2015 unless otherwise specified. References indicate where target values were obtained from. A full list of summary statistics is available in the appendix (p 11). Adults are defined as individuals aged 18 years or older. PWID=people who inject drugs.

Table 1: **Key summary statistics used for calibrating the hepatitis C virus transmission model for Georgia**

PWID was obtained from a Cochrane review.[28] Because of uncertainty in the efficacy of needle and syringe programmes and associated behavioural changes, we fitted the population-level effectiveness of needle and syringe programmes among PWID to capture an observed halving in HCV prevalence among young PWID (<30 years) over 1998–2006 (table 2; appendix p 15).

The general population HCV transmission rate was also allowed to reduce over 1994–2000 to account for reductions in medical risks coinciding with restructuring of the health system and the introduction of new regulations including blood donor screening from 1997.[13,14]

	Prior range*	Posterior median (IQR)
Average duration of injecting (years) among PWID aged <29 years	5–50	17·3 (10·9–29·8)
Average duration of injecting (years) among PWID aged 30–49 years	5–50	38·1 (30·6–44·3)
Average duration of injecting (years) among PWID aged ≥50 years	5–50	29·5 (18·6–38·4)
Standardised mortality ratio for PWID[26]	7·2–11·3	9·0 (8·1–9·9)
Year that increase in PWID recruitment started[10,11]	1980–95	1987 (1984–90)
Duration of period of increase in PWID recruitment (years)	1–30	18·4 (13·0–22·4)
Year that decrease in general population transmission started[13,14]	1994–2000[13,14]	1997 (1995–1998)
Relative risk of HCV transmission in general population after decrease	0·01–0·50	0·22 (0·12–0·34)
Relative risk of HCV transmission on OST[28]	0·40–0·63[22]	0·52 (0·47–0·57)
Relative risk of PWID HCV transmission risk due to NSP from 2002†	0·00–1·00	0·26 (0·14–0·42)
Relative risk of PWID HCV transmission risk due to NSP from 2012	0·00–1·00	0·19 (0·10–0·29)

References indicate where prior ranges were obtained from. PWID=people who inject drugs. HCV=hepatitis C virus. OST=opioid substitution therapy. NSP=needle and syringe programmes. *All priors were uniformly distributed. †NSP have been available since 2001, with a large project for preventing HIV/AIDS beginning in 2002.[29,30]

Table 2: **Selected parameters used in HCV transmission model for Georgia**

	No, mild, or moderate liver disease	Cirrhosis or decompensated cirrhosis
May 1, 2015–Feb 29, 2016		
Total number treated	2800*	3779†
Per-protocol SVR	1395/1564 (89·2%)	2245/2960 (75·8%)
Intention to treat SVR	1395/2228 (62·6%)	2245/4346 (51·7%)
Adjusted SVR‡	1765/2201 (80·2%)	2963/4057 (73·0%)
March, 2016–February, 2019		
Total number treated	41 474§	6259¶
Per-protocol SVR	25 954/26 314 (98·6%)	4497/4665 (96·4%)
Intention-to-treat SVR	25 954/34 024 (76·3%)	4497/6738 (66·7%)
Adjusted SVR‡	30 104/33 826 (89·0%)	5573/6467 (86·2%)

From May 1, 2015, to Feb 29, 2016, patients were treated with sofosbuvir-based (with or without ribavirin) regimens and from March 1, 2016, to Feb 28, 2019, they were treated with ledipasvir-sofosbuvir combination-based regimens. SVR=sustained virological response. *68 patients with no or mild liver disease and 2732 patients with moderate liver disease. †3757 patients with cirrhosis and 22 patients with decompensated cirrhosis. ‡The adjusted SVR assumes patients that completed treatment had the per-protocol SVR rate and that 55% of patients lost to follow up during treatment were cured on the basis of studies of shorter treatment regimens[32] (appendix p 7). §21 608 patients with no or mild liver diseases and 19 866 with moderate liver disease. ¶5659 patients with cirrhosis and 601 patients with decompensated cirrhosis.

Table 3: **Total treatment numbers and SVR rates for Georgia's hepatitis C elimination programme, by level of liver disease**

Model calibration

We used a Markov Chain Monte Carlo Approximate Bayesian Computation (MCMC-ABC) approach to calibrate the model (appendix p 7).[31] The method computes a probability distribution of model parameter values (the posterior) that constrain the initial prior ranges, producing model fits that incorporate uncertainty in the model parameters and calibration data. The parameter sets identified through MCMC-ABC were then filtered to only retain those within 95% CIs of the chronic hepatitis C prevalence for all adults (4·5–6·3) and adult women (1·6–2·9) from the 2015 national prevalence survey[8] and for PWID (45·5–56·1) from the 2015 biobehavioral surveys.[17] These filtered runs were termed the baseline model fits and were used to estimate the median and 95% credible interval (CrI) or central 95% range of all model projections.

Intervention analyses

We estimated the progress that Georgia has made toward its elimination goal by modelling the effect of all direct-acting antiviral treatments given from May 1, 2015, to Feb 28, 2019. The model used monthly treatment initiation data for the elimination programme, accounting for severity of liver disease and the initial targeting of patients with cirrhosis (table 3; appendix p 12).[9] Adjusted cure rates were used, calculated separately for patients with or without cirrhosis. These cure rates assumed the per-protocol sustained virologic response rate (table 3) for the 78% of patients who completed treatment among those who initiated it, and a reduced sustained virologic response rate (55%) for the remaining individuals that did not complete treatment, based on studies of shorter treatment regimens (appendix p 7).[32]

Effect was estimated in terms of the relative decrease in incidence and prevalence from Jan 1, 2015 (with treatment given from May 1, 2015), to Feb 28, 2019, and of the deaths and infections averted compared with a counterfactual of no treatment over this period. The future benefits of these treatments were also estimated up until 2030, assuming treatment stopped after Feb 28, 2019.

We then estimated the effect of either maintaining the current treatment rate (approximately 1000 patients treated per month from Aug 1, 2017, to Feb 28, 2019) or scaling-up treatment rates to achieve the 90-95-95 treatment target set by the Georgian Government (equivalent to treating 128 250 individuals during 2015–20). Lastly, we estimated the treatment rate required from the start of the programme and from March 1, 2019, to achieve the 90% reduction in prevalence set by the Georgian elimination target. For each strategy, we also estimated the effect on incidence and the number of prevented infections and deaths by the end of 2020.

Sensitivity analysis

In our baseline intervention scenarios, we assumed that all individuals eligible for treatment were equally

likely to be treated from March 1, 2019. However, the degree to which PWID receive treatment and whether individuals with cirrhosis should be preferentially treated going forward is uncertain. We, therefore, did a sensitivity analysis to assess how the required treatment rate to achieve a 90% decrease in prevalence by 2020 would change if: individuals with cirrhosis are targeted (80% of infected individuals with cirrhosis are treated annually); PWID are not treated; or PWID are targeted for treatment at twice the rate of other groups.

We also did sensitivity analyses to assess how the treatment target would change if: the treatment programme achieved the upper bound (per protocol) or lower bound (intention to treat) sustained virologic response rates for all patients; existing needle and syringe programmes in Georgia had the effectiveness estimated for Europe by a recent Cochrane review (risk ratio 9–62% if on needle and syringe programmes);[28] opioid substitution therapy coverage doubled from 2016, to 9000 PWID covered in 2019; no peak in PWID recruitment occurred; or treatment scale-up was delayed for 6 months. Lastly, we used analysis of covariance to calculate the variance in the number of treatments required to reach elimination that is explained by uncertainty in each parameter, for the baseline treatment scenario.

All analyses were done with Matlab version R2016b or R version 3.5.1.

Role of the funding source

The funders of the study played no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The Bayesian MCMC-ABC routine produced 554 baseline model fits that agreed well with general population and PWID demographic and chronic hepatitis C prevalence data (appendix pp 17, 18), with considerable uncertainty in the PWID population size, reflecting the uncertainty in the data described in the Methods. Fits to summary statistics and posterior distributions of fitted parameters are shown in the appendix (pp 19, 20).

The baseline model fits project that the overall adult chronic hepatitis C prevalence and incidence have decreased since 2000, with both continuing to decline during 2015–20 in the absence of treatment by 11% (CrI 2–18; prevalence) and 14% (7–20; incidence; figure 2). These decreases imply a reduction in the number of new infections each year from 6700 (3542–11076) to 5897 (3059–9920) during 2015–20. Conversely, over the same period, HCV-related mortality is expected to increase by 14% (7–25), from 590 (285–1001) deaths in 2015, to 676 (344–1091) deaths in 2020.

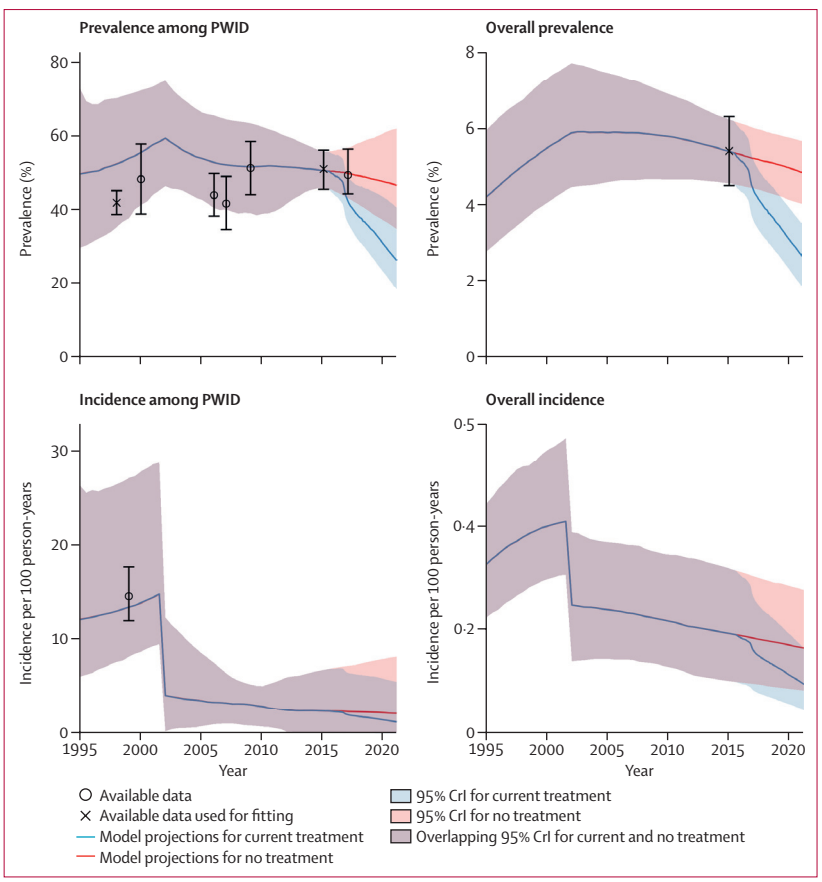

Figure 2: **Chronic hepatitis C prevalence and incidence among adult PWID and the overall adult population over time**

Data are prevalence (95% CI) or incidence (95% CI). Model projections for current treatment (red line) incorporate actual treatment numbers from May 1, 2015, to Feb 28, 2019, and assume a treatment rate of 1000 individuals initiating treatment per month continuing from March, 2019. CrI=credible interval. HCV=hepatitis C virus. PWID=people who inject drugs.

Projections suggest the PWID population peaked in 2002 (128 815, CrI 71 855–203 164) but declined to 64 420 (25 647–121 190) by 2018 (appendix p 21), with the HCV incidence among PWID decreasing by 76% (37–95) during 2000–05 (figure 2). These parallel decreases are required to ensure the model replicates the observed ageing among PWID and the decrease in HCV infection among young PWID. The HCV incidence among PWID decreased further, without treatment, from 2·4 new cases (0·19–6·8) per 100 person-years in 2015, to 2·2 new cases (0·15–8·0) in 2020 (figure 2).

Our model projects that the 54 313 treatments delivered between May 1, 2015, and Feb 28, 2019, have decreased the national prevalence of adult chronic hepatitis C by 37% (CrI 30–44), with incidence decreasing similarly (37%, 29–44; figure 3). This decrease prevented 252 (134–389) HCV-related deaths (mortality decrease by 14%, 3–30) and 3516 (1842–6250) new HCV infections by Feb 28, 2019, increasing to 3181 (1992–4393) the number of HCV-related deaths and to 20 907 (10 335–37 585) the

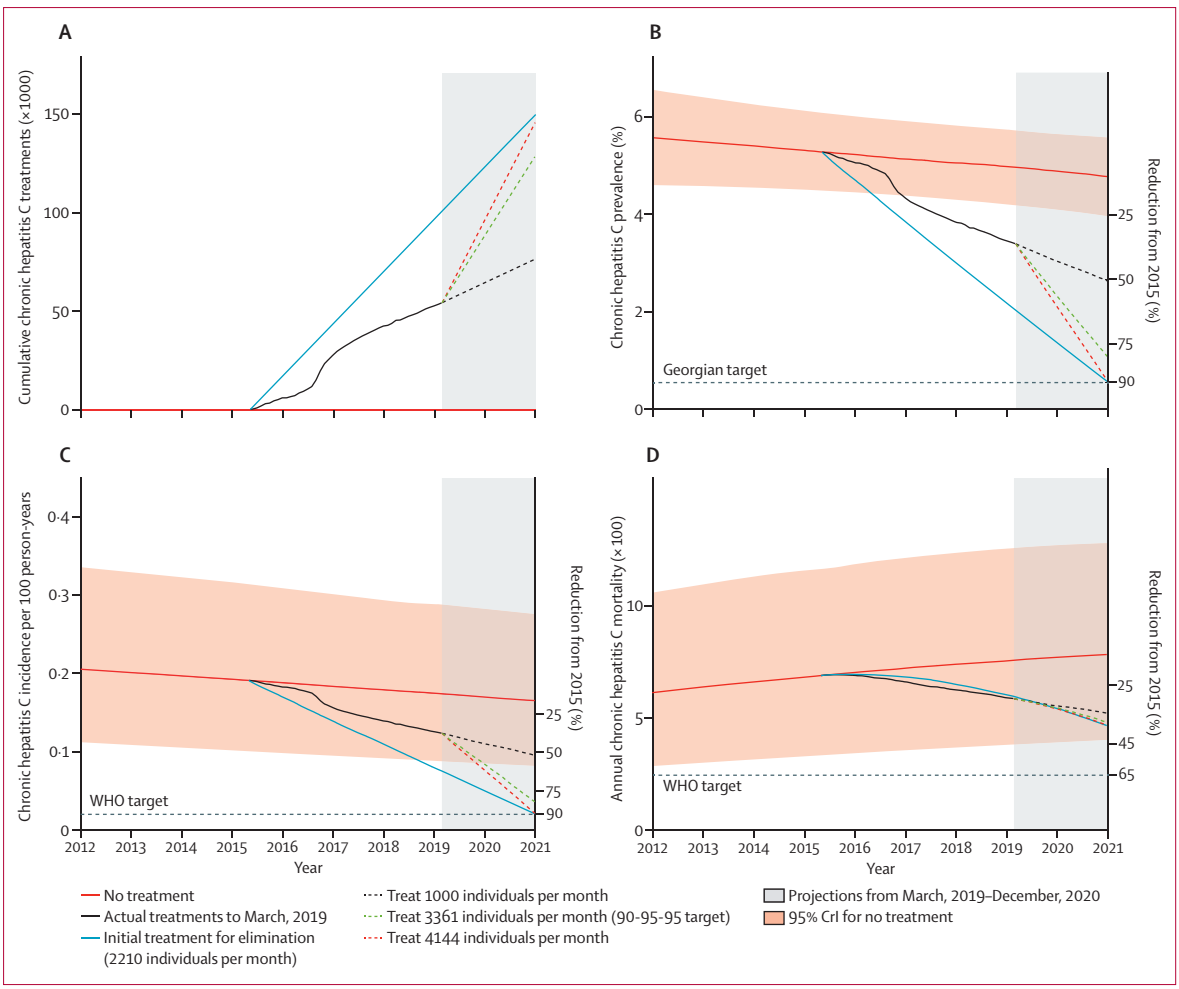

Figure 3: **Model projected interim effect at the end of February, 2019, and future effect of different treatment scenarios at the end of 2020**
(A) Cumulative chronic hepatitis C treatments, (B) adult chronic hepatitis C prevalence, (C) adult hepatitis C incidence, and (D) annual hepatitis C mortality over time. x-axis tick marks indicate the beginning of each labelled year. CrI=credible interval.

number of HCV infections averted if benefits are tracked to 2030.

Assuming all eligible individuals have equal access to treatment, continuing current treatment rates (1000 individuals initiating treatment per month) will halve chronic hepatitis C prevalence (decrease by 51%, CrI 42–61, to 2·7%, 1·9–3·5) and incidence (decrease by 51%, 40–62, to 0·097, 0·046–0·16) by 2020 (figures 3, 4), reaching a median 90% reduction in 2026, and mortality reaching a 65% reduction in 2028 (appendix p 25).

To reach Georgia's 90-95-95 treatment target by 2020, treatment rate needs to increase to 3361 individuals initiating treatment per month from March 1, 2019. This scale-up would achieve an 80% (CrI 68–96) reduction in prevalence and an 80% (66–96) reduction in incidence of chronic hepatitis C by 2020 (figure 4), a median reduction of 90% in 2021.

To reach a 90% reduction in prevalence by 2020, a monthly treatment rate of 2210 (CrI 1799–4000) individuals starting treatment per month would have been required over 2015–20. However, with the achieved treatment rates to Feb 28, 2019, treatment now needs to scale-up to a median of 4144 (2963–5322) individuals starting treatment per month from March 1, 2019, to reach the 90% reduction in prevalence by 2020. This scale-up would decrease HCV incidence by 90% (88–90) and chronic hepatitis C related mortality by 31% (CrI 18–46) by 2020, with mortality reaching a 65% reduction by 2025. Variability in the number of treatments required for achieving the 90% reduction in prevalence by 2020 is mainly due to uncertainty in the annual birth rate (35·9% of variation; appendix p 13) and parameters related to the transient peak in injection drug use initiation (49·0% of variation).

If, instead of equal access to treatment, individuals with cirrhosis are preferentially targeted from March 1, 2019 (80% of cirrhosis patients treated each year), then the same treatment rate (4144, CrI 2963–5323, individuals starting treatment per month; figure 5) would be needed to achieve a 90% reduction in prevalence by 2020 and the

same decrease in mortality would occur (31% decrease, 18–46). If PWID are not treated from March 1, 2019, then a 90% decrease in prevalence will not be possible because current PWID make up a high proportion of prevalent infections (13–37%, in 2015). However, it makes little difference whether PWID are treated at a higher rate or equally to the rest of the population, with both scenarios requiring the same treatment rate to achieve a 90% reduction in prevalence (figure 5; appendix pp 22, 23).

The baseline projections assume an adjusted sustained virologic response rate (table 1) and a substantial effect of needle and syringe programmes. If, instead, the upper-bound, per-protocol, sustained virologic response rate is assumed, the monthly treatment rate from March 1, 2019, reduces to 3579 (CrI 2485–4650) individuals initiating treatment per month, whereas it increases to 5167 (3796–6519) individuals initiating treatment per month if the intention-to-treat, sustained virologic response rate is used (it assumes that only those not attending the sustained virologic response visit are not cured; figure 5). The necessary treatment rate only changes marginally if a reduced efficacy of needle and syringe programmes[28] is used (4114, 2938–5734, individuals initiating treatment per month) or if opioid substitution therapy coverage is doubled (4141, 2952–5316). If no peak in PWID recruitment is included, then the required treatment rate increases slightly to 4443 (2941–6223) individuals initiating treatment per month, but the model no longer fits the calibration data well (appendix p 24). Lastly, if treatment scale-up is delayed by 6 months to Sept 1, 2019, the required monthly treatment rate increases to 5271 (3796–6519) individuals initiating treatment per month.

Discussion

Georgia has implemented an ambitious hepatitis C elimination programme which aims to reduce the prevalence of hepatitis C by 90% by 2020. Hepatitis C treatment has been scaled-up considerably since 2015, with more than 54 000 HCV-infected individuals treated from an estimated 150 000 infected individuals. Our model projections suggest this programme has reduced hepatitis C prevalence and incidence by 37%, since 2015, and will halve prevalence and incidence by 2020. However, the current treatment rate (approximately 1000 individuals initiating treatment per month) needs to be quadrupled to achieve the target of reducing prevalence by 90% by 2020. Strategies also need to maintain high rates of treatment completion, because decreased sustained virologic response rates will further increase the treatment rate required to reach the elimination target. In addition, PWID must be treated. Although PWID can be difficult to reach and face structural and social barriers to engagement in the elimination programme,[33] ongoing efforts within the programme to decentralise care to harm-reduction centres and to follow up patients previously lost to follow-up are likely to increase treatment among PWID.[14]

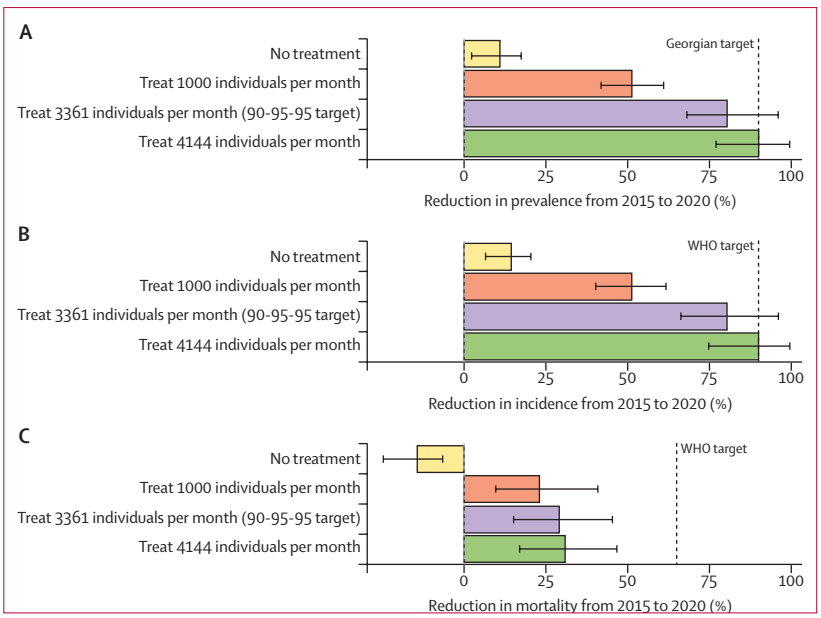

Figure 4: **Percent reduction in chronic hepatitis C prevalence (A), incidence (B), and mortality (C) from 2015, to the end of 2020, under different treatment strategies initiating in March 1, 2019**
Data are median (credible interval). The no treatment (yellow) scenario (from 2015) is also shown, otherwise scenarios assume achieved treatment rates until February, 2019, followed by continuing treatment at indicated rate from March, 2019.

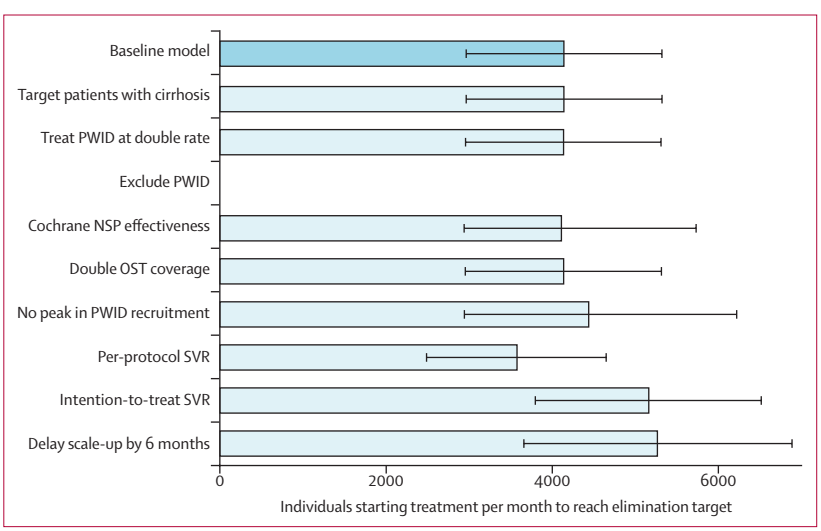

Figure 5: **Sensitivity analysis of treatment rate needed under alternative model scenarios in comparison with baseline model to reach a 90% reduction in chronic hepatitis C prevalence by end of 2020**
Data are median (credible interval). Treatment rates are for March, 2019, onwards except for the scenario, delay scale-up by 6 months, in which the treatment rate continues at 1000 individuals starting treatment per month until September, 2019, and then is scaled up. In scenario, exclude PWID, elimination is not possible at any level of treatment scale-up. NSP=needle and syringe programme. OST=opioid substitution therapy. PWID=people who inject drugs. SVR=sustained viral response.

In addition to Georgia's own elimination goals, WHO has set a global target to reduce HCV-related mortality by 65%. Even if hepatitis C treatment in Georgia is scaled up to reach the target of 90% prevalence reduction, it will still not meet the WHO mortality target by 2020. This result is caused by extensive liver damage among

currently infected individuals (18% of those who initiated treatment had cirrhosis [unpublished data]), which limits the short-term mortality benefits of treatment. Nevertheless, Georgia is still on track to reach the WHO elimination target for mortality (and incidence) by 2030, confirming previous modelling projections.[34]

Importantly, our modelling suggests the prevalence and incidence of hepatitis C in Georgia were already in decline before the hepatitis C elimination programme began in 2015 (figure 2). The modelled decline was largely due to improvements in harm-reduction measures paired with a diminishing PWID population, which reduces the contribution of injection drug use to overall transmission. Because the epidemic is in decline, it is easier to achieve the elimination target, highlighting the important role that prevention interventions for PWID can have. In the general population, the risk of iatrogenic HCV transmission still persists. Developing infection control measures to reduce these risks is a key part of the elimination programme.[35]

Case-finding and linkage-to-care initiatives will be essential for reaching Georgia's elimination targets. These interventions might be difficult among PWID in particular, and although the contribution of PWID to the hepatitis C epidemic has declined, they still represent an important component of the chronic hepatitis C burden, so testing and treatment must be accessible to them. Increasing linkage to HCV treatment, in particular for PWID through harm-reduction interventions, is a goal of the elimination programme.[14] HCV treatment at harm-reduction sites is being piloted,[36] and HCV testing at these sites has increased by five times since the start of the elimination programme.[36] In addition, a pilot programme in Tbilisi showed the feasibility of achieving high cure rates among PWID.[37] Despite these positive signs, there are still barriers for PWID linking to care,[33] and there is still uncertainty on the number of PWID being treated, because of their non-disclosure of national identity numbers required for linking screening and treatment data.[36] This limits the evaluation of progress towards elimination.

This is the first study to evaluate the interim effect and treatment targets of an ongoing national-level hepatitis C elimination programme by using detailed modelling with in-depth data from the programme.[38–40] A second serosurvey is planned for early 2020s to evaluate if the target effect has been achieved, the timing of which will be guided by modelling.

The main limitations of our analysis relate to small amount of data on how HCV transmission has changed over time, in the general population and because of injection drug use. Our model suggests a declining epidemic in terms of both prevalence and incidence, which fits available data (from the 2015 national prevalence survey) on reductions in chronic hepatitis C prevalence among new PWID over time and young male adults having a low chronic hepatitis C prevalence in 2015. However, the only available comparison of HCV prevalence in the general population (from a survey done in Tbilisi in 2001–02),[41] suggests a stable or increasing prevalence of seropositivity (6·7%, 95% CI 5·7–7·9, in 2001–02 compared with 9·4%, 6·9–12·6, in Tbilisi according to the 2015 national survey). The Tbilisi survey was not included in our fitting process because of uncertainty in its comparability with the 2015 national survey, resulting from the clinic-based sampling methods used. If the epidemic is increasing as suggested by these data, then our projections (data not shown) suggest the treatment requirements for elimination will be higher than what we estimated (approximately 5000 individuals initiating treatment per month). Additionally, both the 2001–02 study and 2015 national survey were household-based surveys and, therefore, did not include prisoners or homeless people, potentially leading to an underestimation of the burden of chronic hepatitis C. It is important that further work evaluate the importance of this issue.

HCV-related mortality was not consistently recorded in Georgia before 2015, and although this recording is being improved as part of the elimination programme, complete data were not yet available for this analysis.[14] New data will improve our model calibration. Furthermore, our model assumed a stable population for Georgia, despite projections suggesting it might decrease (it decreased by 5% during 2010–15).[42] This decrease should not have an important effect on our projections because the changes are quite small.

Data had limitations on many other parameters, including being reliant on self-reported data about PWID demographics. To account for these limitations, we allowed for uncertainty in model parameters while remaining consistent with available data. In addition, we did sensitivity analyses that made alternative assumptions about the effectiveness of needle and syringe programmes or the degree to which PWID were treated; and although these changes did not affect our elimination projections, except if PWID were not treated at all, additional studies could still help reduce these uncertainties.

One of the main limitations for translating our results into recommendations for the Georgian HCV elimination programme is that the model does not incorporate case-finding, so it cannot identify what screening strategies are needed to achieve required rates of chronic hepatitis C treatment. In the early stages of the programme, many individuals with chronic hepatitis C were already aware of their infection and came forward for treatment.[9] General population and targeted screening strategies are also underway, with 106 057 positive antibody screening tests done in health-care settings, harm-reduction services, designated public screening centres, and in prisons as of April 2019.[34] Other screening and linkage-to-care strategies are also being piloted or scaled up to further increase the identification and treatment of undiagnosed infections, including treatment within

harm-reduction services, door-to-door and workplace-based testing, simplification of the treatment pathway to encourage retention, and reducing the co-payment for patients.[14] It is important that these and other possible strategies are evaluated to determine the most efficient way to achieve elimination,[43] which could help other countries work toward their own elimination goals.

Georgia has committed to eliminating hepatitis C as a public health threat, with the ongoing national programme achieving high levels of treatment uptake. Data from the programme and our modelling indicate an urgent need to improve case-finding, referral, and treatment interventions for reaching Georgia's targets of hepatitis C elimination by 2020. Decision makers in Georgia will need to evaluate what is feasible for achieving hepatitis C elimination. This assessment will require considering what is currently limiting treatment numbers and how these issues can be remedied. Importantly, the treatments already achieved have had major effects on HCV transmission in Georgia, and even if the elimination targets are not feasible by 2020, Georgia will still be one of the first countries to eliminate HCV ahead of the WHO target. Lessons learnt from Georgia are transferable to other countries that are scaling up interventions to prevent hepatitis C.[35] In particular, our study indicates the importance of identifying the characteristics and dynamics of an epidemic to make reliable impact projections.

Contributors

JGW and PV led the study. JGW developed the model on the basis of preliminary models developed by HF, AGL, NKM, and PV, did all modelling analyses, wrote the first draft of the paper with guidance from PV, and analysed data from behavioural surveys of people who inject drugs in Georgia. The concept for the study was developed with TK, MH, NKM, JM, FA, and MN, and PV. SS, LH, and LG analysed data from the Georgian hepatitis C virus programme. Data were contributed by MA, AA, DB, MB, IC, IKh, IKi, MHK, DO, LS, KS, TT, and MZ, and gathered under the supervision of DS, AG, and VK. All authors contributed to the interpretation of results and writing the report and approved the final version.

Declaration of interests

HF reports an honorarium from MSD. MH reports personal fees from Gilead, Abbvie, and MSD. NKM reports unrestricted research grants and honoraria from Gilead and Merck. PV has received unrestricted research grants from Gilead and honoraria from Gilead and AbbVie. All other authors declare no competing interests.

Data sharing

Model code will be made available on request to the corresponding author.

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Treatment outcomes of patients with chronic hepatitis C receiving sofosbuvir-based combination therapy within national hepatitis C elimination program in the country of Georgia

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Abstract

Background: Georgia has one of the highest HCV prevalence in the world and launched the world's first national HCV elimination programs in 2015. Georgia set the ambitious target of diagnosing 90% of people living with HCV, treating 95% of those diagnosed and curing 95% of treated patients by 2020. We report outcomes of Sofosbuvir (SOF) based treatment regimens in patients with chronic HCV infection in Georgia.

Methods: Patients with cirrhosis, advanced liver fibrosis and severe extrahepatic manifestations were enrolled in the treatment program. Initial treatment consisted of SOF plus ribavirin (RBV) with or without pegylated interferon (INF). Sustained virologic response (SVR) was defined as undetectable HCV RNA at least 12 weeks after the end of treatment. SVR were calculated using both per-protocol and modified intent-to-treat (mITT) analysis. Results for patients who completed treatment through 31 October 2018 were analyzed.

Results: Of the 7342 patients who initiated treatment with SOF-based regimens, 5079 patients were tested for SVR. Total SVR rate was 82.1% in per-protocol analysis and 74.5% in mITT analysis. The lowest response rate was observed among genotype 1 patients (69.5%), intermediate response rate was achieved in genotype 2 patients (81.4%), while the highest response rate was among genotype 3 patients (91.8%). Overall, SOF/RBV regimens achieved lower response rates than IFN/SOF/RBV regimen (72.1% vs 91.3%, $P < 0.0001$).
In multivariate analysis being infected with HCV genotype 2 (RR =1.10, CI [1.05–1.15]) and genotype 3 (RR = 1.14, CI [1.11–1.18]) were associated with higher SVR. Patients with cirrhosis (RR = 0.95, CI [0.93–0.98]), receiving treatment regimens of SOF/RBV 12 weeks, SOF/RBV 20 weeks, SOF/RBV 24 weeks and SOF/RBV 48 weeks (RR = 0.85, CI [0.81–0.91]; RR = 0.86, CI [0.82–0.92]; RR = 0.88, CI [0.85–0.91] and RR = 0.92, CI [0.87–0.98], respectively) were less likely to achieve SVR.

Conclusions: Georgia's real world experience resulted in high overall response rates given that most patients had severe liver damage. Our results provide clear evidence that SOF plus IFN and RBV for 12 weeks can be considered a treatment option for eligible patients with all three HCV genotypes. With introduction of next generation DAAs, significantly improved response rates are expected, paving the way for Georgia to achieve HCV elimination goals.

Keywords: HCV, Elimination, DAAs, SVR, Georgia

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Background

Globally, an estimated 71 million people are chronically infected with hepatitis C virus (HCV), and 400,000 die annually from hepatitis C-related liver diseases [1]. Management of HCV infection has been revolutionized after the availability of direct acting antivirals (DAAs), and Sofosbuvir (SOF) was the first widely introduced DAA [2, 3]. Clinical trials have demonstrated high efficacy of SOF-based regimens in patients infected with genotypes 1–6 [4–8].

Georgia has one of the highest HCV prevalence rates among general population in the world [9], and launched the world's first national HCV elimination program in 2015 [10]. The elimination program has adopted a comprehensive strategy that addresses both prevention and treatment of HCV infection. A key component of the program is the provision of DAAs free of charge to all Georgian citizens; this was made possible through an agreement with Gilead Sciences to donate DAAs. Georgia has set itself the ambitious target of diagnosing 90% (135,000 persons) of people living with HCV, treating 95% (128,000 persons) of those diagnosed and curing 95% (121000) of treated patients by 2020 [9]. We report outcomes of SOF-based treatment regimens in patients with chronic HCV infection in the country of Georgia.

Methods

All Georgians aged 18 years or older that are infected with HCV are eligible for the free of charge treatment program. The hepatitis C elimination program was launched on 28 April 2015. All patients treated from launch through 31 October 2018 are included in the analysis. Treatment-naive and experienced patients with cirrhosis (including decompensated cirrhosis), advanced liver fibrosis, severe extrahepatic manifestations, HCV re-infection after liver transplantation and HIV-coinfection were prioritized for enrollment in the treatment program. Initially, DAA treatment was exclusively SOF based and included ribavirin (RBV) with or without pegylated interferon, depending on the HCV genotype, per national guidelines. From February 2016, more effective, interferon free DAA combination - sofosbuvir and ledipasvir (SOF/LDV) was introduced, and treatment regimens were revised. Beginning in June 2016, treatment criteria were relaxed allowing enrollment of all HCV infected persons regardless of level of liver fibrosis, to be treated. Treatment guidelines were established by a committee composed of treatment experts from Georgia in consultation with international experts. Based on eligibility of interferon therapy all HCV genotype 1 and 3 patients received SOF plus, Pegylated interferon (IFN) and RBV for 12 weeks or SOF plus RBV for 24 weeks. HCV genotype 2 treatment naïve patients without cirrhosis were treated with the 12-week combination of SOF plus RBV, while cirrhotic patients and those with prior treatment failure received the 12-week regimen of SOF plus IFN and RBV or the 20-week regimen of SOF plus RBV based on eligibility of interferon. Patients with decompensated cirrhosis received SOF plus RBV for 48 weeks.

Treatment was initially limited to four sites in Tbilisi, and later expanded with sites from other cities within Georgia; by October 2018, 31 sites were providing HCV treatment in the country. The HCV treatment program providers also participated in Project ECHO (Extension for Community Healthcare Outcomes).

A national HCV treatment database was established, which collected standard data for each patient enrolled in treatment program. Each treatment site was responsible for data entry for each enrolled patient. Data were de-identified and sociodemographic, clinical and laboratory data were extracted from national HCV treatment database. Characteristics measured included: age, gender, HCV RNA, FIB-4 test score, METAVIR score, HBsAg, treatment regimen, HCV genotype and city where treatment was provided. Sustained virologic response (SVR) was defined as undetectable HCV RNA at least 12 weeks after the end of treatment. The presence of cirrhosis was confirmed by vibration-controlled transient elastography or acoustic radiation force impulse elastography (ARFI) compatible with stage F4 fibrosis (≥14.5 kpa)_by METAVIR. Decompensated cirrhosis was defined as the presence of current or past ascites, hepatic encephalopathy and variceal haemorrhage etc. SVRs were calculated using both per-protocol and modified intent-to-treat (mITT) analysis. Per-protocol approach included only those with complete SVR data, while in mITT analysis persons discontinuing treatment were also included. Persons who died or had no SVR test > 24 weeks after completing treatment were excluded from analysis.

Statistical analysis

All analyses were performed with SAS version 9.3 software (SAS Institute, Inc., Cary, NC, USA). Variables were categorized as follows: age category: 18–44, 45–60, and > 60; HCV RNA category: < 800,000 IU/mL vs. ≥800,000 IU/mL; FIB-4 test: <1.45, 1.45–3.25 and > 3.25; METAVIR score: <F4 and F4. We used the chi-square or Fisher's exact to compare differences in categorical variables with SVR. We performed a multivariate logistic-regression analysis involving baseline demographic, clinical and laboratory characteristics to identify independent predictors of SVR. A p-value < 0.05 was considered significant. The final model included

variables associated ($p < 0.05$) with SVR in the bivariate analysis. The results are presented with a Risk ratio (RR) and 95% Confidence intervals (CIs). Results for patients who completed treatment and tested for SVR through 31 October 2018 were analyzed. The study was approved by the Institutional review board of the Infectious Diseases, AIDS and Clinical Immunology Research Center, Tbilisi.

Results

A total of 7342 patients with chronic HCV infection received SOF-based therapy from April 28, 2015 until October 31, 2018 and 5079 had complete SVR data.

The pretreatment demographics, clinical and laboratory characteristics of patients with complete SVR data are described in Table 1. Most patients, 2838 (55.9%) were age 45–60 years, 4381 (86.3%) were males and 2783 (57.9%) had stage F4 fibrosis (by METAVIR). Overall, 1724 (33.9%) of the patients had HCV genotype 1, followed by HCV genotype 3, 2305 (45.4%) and HCV genotype 2, 1047 (20.6%). Only 3 patients were infected with HCV genotype 4. Majority of patients were treated with IFN/SOF/RBV for 12 weeks (52.1%), followed by SOF/RBV for 24 weeks (27.9%), SOF/RBV for 20 weeks (7.8%), SOF/RBV for 12 weeks (7.2%), and SOF/RBV for 48 weeks (5.0%).

A total of 521 persons discontinued treatment, with the most common causes for not completing treatment being death (48.8%; $n = 254$), self-discontinuation (19.6%; $n = 102$), and loss to follow up (15.9%; $n = 83$). Among those who died during treatment, the majority 299/521 (57.4%) had severe liver disease (METAVIR scores of F3 or F4).

A total of 5079 persons with complete SVR data and 521 persons who discontinued treatment, were included in treatment efficacy analysis (total 5600 persons). Total SVR rate was 82.1% (4170/5079) in per-protocol analysis and 74.5% (4170/5600) in mITT analysis.

Of those with an SVR12, the lowest response rate was observed among genotype 1 patients (1198/1724; 69.5%), intermediate response rate was achieved in genotype 2 patients (852/1047; 81.4%), while the highest response rate was among genotype 3 patients (2117/2305; 91.8%). There were only 3 patients with genotype 4 and all were cured.

Overall, SOF/RBV regimens achieved lower response rates than IFN/SOF/RBV regimen (72.1% vs 91.3%, $P < 0.0001$). This difference was seen in all genotypes (57.0% vs 80.8%, $P < 0.0001$ for genotype 1; 76.9% vs 96.3%, $P < 0.0001$ for genotype 2 and 82.5% vs 96.9%, $P < 0.0001$ for genotype 3 respectively) (Fig. 1).

Multivariate analysis (Table 2) showed that when controlling those factors which were significantly associated with SVR in bivariate analysis, being infected with HCV genotype 2 (RR =1.10, CI [1.05–1.15], $P = 0.001$) and genotype 3 (RR = 1.14, CI [1.11–1.18], $P < 0.0001$) were associated with higher SVR. Patients with cirrhosis (RR = 0.95, CI [0.93–0.98], $P < 0.0001$), receiving treatment regimens of SOF/RBV 12 weeks, SOF/RBV 20 weeks, SOF/RBV 24 weeks and SOF/RBV 48 weeks (RR = 0.85, CI [0.81–0.91], $P < 0.0001$; RR = 0.86, CI [0.82–0.92], $P < 0.0001$; RR = 0.88, CI [0.85–0.91], $P < 0.0001$ and RR = 0.92, CI [0.87–0.98], $P = 0.005$, respectively) were less likely to achieve SVR.

Discussion

This study from Georgia is one of the largest real-world cohorts examining outcomes of HCV treatment with SOF based regimens, among patients with severe liver disease. We assessed real-world efficacy of SOF plus RBV with or without IFN in these difficult-to-treat patients with chronic hepatitis C. Our study demonstrated that SOF-based regimens can result in high overall SVR rates, similar to SVR rates achieved in clinical trials [11, 12]. While newer combination DAAs are now available, SOF is now one of the most readily available DAAs worldwide, at affordable prices in many low middle income countries, and as such, these findings have relevance today. In particular, the acceptable SOF plus RBV outcomes among the most severely ill patients, regardless of genotype are highly relevant.

In our study response rates among patients with HCV genotype 2 were lower than reported in clinical trials and real-life studies which showed high efficacy of SOF plus RBV combination treatment among HCV genotype 2 patients including those with cirrhosis and/or treatment experience [8, 12–15]. Lower efficacy of treatment in genotype 2 patients may have been associated with a reported high prevalence of HCV recombinant form 2 k/1b among Georgian HCV genotype 2 patients [16]; these patients do not respond well to standard treatment for genotype 2 and regimens used for genotype 1 seem to be more effective [17]. Therefore there is a need for reassessing existing modalities for the management of HCV genotype 2 infection, especially in areas with high prevalence of HCV recombinant form 2 k/1b [18].

We observed high cure rates in HCV genotype 3 patients that are one of the most challenging subpopulations to treat [19]. IFN-based regimens were superior to SOF/RBV alone. The results of clinical trials showed that HCV genotype 3 patients achieved higher SVR12 rates with a 12 week SOF and RBV in combination with IFN that patients who were treated with SOF and RBV alone [12].

Our findings support use of a 12 week regimen of SOF plus RBV in combination with IFN as a treatment option for eligible HCV genotype 3 patients in settings, where

Table 1 Baseline characteristics of adult persons with complete SVR data treated with SOF-based regimens by HCV genotypes within the national hepatitis C elimination program, April 28, 2015 – October 31, 2018

Characteristic	TOTAL		Genotype 1		Genotype 2		Genotype 3		Genotype 4	
	n	%	n	%	n	%	n	%	n	%
Age category, n (%)										
18–45	1635	32.2	386	22.4	299	28.6	948	41.1	2	66.7
45–60	2838	55.9	944	54.8	630	60.2	1264	54.8	.	.
60+	606	11.9	394	22.9	118	11.3	93	4.0	1	33.3
Gender, n (%)										
Female	698	13.7	486	28.2	101	9.6	110	4.8	1	33.3
Male	4381	86.3	1238	71.8	946	90.4	2195	95.2	2	66.7
HCV RNA categories, n (%)										
< 800,000 IU/mL	2922	57.7	901	52.5	625	59.8	1393	60.5	3	100.0
≥ 800,000 IU/mL	2145	42.3	816	47.5	420	40.2	909	39.5	.	.
FIB-4 Test										
< 1.45	200	5.7	65	6.0	51	7.0	84	5.0	.	.
1.45–3.25	1763	50.2	491	45.0	403	55.1	868	51.5	1	50.0
> 3.25	1546	44.1	535	49.0	277	37.9	733	43.5	1	50.0
Metavir score										
< F4	2021	42.1	676	39.8	516	50.9	827	39.6	2	66.7
F4	2783	57.9	1021	60.2	497	49.1	1264	60.4	1	33.3
Liver function tests, n (%)										
ALT >2 X ULN	2585	51.0	731	42.5	466	44.6	1385	60.2	3	100.0
AST >2 X ULN	2604	51.4	783	45.6	442	42.3	1376	59.8	3	100.0
Billirubin >1.1 mg/dL	4423	87.3	1520	88.5	928	88.8	1972	85.7	3	100.0
Albumin < 35 g/L	2001	39.5	670	39.0	469	44.9	862	37.4	.	.
INR >1.49	687	13.6	260	15.1	132	12.6	295	12.8	.	.
Co-infections, n (%)										
HBsAg+	108	2.2	28	1.7	19	1.9	61	2.8	.	.
HBsAg-	4777	97.8	1666	98.3	985	98.1	2123	97.2	3	100.0
Treatment regimen, n (%)										
IFN/SOF/RBV (12 wk)	2646	52.1	905	52.5	240	22.9	1500	65.1	1	33.3
SOF/RBV (12 wk)	364	7.2	3	0.2	360	34.4	1	0	.	.
SOF/RBV (20 wk)	395	7.8	3	0.2	392	37.4	.	.	.	.
SOF/RBV (24 wk)	1418	27.9	695	40.3	7	0.7	714	31	2	66.7
SOF/RBV (48 wk)	256	5	118	6.8	48	4.6	90	3.9	.	.
City of treatment site, n (%)										
Tbilisi	3800	74.8	1294	75.1	819	78.2	1684	73.1	3	100
Kutaisi	362	7.1	148	8.6	72	6.9	142	6.2	.	.
Batumi	501	9.9	177	10.3	67	6.4	257	11.1	.	.
Zugdidi	328	6.5	90	5.2	81	7.7	157	6.8	.	.
Gori	42	0.8	6	0.3	5	0.5	31	1.3	.	.
Rustavi	40	0.8	9	0.5	3	0.3	28	1.2	.	.
Lanchkhuti	4	0.1	.	.	.	.	4	0.2	.	.
Gurjaani	2	0	.	.	.	.	2	0.1	.	.

SOF Sofosbuvir, *RBV* Ribavirin, *IFN* Interferon

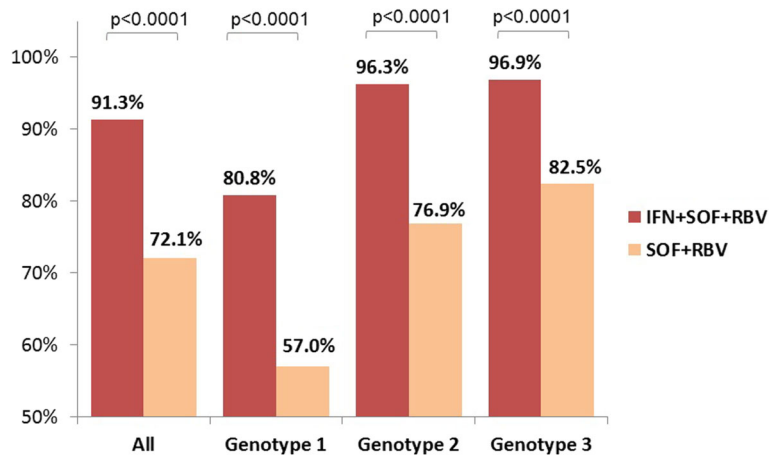

Fig. 1 SVR rates by treatment regimens and genotype ($n = 5076$)

new highly potent and well-tolerated DAAs against genotypes 2 and 3 are not available. Our results suggest the use of SOF/RBV combination for 24 weeks as an option for patients who cannot tolerate IFN.

After examining host and viral factors we found that presence of cirrhosis, and receiving IFN-free regimens were associated with lower SVR in a multivariable model. The low rates of response among cirrhotic patients is consistent with previous studies.

One strength of this study is the large number of patients as well as standardized treatment guidelines and standardized data collection. The diversity of our cohort with respect to sex, age, and genotype distribution makes our findings generalizable, reflecting reported real-world outcomes. Our study has several limitations. First, data from patients in whom prior treatment had failed, was not collected. Second, liver fibrosis was assessed by multiple noninvasive indices, each of which have limitations on accuracy [20–22]. The national treatment database, which captures information on all hepatitis C patients enrolled in the program, provides accurate treatment related information on a national level. However it does not contain detailed information on some variables, including comorbidities (diabetes mellitus, kidney failure, extrahepatic manifestations etc.) as well as nature of deaths, adverse events and reasons of self-discontinuation. Also data available in the national system has limited ability to answer questions as to why people are lost to follow-up along the continuum of care. Significant number of patients who were lost to follow-up after treatment completion is a serious challenge of the treatment program. However, in 2017 the program offered SVR assessment free of charge that would lead to reducing missing SVR data.. Despite notable progress of the Georgia HCV elimination program, challenges to Georgia achieving the national targets for HCV elimination by 2020 remain. Pangenotypic DAAs that are effective across the different genotypes of HCV introduced in late 2018 could have a substantial impact on improving access and simplifying diagnosis and treatment.

Conclusion

In conclusion, in this large cohort study, a combination of SOF and weight-based RBV with or without IFN appeared to be an effective regimen to treat chronic HCV-infected patients, especially for HCV Genotype 2 and 3 patients. SOF formed the foundation of the HCV elimination program in Georgia. Cure rates in patients without cirrhosis were high, which are comparable with those reported in clinical trials. However, consistent with previous studies, the presence of liver cirrhosis were associated with lower SVR12 rates. Our results provide clear evidence that SOF plus IFN and RBV for 12 weeks can be considered a treatment option for eligible patients with all three HCV genotypes. With the introduction of next generation DAAs, replacement of IFN-based regimens by IFN-free regimens and significantly improved response rates are expected, paving the way for Georgia to achieve the goal of HCV elimination. High cure rates obtained with SOF/LDV combinations for all HCV genotypes within Georgia program highlights effectiveness of service delivery model, which is based on simplified modalities that can be successfully replicated in non-specialty settings, which is important in light of ongoing decentralization process. Strong governmental commitment coupled with effective local and international partnerships provide a basis for turning the ambitious goal of elimination into reality.

Table 2 Treatment outcomes and associated factors among adult persons with complete SVR data receiving SOF-based regimens within the national hepatitis C elimination program, April 28, 2015 – October 31, 2018

	Total N	Achieved SVR		Bivariate analysis			Multivariate analysis		
		N	%	RR	95% CI	*p* value	RR	95% CI	*p* value
Age category									
18–45	1635	1440	88.07	1					
46–60	2838	2259	79.60	0.90	0.88–0.93	<0.0001			
60+	606	471	77.72	0.88	0.84–0.92	<0.0001			
Gender									
Female	698	560	80.23	1					
Male	4381	3610	82.40	1.03	0.99–1.07	0.18			
HCV Genotype									
1	1724	1198	69.49	1			1		
2	1047	852	81.38	1.17	1.12–1.22	<0.0001	1.10	1.05–1.15	<0.0001
3	2305	2117	91.84	1.32	1.28–1.37	<0.0001	1.14	1.11–1.18	<0.0001
4	3	3	100.00	–	–	–	–	–	–
HCV RNA categories, n (%)									
< 800,000 IU/mL	2922	2408	82.41	1					
≥ 800,000 IU/mL	2145	1754	81.77	0.99	0.97–1.02	0.56			
FIB-4 Tests									
< 1.45	200	177	88.50	1			1		
1.45–3.25	1763	1573	89.22	1.01	0.96–1.06	0.76	1.00	0.93–1.07	0.95
> 3.25	1546	1166	75.42	0.85	0.80–0.90	<0.0001	0.95	0.87–1.02	0.17
Metavir score									
< F4	2021	1761	87.14	1			1		
F4	2783	2161	77.65	0.89	0.87–0.97	<0.0001	0.95	0.93–0.98	0.0001
Co-infections									
HBsAg-	4777	3897	81.58	1					
HBsAg+	108	89	82.41	1.01	0.92–1.10	0.82			
Treatment regimen									
IFN/SOF/RBV (12 wk)	2646	2416	91.31	1			1		
SOF/RBV (12 wk)	364	276	75.82	0.83	0.78–0.88	<0.0001	0.85	0.81–0.91	<0.0001
SOF/RBV (20 wk)	395	302	76.46	0.84	0.79–0.89	<0.0001	0.86	0.82–0.92	<0.0001
SOF/RBV (24 wk)	1418	979	69.04	0.76	0.73–0.78	<0.0001	0.88	0.85–0.91	<0.0001
SOF/RBV (48 wk)	256	197	76.95	0.84	0.79–0.90	<0.0001	0.92	0.87–0.98	0.005
City of treatment site									
Tbilisi	3800	3127	82.29	1			1		
Kutaisi	362	272	75.14	0.91	0.86–0.97	0.004	0.96	0.92–1.01	0.10
Batumi	501	435	86.83	1.06	1.02–1.10	0.005	1.01	0.97–1.05	0.60
Zugdidi	328	258	78.66	0.96	0.90–1.01	0.13	0.96	0.92–1.00	0.07
Gori	42	40	95.24	1.16	1.08–1.24	<0.0001	1.01	0.87–1.17	0.91
Rustavi	40	32	80.00	0.97	0.83–1.14	0.72	0.95	0.80–1.13	0.55
Lanchkhuti	4	4	100.00	–	–	–	–	–	–
Gurjaani	2	2	100.00	–	–	–	–	–	–

SOF Sofosbuvir, *RBV* Ribavirin, *IFN* Interferon, *CI* Confidence interval, *RR* Risk ratio, *SVR* Sustained virologic response

Abbreviations
CI: Confidence intervals; DAAs: Direct acting antivirals; HCV: Hepatitis C virus; INF: Pegylated interferon; mITT: modified intent-to-treat; RBV: Ribavirin; RR: Risk ratio; SOF: Sofosbuvir; SVR: Sustained virologic response

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Authors' contributions
Concept and design (TT, AG, FA, NC, AA), statistical analyses (SS, NC, AA), interpretation of the data (TT, AG, MN, LS, JM, SS, LG, MB, DM, VK, ME, NC, AA, VK, FA), drafting the manuscript (TT) and critical revision of the manuscript for intellectual content (TT, AG, MN, LS, JM, SS, LG, MB, DM, VK, ME, NC, AA, VK, FA). All authors read and approve the final manuscript.

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Availability of data and materials
The data that support the findings of this study are property of Georgia's HCV elimination program. In case the data is requested, please contact scientific committee of Georgia's HCV elimination program (Secretary Dr. Tinatin Kuchuloria, email: drkuchuloria@yahoo.com).

Ethics approval and consent to participate
The study was approved by the Institutional review board of the Infectious Diseases, AIDS and Clinical Immunology Research Center, Tbilisi.

Consent for publication
Not Applicable.

Competing interests
The authors declare that they have no competing interests.

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