Asociación Colombiana de Hepatología

SCREENING FOR HEPATITIS C IN PEOPLE WHO INJECT DRUGS IN ARMENIA-COLOMBIA

A. TECHNICAL APPROACH

Problem statement and justification

Hepatitis C virus (HCV) infection causes acute and chronic liver disease and can lead to cirrhosis, liver failure, or hepatocellular carcinoma. Globally, an estimated 58 million people are chronically infected with hepatitis C virus, with around 1.5 million new infections per year (1). The World Health Organization (WHO) estimated that in 2019, approximately 290,000 people died from hepatitis C, mainly from cirrhosis and hepatocellular carcinoma (primary liver cancer) (1).

Despite undeniable advances in the treatment of hepatitis C infection and the WHO strategy to eliminate hepatitis C by 2030 (2), this infection continues to be a major public health problem globally, for which there is no vaccine, and access to diagnosis and treatment is low, however, antivirals can cure more than 95% of cases of this infection (1). Acute HCV infection is usually asymptomatic, and it is estimated that between 15% and 45% of infected people clear the virus spontaneously without any treatment. The other cases (55% to 85% of people) develop chronic HCV infection, and among these, there is a high (15% to 30%) estimated risk of liver cirrhosis in the absence of therapeutic intervention (1). Due to the largely asymptomatic nature of HCV infection, many HCV-positive individuals are unaware of their HIV status. Others have been diagnosed but cannot get treatment. Lack of rapid and reliable diagnosis and high cost and limited access to treatment are barriers to disease control and elimination (3).

People who inject drugs (PWID) are at increased risk for HCV. Several studies have reported high HCV prevalence rates, especially among PWID (4–6). Worldwide, there are around 11 million PWIDs (7). Approximately 39.4% have viremic HCV infection (8). It is estimated that between 23% and 39% of new HCV infections occur among PWID, and one in three HCV deaths are attributable to injection drug use (9). In some regions, such as Eastern Europe and Central Asia, HCV prevalence rates are particularly high. Additionally, there are approximately 2.3 million coinfections between HIV and HCV worldwide, of which more than half (1.3 million) occur in PWID (7). The coexistence of these two health conditions leads to

accelerate the progression of liver disease and complicate treatment for HIV. The global prevalence of HCV in 2019 among PWID was 50.2%, which is equivalent to 5.6 million people who inject drugs and live with hepatitis C. Four countries (Brazil, China, Russia, and the United States) have most people with recent injection drug use living with HCV. Together, these countries represent more than half (51%) of all people with recent injection drug use living with HCV worldwide (10).

PWID are usually exposed to a higher risk of various infectious diseases, mainly due to their drug consumption behaviors and habits, in addition to the risks and harms associated with the respective routes of self-administration (11,12). Needle sharing among intravenous drug users is a major risk factor for HCV infection (13). The behavior of illicit drug users may increase the risk of viral infections through choice of drug, frequency of use, and sharing of paraphernalia, as well as unprotected sexual activity, multiple sexual partners, and prostitution (25). Several studies indicate that drug users have played a key role in the global spread of HCV (5.14).

In Colombia, the prevalence of hepatitis C among PWID has been measured locally in some cities of the country. The first measurement was carried out with the 2002 study in Bogotá. Later, in 2014 it was held in Bogotá, Pereira, Medellín, Cucuta and Armenia. The figures at that time already indicated a clear impact by this virus in this population. In Bogotá it went from 1.7% in 2002 to 6.7% in 2014. The cities with the lowest prevalence in 2014 were Cucuta with 21.4% and Armenia with 30.9%, while in Medellín the estimated prevalence It was 35.6% and in Pereira it was 44.4% (15). For 2021, the prevalence of hepatitis C was measured in Bogotá, Medellín, Santiago de Cali, the metropolitan area of Pereira-Dosquebradas, Medellín, Cucuta and Armenia (15,16). The results of prevalence of antibodies against hepatitis C were as follows: Cali with 80.2%, is the city with the highest reactivity, followed by Pereira and Dosquebradas with 71.4%, Armenia with 69.6% and Cucuta with 62.8% (15,16). In Medellín, antibody reactivity was found in 32.7% of PWIDs and in Bogotá in 10.7% of them. The comparison of the findings between this study and the CES University study in 2014 shows a slight reduction in the hepatitis C figures in Medellín, and an increase of several percentage points in Bogotá, Pereira –Dosquebradas, Cucuta and Armenia. There is no previous data on hepatitis C for Santiago de Cali.

With the promising effectiveness of antivirals to treat the infection and prevent transmission (17), WHO declared the intention to eliminate viral hepatitis by 2030 (18). Targets for

elimination include an 80% decrease in new HCV cases, 90% of infections diagnosed, 80% of infections receiving treatment, and 65% reduction in HCV-related deaths. However, most people with HCV are unaware of their status due to asymptomatic infection, low screening, and, among those screened, limited diagnosis and linkage to care (19,20). The lack of accurate national HCV surveillance systems, particularly for key populations such as PWID, contributes to the challenges of HCV control and elimination (21). Additional studies are needed to improve HCV screening, evaluation, and treatment to reduce the burden of HCV infection among PWID.

In accordance with the above, the objective of this study is to estimate the prevalence of anti-HCV antibodies in PWID between 18 and 65 years of age in the municipality of Armenia (Quindío) through public health strategies such as screening that allows characterize the affected people and facilitate access to diagnosis and treatment.

Theoretical framework and state of the art

Hepatitis C has constituted a major public health problem worldwide, causing liver failure, cirrhosis, hepatocellular carcinoma, and acute and chronic hepatitis C infections with a high mortality rate. Although risk factors commonly associated with the transmission of HCV infection include blood transfusion from unscreened donors, unsafe therapeutic injections, and other healthcare-related procedures, the majority of new and existing infections in most countries have occurred as a result of injection drug use (22).

PWID engage in high-risk behaviors and are at risk of contracting or transmitting viral infections such as human immunodeficiency virus (HIV) and hepatitis. That's because viruses are transmitted through blood and other body fluids. Generally, contagion occurs in two ways: a) when a person injects drugs and shares needles, or other items used for consumption and b) when drugs affect judgment, and the person has unprotected sexual relations with a partner. infected. This can happen to men and women alike (23,24).

Among PWIDs, the main route of transmission is through the exchange of drug preparation and injection equipment (for example, syringes, needles, filters, etc.) (25). HCV is resistant and is able to survive on drug preparation equipment (e.g. needles, syringes, filters, etc.) for several days or weeks (26). Furthermore, the risk of HCV transmission is greater than (1) HIV infection, consistent with greater transmission from exposure to contaminated injections

(2.5-5.0% for HCV vs. 0.5%-2.0% for HIV), and a higher prevalence of HCV than HIV among people who inject drugs (and therefore risk of exposure) (27).

WHO has identified strategies for the prevention, detection and treatment of infections caused by HCV and other hepatitis viruses worldwide to reduce the number of such infections (1). Better detection of undiagnosed cases, greater availability of treatment and better coordination of care are important components of the elimination strategy (1). In addition to primary prevention strategies such as opioid replacement therapies and needle and syringe programs, early diagnosis, and treatment of HCV in PWID, which is considered a high-risk group, will help reduce complications and mortality. HCV-related mortality, especially in PWID. The “treatment as prevention” approach is gaining importance in treatment guidelines, because eradication of HCV infection through early diagnosis and treatment would impact both individual well-being and reduce the spread of HCV infection the disease in PWID (28–30). PWID have been considered a difficult group to reach, manage, and treat because HCV treatment management in these individuals is challenging and they have a higher risk of reinfection (31).

Initially, HCV treatment guidelines excluded PWIDs from consideration, citing concerns about adherence, increased susceptibility to side effects, and reinfection (32). However, there is now compelling evidence that HCV treatment is safe and effective among PWID (33). International guidelines now recommend treatment for PWID after individualized evaluation (3. 4).

Any attempt to avert the threat to public health care posed by the impending burden of HCV among PWID will urgently require innovative changes to alter the currently inefficient system for care of HCV infection among this vulnerable population. A relevant expansion of treatment among PWID is impossible without massively reducing barriers to care. Low awareness, among patients, healthcare providers, policy makers, political leadership and the general public, as well as discrimination and stigmatization of PWID are the main barriers for people who inject to access the HCV care (35,36). Many of these barriers are the result of the criminalization of drug use (37). Repressive drug policy is hindering effective public health measures for people who inject drugs and, therefore, increasing the HCV and HIV epidemic in this population (38).

Objectives

General objective

To estimate the prevalence of hepatitis C antibodies through rapid test screening and identify the behaviors associated with infection in people between 18 and 65 years of age who inject drugs in the city of Armenia.

Specific objectives

- Estimate the size of the population of people who inject drugs in the city of Armenia.
- Estimate the prevalence of antibodies against HCV in PWID.
- Socio-demographically characterize the study population.
- Describe the epidemiological characteristics of PWID with positive antibodies for HCV.
- Identify behaviors associated with HCV infection among PWID.
- Determine the proportion of PWID with positive HCV antibodies and positive HCV viral load.
- To carry out an exploratory analysis of the association of positive cases and the different risk factors for HCV infection among PWID.
- To quantify how many PWID with positive viral load for HCV were able to access the management route and treatment.

B. METHODOLOGICAL APPROACH

Type of study

An anonymous, confidential analytical cross-sectional study will be carried out, in which the prevalence of hepatitis C will be estimated, the behaviors associated with the consumption of psychoactive substances by injection will be analyzed in people between 18 and 65 years old who inject drugs in the city of Armenia.

Population and sample

Population

The universe for this study was people between 18 and 65 years old who have injected drugs in the last six months in Armenia and the participants were selected through the implementation of the respondent-driven sampling (RDS).

Inclusion and exclusion criteria

Inclusion criteria

- Be between 18 and 65 years old.
- Having injected psychoactive substances in the last six months.
- Residing in the city or metropolitan area of study in the last six months
- Present the invitation coupon.
- Person with Colombian nationality, Venezuelan migrant population.

Exclusion criteria

- Person who, due to physical, cognitive or limitations derived from the use of psychoactive substances, is not able to answer the survey autonomously.
- Person who is in a state of consumption and is prevented from responding to the survey.
- Person who refuses to collaborate in the study.

Sampling frame

Statistical units

The statistical units of analysis, observation and sampling are the key population of Armenia.

Target population size

Sample sizes and precision for estimating a population proportion.

Population size (for finite population correction factor or fcp) (N): 580[1]

Hypothetical % frequency of the outcome factor in the population (p): 77.80%[2]+/-5

Confidence limits as % of 100(absolute +/-%) (d): 5%

1Patients treated at the Armenia City Listening Center between 2016-2023.
2Estimated based on the 2021 prevalence (62.80%), along with the growth speed of 5% per year.

Design effect (for group surveys-EDFF): 1

Sample size (n) for various confidence levels.

Interval Trust (%)	Size of the sample
95%	186
80%	98
90%	145
97%	213
99%	260
99.9%	331
99.99%	377

Sample size n = [EDFF*Np(1-p)]/ [(d2/Z21-α/2*(N-1) + p*(1-p)]

Source: Results from OpenEpi, version 3, the SSPropor open-source calculator

The sample size may vary by up to 10%, taking into account (i) the methodological adjustments that are made once the study begins, in which case the sample size will be adjusted.

Sample size 205 individuals.

Sample design

Due to the type of population (PWID), it is not possible to have a known sampling frame that allows designing a conventional probabilistic sample, so a chain reference sample will be taken based on those who respond (respondent driven sampling -RDS), a method that has proven its usefulness to access hard-to-reach populations (15,16). Respondent-driven sampling is a network-based sampling method, which makes it possible to draw statistically valid samples from previously unreachable groups. It is based on long referral chains and therefore several waves of recruitment. Likewise, several waves of recruitment make it possible to ensure that the final sample is independent of the seeds and this sample is similar to the population of the network from which the sampling was done (16). For example, in the prevalence study in 2021, the method estimated a population of 463 (95% CI: 431-497) people who inject drugs. Regarding completeness, through the RDS methodology, 53.4% of the population were identified and the method estimates that 80.19% of the population in the city of Armenia was identified[3] (16).

The seeds are those leaders of the population who begin the information gathering process.

3https://www.minjusticia.gov.co/programas-co/ODC/Documents/Publicaciones/Informe%20de%20Resultados%20de%20Investigacio%CC%81n%20PID%20Armenia-Cu%CC%81cuta%20Marzo%202022. pdf

In this sampling it is necessary to link the referral with the interviewee, which is achieved through coupons marked with the RDS code (unique number) that allows identifying all the referrals of a seed and therefore its social network. Likewise, the reference quota is controlled with a maximum number of coupons, which for this study would be three per interviewee, which allows limiting “recruiter” bias; coupons are an inclusion criterion that allows determining whether the person was eligible for participate and essential to preserve the link between referent and referred.

Respondents recruit their peers, as in network-based samples, and researchers keep track of who recruited whom and their number of social contacts. A mathematical model of the recruitment process then weights the sample to compensate for non-random recruitment patterns. This model is based on a synthesis and extension of two areas of mathematics, first-order Markov chain theory (i.e., sampling occurs with replacement, the sample becomes independent of the seeds). And biased network theory, which were not part of the standard toolset of mathematical sampling theory. The resulting statistical theory, called RDS, allows researchers to provide unbiased population estimates and measures of the precision of those estimates.

Variables

The dependent variable would be the identification of HCV antibodies, which is qualitative with nominal measurement as presence (positive) or absence of the virus (negative). The questions that will make up the survey will be the independent variables, whose nature is qualitative or quantitative and the measurement levels are nominal and ratio, such as age, number of times per day in which you inject, number of people with whom you have shared syringes and needles, injection equipment, number of casual or commercial couples, among others.

Collection of information and sampling procedure

Once approval has been obtained from the research ethics committee for this study, in the first phase people called seeds are selected, a record of the identified population will also be made, and the first part of the capture-recapture methodology will be applied. In the second phase of expansion, it is expected to recapture the population and estimate the population, with which the waves of the RDS methodology are carried out.

The researcher initially searches for individuals (called seeds) who belong to the population

of interest and who know a measurable number of people in that population. The seed is contacted, invited to the headquarters, the survey and the defined biological samples are applied, and they are given the three coded coupons that also contain the information about the study, the headquarters, and the opening hours. Each seed will deliver the coupons to known people who meet the eligibility criteria. Once the seeds have delivered their coupons to their peers, they are expected to come to the headquarters to participate, once the information collection process is completed. In this way, the enrollment process is developed in waves until the predefined sample size is reached. Each coupon contains information about the headquarters, including the address, opening hours and contact telephone number, as well as the RDS code assigned to each participant, which allows identifying who recruited whom and reconstructing the chain of referrals or recruitment.

Potential participants will be presented with the purposes of the research, and it will be asked if they are interested in participating. The informed consent will be read and explained to them, and they will subsequently be asked to sign the consent. The standardized information collection phase will then proceed. These individuals will undergo pre-test counseling, a presumptive rapid test for HCV, and if positive, contact information will be requested for post-test counseling.

The collection of information on social and demographic variables, risk factors associated with HCV infection, and access to the health system will be carried out with the application of a structured survey conducted by a previously trained interviewer. You will explore social and demographic characteristics, social networks, drug use and injection, sexual behavior, sexually transmitted infections, HCV knowledge, and rapid test results and viral load.

The sample will be taken by trained personnel (indications for storage, application and reading of each test), through capillary puncture of the pad region of the fingers of the right hand, after asepsis and antisepsis, the rapid HCV diagnostic test will be used. Ab Plus Rapid test with INVIMA registration 2018 RD-0002353-R1 with operational characteristics that allow it to be performed at the point of care, obtaining a result in 15 to 20 minutes. This rapid HCV antibody test may be replaced by another with similar operating characteristics (sensitivity and specificity). The recommendations described by the test manufacturer will be followed (Annex 1). If it is reactive, it will be defined as a presumptive result because it is a screening test that requires confirmation of diagnosis, through a ribonucleic acid (RNA) detection test (viral load) in accordance with the provisions of the Hepatitis C Guide of the

Ministry of Protection Social (2019) to establish the diagnosis of chronic infection and in the case of obtaining a positive result in the latter, the HCV infection will be confirmed, and the participants will be channeled to health services for the respective treatment through of your EAPB.

All information obtained will be recorded and processed individually (case by case) through a digital information system with backup in the cloud in real time using a Case Report Form (CRF) capture format, with the use of a tablet. This will allow daily monitoring of the behavior of RDS sampling. The information will be guarded and encrypted for the exclusive use of the main researchers belonging to the Colombian Association of Hepatology, a final report will be presented. The information will be anonymized for your use.

Quality assurance procedure

To control information biases, an instrument applied and reviewed in previous research, and which is part of the updated protocols for these studies will be used; Likewise, as a measure to control information bias in interviewers, training will be carried out in the proper handling of the collection instrument. In addition to the above, the coordinators will review the interviews collected by the interviewers to corroborate their correct completion. In the process of controlling the interviewee's information biases, the confidentiality of the information provided by the population is guaranteed.

To control selection bias, the recognized sampling methodology of “Respondent Driven Sampling” is used. With the selection of the seeds, special care is taken to identify the properties of the social network (identification of subgroups, connectivity, personal network); the acceptability of the study (interest, possible reasons for not participating); the identification of seeds (large and diverse social network, leaders or well-known, support the study, enthusiastic); and take special care of logistics (site, schedules, coupon design, staff profile).

Type of error/bias	Description	Control
Selection bias	Include people who meet inclusion criteria.	A short screening-type questionnaire will be designed to identify people. The person performing the screening must be experienced. Compliance with study inclusion/exclusion criteria.

		Precise definition of the objectives and scope of the study to field personnel. Pilot test.
Information bias	Data quality Source of information Intra and interobserver errors Unanswered questions	Staff training. Application and evaluation of the pilot test. Supervision of the personnel who carry out the collection. Personnel with experience on the subject.

Pilot test

To implement the research protocol, ten people will be included (1 seed and 9 referrals), who inject drugs, the collection instrument will be applied where the clarity of the instrument will be evaluated and the field work manual will be adjusted (terms used, coherence of the content, order of the questions), the time of application, the disposition of the interviewers, the ability to generate confidence in the participants and finally the acceptance of the respondents. After carrying out the pilot test, it is expected to obtain the final version of the instrument and procedures.

Data analysis plan

The RDS itself estimates the sampling errors described through measures such as homophily, heterophily, and proportional estimates of the population. Initially, homophily will be calculated, which describes the extent of the ties of the social network inside or outside it. The homophily/heterophily scale is between 1 and -1, where 1 indicates that all participants with certain characteristics invited someone with the same characteristics, while -1 indicates that all participants with a certain characteristic invite someone with one characteristic. opposite or different; 0 (zero) was the point at which participants randomly invited other individuals from the population of all possible invitees.

The RDS technique uses the information available in the sample about the social network to obtain asymptotically unbiased estimators of the proportions of the population in the different groups in which they want to be characterized. These estimators are called population prevalence estimators.

Descriptive statistics (frequencies and percentages) will be estimated. For continuous quantitative variables, measures of central tendency (average and median) and measures of dispersion (variance, standard deviation) will be estimated.

A descriptive analysis of the characteristics of the population under study will be carried out, according to the socio-demographic variables: sex, age, educational level, stratum, insurance, in addition the prevalence of HCV and the proportions of the sample and the population will be obtained. according to the risk behavior variables associated with infections. All these analyzes are carried out by estimating the population with their corresponding 95% confidence intervals.

Possible relationships between sociodemographic variables, risk factors and documentation of positive antibodies for HCV will be explored. For this purpose, a bivariate analysis will be proposed using chi-square tests to explore the proposed associations. The test allows us to determine, for each pair of variables, the existence or not of the relationship through the difference between the value that should result if the two variables were totally independent, and the one observed in the data. The greater the difference, the greater the relationship between the variables.

The significance between the relationships will be determined by the p-value of the test, a value less than 0.05, it is accepted that there is a statistical association between the two variables analyzed.

The processing will be carried out in the RDSAT® version 5.6 program.

C. WORK PLAN

Phase 1. Exploratory component

With the purpose of making an approach and identifying barriers to the study and possible alternative solutions to consumption contexts, as well as establishing inter-institutional alliances that facilitate communication with research subjects called seeds, an exploratory phase will be carried out through the use of a qualitative technique that enables the collection and construction of data that enriches the information obtained by the subsequent application of the structured survey that underpins the present study.

We will seek to identify characteristics of the social network: subgroups, connectivity, personal network, the acceptability of the study, interest, possible reasons for not

participating, as well as define logistical aspects, such as the site for collecting information, schedules, coupon design and the profile of the personnel who will serve the prioritized populations.

Through interviews with representatives of various institutions in Armenia who, from research, care, and treatment, offer the research team a general overview of the context and care routes; and from there provide elements that guide field work and the analysis of the information obtained from the surveys.

After prioritizing institutions, they will be inquired about the description of the problem, characterization of the populations, institutional experiences, research, territorial location, methods of approach, risk behaviors and practices for HCV infection, among others. The estimated time to complete the exploratory phase will be two months, this includes the collection, analysis and interpretation of the data and the understanding of the conditions found.

Interviews with key informants

These people are considered experts in the social and cultural context of PWIDs, with the objective of understanding the context and behavior of users; example of key informants: people who have worked with populations, people from institutions, NGOs, among others. In this first phase, the capture technique, already described previously, will also be applied.

Phase 2. Quantitative component

Hidden populations have two basic characteristics: first, they lack a sampling frame, so their size and real margins are unknown; and second, the people who belong to them are especially wary of offering information to researchers since they normally follow stigmatized, frowned upon or illegalized behaviors, therefore, locating them can be difficult.

This limitation is intended to be resolved with the RDS sample design, by applying a coupon system that limits the possibility for each informant to select no more than three informants, to nullify the biases caused by the presence of semi-professional recruiters or by a desire for super-collaboration of some people that causes an overrepresentation of the networks of a specific individual. Social support vouchers will be used for respondents to promote inclusion and diversity, which encourage them to have other referrals and they must travel to a place to carry out the entire collection and sampling procedure.

The seed must be very well selected, with whom respect for privacy, confidentiality, and respect for autonomy will prevail, explaining that the coupon system will become effective when the referred person agrees to go to the predetermined place to carry out the collection procedure. of information and the social support bonus system, aims to recognize the costs generated by transportation, transfer, informing their social networks about the characteristics of the project and that this could in no way affect them due to the nature of confidentiality. of this research.

Field work (quantitative phase)

This stage begins with the process of selecting the interviewers to collect information and who meet the requirements of education, training and work experience; It is expected to have a nursing assistant for the collection process; and will be trained in voluntary testing for HCV; It is proposed that interviewers can carry out different activities such as screening, identification of injecting drug users (IDU) and reception tasks. At the same time, the instrument is reviewed and adjusted.

Once the first version of the adjusted survey is approved, the pilot test will be carried out, to test the methodological design, calculate the completion time, adjust the project schedule, verify the required attitude of the staff and the most appropriate techniques. for quality control.

The work team will have the following elements to carry out the field work: identification badge, institutional information, informed consent, survey, and pen, in addition to the implements for taking blood samples.

Instructions for the personnel who carry out the collection.

The personnel who carry out field work have five days of prior training; In the training, the procedures will be reviewed, and exercises will be carried out seeking to practice what has been learned. This training should be used to ask questions about any procedure to avoid errors in actual counseling and interviews.

During the collection process, we will insist on the importance of having absolute knowledge of the topic, conducting the surveys in private, asking questions exactly as the question is formulated in the survey. Asking the questions slowly to make sure the person understood (in people who require it).

According to previous studies, completing the survey will not last more than approximately 60 minutes. The entire information collection process that includes informed consent, application of the survey, pre-test counseling and sample collection will last approximately one hour and thirty minutes.

Throughout the process, one of the researchers with extensive experience in the topic of public health surveillance will coordinate the actions on the ground with personnel, also with experience in the collection process; That is to say, during the training-concertation-study process of HCV seroprevalence -post-test counseling, monitoring and accompaniment will be carried out on the populations, in the same way the provision of services will be managed before the territorial entity of Armenia and the corresponding health entities. of patients' health according to the type of insurance.

Procedure for selecting possible seeds

Key informants: the first moment will aim to contact key informants who can allow access to the seeds; For this purpose, different population groups were approached: for example, people in a situation of prostitution, research, care and/or treatment institutions, among other agents who are considered key informants during the investigation.

Seed selection: to access and identify the seeds there will be an experienced team, key informants from the institutions or organizations that work with key populations, some natural leaders.

To establish the status of the person as a key population, a small screening questionnaire will be designed in which we will seek to establish their status, possible history of participation in the study, some socio-demographic data (age, gender, origin, area of housing, origin of the network, potential of known people, willingness to also involve them in the study). Individuals who are not eligible will be offered information regarding the practice, risks, the possibility of referral to an institution for counseling or treatment, and the referral potential of other individuals who may meet the inclusion criteria is explored.

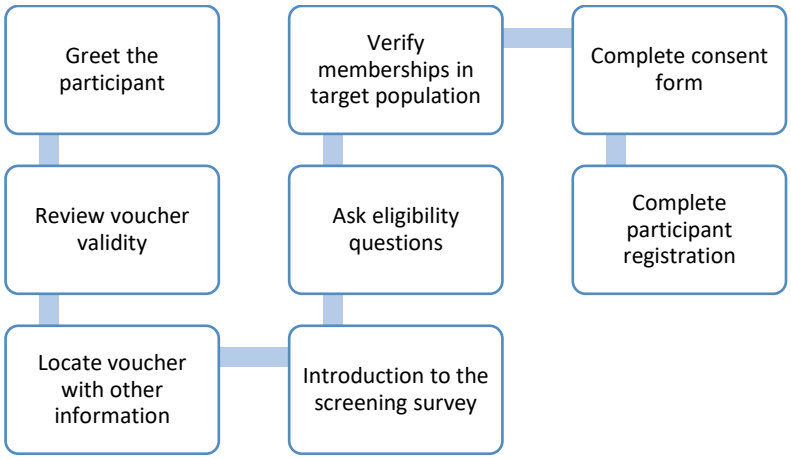
Information collection (expansion phase)

The person will be summoned to the place where the process will be carried out, upon arrival at the site their eligibility is confirmed, if not eligible, the participant will abandon the study, otherwise the informed consent will be read, the participant will be registered in the study, the structured survey is carried out, then pre-test counseling is provided and the blood

sample will be taken, performing the rapid test for HCV. The cases will receive the results at this same appointment, carrying out post-test counseling.

Each interview location will have its own screening area in which potential participants will be screened before being admitted to the interview area, this will reduce the chances of a disgruntled or disruptive person disturbing registered participants or staff. During the screening procedure, the person performing the screening will ensure the following: the potential participant has an appropriate coupon (correct identification number) and signs the informed consent.

Steps for user detection



Source: self-made

When the screening steps are completed, the person enrolls in the study and continues with the interview. Currently, a registration as a participant is completed.

In the survey area

After greeting, the survey is carried out, followed by pre-test counseling (VHC) and the blood sample is taken. After completing the survey, the participant is informed about the opportunity to recruit voluntarily the importance for the project and the opportunity to receive a social support bonus for each eligible person recruited. If the participant is interested, they will be indicating the way and how to do it, each participant needs a coupon to participate in the study.

Coupons

Each of the participants is asked about the number of acquaintances, the coupon system limits the possibility for each informant to select only three future informants, to nullify the biases caused by the presence of semi-professional recruiters or by a desire for super-collaboration by some people that would cause an overrepresentation of the networks of a specific individual.

Instructions for recruitment

- They must bring their coupons with them to the site, if the referral does not bring their coupon, they cannot participate in the survey.
- Coupons are limited, it is recommended to give the coupons to people you know who meet the criteria as soon as possible.
- One hour and 30 minutes are required to complete the interview and sample collection.
- Those referred will receive a social support bonus if they complete the interview and sample collection.
- Referrals who are not eligible (not meeting inclusion criteria), participants who do not sign the informed consent, who had already participated and if the person sells their coupons are not considered (only the social support voucher will be given to the person to whom which they were delivered).

Social network

They will be consulted about the following aspects corresponding to the social network, having the protocol it is expected to have at least the following information:

- How many people do you know (you know them, and they know you)?
- Of them, how many are over 18 years old?
- And of them, how many have you seen in the last month?
- Each person receives three (3) coupons to recruit others.
- The study will end when the required sample size is met.
- A day is scheduled to deliver the social support vouchers.

Delivery of social support bonuses

- Reiterate the recruitment process to the participant.
- Deliver the primary social support bonus.
- Confirm to the participant that they have completed all steps of the study (otherwise have the participant complete them).
- They must bring the coupons, in the part of the detachable assigned for the participants.
- It is investigated whether some people rejected the coupons and the reasons for this situation.
- It is consulted for doubts or questions that the participants have.
- Verify that the recruit is enrolled in the study. Inform the recruiter to return if the previous coupon was not registered.

Other activities

- Ensure the quality of the numbers on the coupons.
- Update the coupon registration form.
- Keep the record of primary and secondary compensation updated.
- Match the identification number on the coupon to the participant's recruiter record.

Coupon Registration

- Record the date of the interview.
- Register the participant's questionnaire code.
- Record the participant's network size.
- Record the identification number of the coupon delivered to the participant.
- Record the identification numbers of the coupons given to the participant to recruit others.
- Record important notes or physical features.
- Record the initials of the interviewer.

Post-test advice

Given the serious ethical implications of developing diagnostic tests, the counseling process includes:

- Provide information and education about HCV.
- Referral to prevention, treatment, and support services. The local and departmental health secretary has previously been informed about this project for the correct identification of the support network and health services.
- Prior to this advisory process, a training session is held for the team responsible for collecting information.

Screening test

The samples are taken by the personnel assigned to the study with training to ensure the quality of the diagnostic process. At the appointment that is made, the rapid test is read to deliver the results.

The sample number will be linked to the survey through a code, which allowed confidentiality and anonymity to be maintained without losing the possibility of monitoring the results in order to return them to the subjects and offer the corresponding advice and follow-up. .

Delivery of results with their respective APV

With the results of the rapid HCV tests, counseling will be carried out after the detection test. The goal is to understand the outcome and provide appropriate information, support, and reference. If the result is negative, counseling offers an opportunity to promote behaviors that reduce infection risks; if the result is positive, to reduce the risk of transmitting the virus to other people. In addition, help must be given to face the result and its consequences on the person's personal life and that of the person's loved ones.

Training for interviewers

The interviewer will be trained in the application of the survey by the technical committee. Therefore, each one of them must attend the training to study the definitions and concepts well and to become familiar with the procedures and questions of the survey and ask questions about any procedure or content that is not clear and so on. Avoid errors as much as possible during field work.

Information processing

Automated processing will be carried out, the instrument will be designed, tabulated and its corresponding database created, tablets will be used with the survey application properly adjusted. The first analysis will be carried out in the RDSAT software[4], a secondary analysis includes other packages such as STATA 10.0, SPSS version 27, with all these programs the statistical analysis of the data and the generation of output tables is carried out.

Results dissemination plan

At the end of the study, the results are shared and a report with publishable results is expected to be generated.

Social support for respondents in promoting inclusion and diversity

It is widely known that RDS is a sampling that requires using compensation bonuses that motivate the participation of a diverse group of PWIDs, and super-recruiters can be controlled and guarantee a close variance between the sample and a population estimate without a high homophily; The vouchers also allow you to cover travel expenses from one place to another, as well as the time invested to carry out the entire collection and sampling procedure.

As recognition, social support equivalent to $40,000 Colombian pesos will be given for participation in the study process cycle and $10,000 Colombian pesos for each recruited peer who was eligible and complied with the entire information collection process in the study. headquarters, for a maximum of three referrals per participating PWID, will be delivered after the administration of the survey and the collection of the blood sample for HCV.

Ethical considerations

The study protocol will be presented to the institutional human ethics committee of the CES University, which is recognized nationally.

4 Respondent Driven Sampling. Available at: http://www.respondentdrivensampling.org/reports/RDSAT60.htm. Accessed January 14, 2011.

The study complies with those established in Resolution 8430 of 1993 of the Ministry of Health of Colombia, according to its article 11 numeral b, it is classified as minimal risk, given that data records were used through common procedures consisting of a taking a blood sample by capillary and/or venous puncture. Furthermore, the criterion of respect for the dignity and protection of the rights and well-being of the participants will prevail.

Written informed consent will be requested from all participants, giving clear and easily understandable information about the objectives of the research. Questions about it will be explained and resolved, and complete freedom to withdraw consent will be given at any time during the study, because the subject considers (Annex 3).

The study will be coordinated by health professionals and the sampling and collection of information will be carried out by trained nursing assistants. The confidentiality of the data collected will be guaranteed, the information obtained will not be used for uses other than the current research process and at the time of disclosure of the information, no sensitive data or data that allows the identification of participating individuals will be published, the procedures will be followed. norms set out in law 1581 of 2012 on habeas data.

The application of rapid tests is governed by current regulations; in particular, by the guidelines for carrying out rapid tests outside the clinical laboratory for the early diagnosis of hepatitis C infection (Resolution 1314 of 2020 of the Ministry of Health and Social Protection).

In the development of this investigative process, the following ethical aspects will be considered by the researchers:

- The integrity of the people interviewed will be respected, regardless of risk behavior, by both the interviewers and the researchers.
- Interviewees will be informed of the terms of confidentiality in the informed consent. Written consent will be requested from the population to carry out the interview and take a blood sample, according to Resolution 8430 of 1993, which regulates research on living beings, according to article 14 of this same resolution, consent is understood. informed the written agreement, by which the research subject authorizes his or her participation in the research, with full knowledge of the nature of the procedures, benefits, and risk to which he or she will be subjected, with the capacity of free choice and without any coercion.

- In the attention of users, the same procedures will be carried out on all of them; it is important to highlight that these instructions will be the same for all users.
- The informed consent that will be signed by all the people who agree to participate in the study will clearly explain the justification and objectives of the research, the procedures that will be carried out, which will also indicate that there are no relevant risks and the benefits. that can be obtained; In addition, the guarantee of receiving an answer to any question and clarification of any doubt about the research and other matters related to the topic and finally the freedom to withdraw your consent at any time and stop participating in the study without thereby create harm in their social environment.
- Since the sample is blood, it will be guaranteed to have qualified personnel to take samples, as well as guarantee all biosafety procedures and proper handling of blood samples.
- The identification number will be linked to the name, telephone number or contact information of the person in a database to which only the study coordination and field work supervision will have access.
- This study is also governed by the provisions of Chapter IV of Decree 1543/97, which establishes: With respect to the right to autonomy, which is none other than self-determination in the full right of the person's faculties, freely and spontaneous for the benefit of the development of their personality, it was very important to include that the practice of the diagnostic test for the detection of antibodies against HCV requires the informed consent of the person, a requirement without which it cannot be carried out.
- The same Decree establishes the obligation to offer counseling (Article 5). And along the same lines, article 6 establishes that the results of tests for diagnosing HCV infection and those for diagnosing sexually transmitted diseases (STDs) must be delivered to the patient by personnel duly trained in counseling.
- There are suitable personnel in the areas that involve the topics of the study, with knowledge and experience to take care of the integrity of the human being to guarantee the well-being of the research subject.
- The privacy of the individual will be protected, identifying them only when the results

require it and they authorize it.

- In relation to confidentiality, Article 34 of Decree 1543/97 establishes that members of the health team who know or provide health care to an infected person are obliged to keep the consultation, diagnosis, and evolution of the disease confidential. and all the information that belongs to your privacy.
- All possible types of risk and the possibility that the research subject will suffer harm as an immediate or delayed consequence of the study will be identified.
- Subject participation will be entirely voluntary.
- The cases of other people who have had risky sexual contact and who are not a key population of the study, will be notified according to the public health surveillance protocol. These actions will be coordinated for this purpose with the territorial entity and specifically with the secretaries of health, the latter will be informed from the beginning of the project about the scope of the research and the actions that will be carried out; positive cases will also be notified within the public health surveillance system of the corresponding entity.

None of the authors have conflicts of interest to declare.

Expected results and impact

Strengthening the scientific community

Expected result/product	Indicator	Beneficiary
Screening for hepatitis C in PWID.	Proportion of PWID with a diagnosis of hepatitis C.	PWID, users affiliated with the SGSSS, benefit plan administrative entities, health personnel.
Linkage to the treatment of confirmed positive cases for HCV infection at the site included in the study.	Proportion of PWID with a diagnosis of chronic hepatitis C who started treatment.	PWID, users affiliated with the SGSSS, benefit plan administrative entities, health personnel.

Social appropriation of knowledge

Expected result/product	Indicator	Beneficiary
Circulation of specialized knowledge: Presentation of results at scientific events (national and international).	Participation in scientific events presenting research results.	Medical-scientific community, decision makers, hospital institutions.
Presentation of results to stakeholders of the Colombian SGSSS.	Participation in an event with different stakeholders of the SGSSS.	Insurers and SGSSS providers, patients nationwide.

Generation of new knowledge

Expected result/product	Indicator	Beneficiary
Research article submitted to a journal indexed in one of the bibliographic citation indexes such as, for example, ISI-Web of Knowledge (Science Citation Index [SCI] and Social Sciences Citation Index [SSCI]) or SCOPUS, Publindex, Lilacs, BVS, Latin index, among others.	Published scientific articles.	Medical-scientific community, decision makers, hospital institutions.

Expected impacts from the use of the results

Expected impact	Term (years) after project completion*	Verifiable indicator	Assumptions*
Improvement in the opportunity to detect new cases of hepatitis C among PWID.	1-4 years	Increase in the incidence rate for hepatitis C.	Medical personnel adherent to the screening and diagnosis algorithm – applicability of this among PWID.
Improvement in the times elapsed between confirmatory diagnosis with PCR and the start of treatment.	1-4 years	Increase in the number of PWID with a diagnosis of chronic hepatitis C who started treatment.	Standardization of the route that allows compliance with all stages for the diagnosis, treatment, and monitoring of PWID with HCV.
Successful completion of treatment between PWID	1-4 years	Increase in the proportion of PID with cure (sustained viral response).	Opportunity in follow-up, adherence of PWID to the treatment scheme.

Expected impact	Term (years) after project completion*	Verifiable indicator	Assumptions*
Changes in the prevalence figures of chronic hepatitis C among PWID.	5-9 years	Trend in crude prevalence of chronic hepatitis C.	Early detection and treatment reduce the risk of transmission.

short (1-4), medium (5-9), long (10 or more)

Schedule of activities

The activities will be executed in 10 months, the first two months of planning the activities, carrying out and submitting the protocol, selecting the field team, two months in the design, and execution of the exploratory phase, including the delivery of the unique object; the following four months of field activities, and the following two months for the delivery of results, and analysis of information, including the reproduction of the final document.

Activities	Start date	Final date
Development of the final protocol, consent reports and approval by the ethics committee.	Month 1	Month 1
Nursing personal training for information capture, sample collection, referral to treatment and follow-up.	Month 2	Month 2
Development phase 1 exploratory component.	Month 3	Month 4
Recruitment of participants – Identification of risk populations to be screened – Screening tests – entry of captured information.	Month 5	Month 7
Monitoring of positive cases –	Month 8	Month 8

Activities	Start date	Final date
treatment route direction.		
Verification of the quality of the information collected.	Month 5	Month 8
Analysis of data.	Month 9	Month 9
Final report presentation.	Month 10	Month 10
Writing and presenting article for publication.	Month 10	Month 10

Human resource

Activities of the city supervisor

Armenia will have a supervisor, who must guarantee that all the procedures defined for field work and completion of the survey are fully complied with. With a professional profile, preferably with postgraduate training in the areas of public health, epidemiology and/or related.

Staff activities

This is the person who is responsible for collecting information in the PWID. To reach the sample proposed in the study protocol, it is required that the interviewer be committed to his or her work, clearly know the functions he or she must perform, be a responsible, orderly, accomplished person, and have certified experience. of work, in addition to having the ability to generate empathy and trust, and to demonstrate that they have the basic knowledge necessary to contribute to the fulfillment of the objective of the study and to pass the evaluation after the training.

Principal investigator career

Javier Enrique Hernández Blanco. Medical specialist in Internal Medicine, Gastroenterology and Digestive Endoscopy, Master in Liver Diseases and Clinical Epidemiology. University Research Professor, president of the Colombian Association of Hepatology (2021-2023). Active participant in the working groups of the National plan for the elimination of Viral

Hepatitis, national lecturer on Viral Hepatitis B and C, former public health advisor to the District Health Secretary of Santa Marta, extensive experience in viral hepatitis screening activities in the community, co-author of the Colciencias project - CALL 777: Prevalence and modeling of Hepatitis C Virus infection in Colombia.

Budget

This project will be carried out by the Colombian Association of Hepatology (ACH), it corresponds to an initiative of the ACH in response to its commitment to join efforts to achieve the World Health Organization's goal of eliminating viral hepatitis by 2030. and is financed with resources from the ACH, which in turn are obtained by the association's own activities and resources obtained from calls for project financing. Leadership in communication and administration of project resources is provided by the ACH.

A final project report will be generated, and the results will be maintained in a consolidated and anonymized manner, without compromising confidential information of the participants.

The ACH is the author of the project, it will provide the resources for its execution. The items covered in the execution of the study do not include the costs of treatment or any clinical management procedures (for example, doctor visits, follow-up laboratories) since they are part of the usual treatment for hepatitis C virus infection. and it is contemplated in Colombian regulations that once the confirmed case of hepatitis C is notified to SIVIGILA (file 340), on a quarterly basis the High-Cost Account downloads that information, includes the participant in the national cohort of high-cost diseases. Hepatitis C establishes communication/audit with the Benefits Plan Administration Company (EAPB) to which the user belongs and guarantees their connection to the treatment, treatment against hepatitis C that is free, without cost for the EAPB or out-of-pocket expense for the user. user and which is acquired in annual purchases by the CAC since 2017 through the centralized purchasing mechanism from the Pan American Health Organization.

Annexes

Annex 1 Anti-HCV antibody detection test

Test principle

The Bioline™ test[5]HCV contains a strip with nitrocellulose membrane pre-coated with recombinant HCV capture antigen (core, NS3, NS4 and NS5) in the test line area (T). The colloidal gold-conjugated protein A and the sample move across the membrane chromatographically to the test zone. There, the antigen-antibody complex of protein A bound to gold particles forms a visible line with a high level of sensitivity and specificity. On the surface, this test device has the letters "T" and "C", which refer to the “test line” and “control line”, respectively. The test line and control line are not visible in the results window until the sample is applied. The control line is a procedural control. The control line should appear if the test procedure is executed correctly, and the control line reagents are operational.

Use

The Bioline™ HCV Test is a rapid in vitro immunochromatographic assay for the qualitative detection of HCV-specific antibodies, in human serum, human plasma (heparin, EDTA and sodium citrate) or blood. Bioline™ HCV is exclusively for professional use as an initial test, as an aid to diagnosis. Reactive specimens should be reflected for additional testing, either using HCV RNA detection technologies or HCV core antigen testing, to identify current HCV infection. This product is intended for use in a population with a high prevalence of HCV or who has a history of HCV exposure/risk behavior, including pregnant women. This test may not be suitable for early diagnosis of infection or for testing blood donation.

Materials included and active ingredients of the main components

1. 25 test devices with desiccant in individual aluminum foil bags.

2. Assay diluent (1 x 5 ml/vial).

3. 25 capillary pipettes (10 µl), 25 safety lancets, 25 alcohol swabs.

5Anti-HCV antibody detection test. Reference 02FK10/02FK16/02FK17. Abbott Diagnostics Korea Inc. Date issued: 2020. 04.

Materials needed, but not provided in the kit: Micropipette, protective gloves, timer, container for biological waste.

Kit Storage and Stability

1. The test kit should be stored at a temperature between 1°C and 30°C. Do not freeze the kit or its components.

2. The assay diluent can be opened and resealed for each assay. The lid should be tightly sealed between each use. The assay diluent is stable until the expiration date if kept at 1 and 30 °C.

3. The test device is sensitive to heat and humidity. Perform the test immediately after removing the test device from the aluminum foil bag. 4. Do not use the test kit after the expiration date. The shelf life of the kit is indicated on the outer packaging.

5. Do not use the test kit if the bag is damaged or the seal has been breached.

Warnings

1. Test devices are for in vitro diagnostic use only. Do not reuse the test device.

2. Follow the instructions properly to get accurate results. The person in charge of testing this product must be a specialist trained to use it.

3. Do not mix or exchange different samples.

4. Do not put the desiccant in the aluminum foil bag in your mouth.

5. Do not mix or interchange components from different lots or other products.

6. Take care to avoid contamination of the container spout when pouring the assay diluent into the sample well.

Sample collection and storage

1. Blood

[Venipuncture collection]

- Perform a venipuncture and place the blood in the collection tube (containing anticoagulants, such as heparin, EDTA, and sodium citrate).
- If the test is not performed immediately on the blood sample, it should be refrigerated at

2°C to 8°C.

- If the blood sample is stored between 2°C and 8°C, the test should be performed within 3 days of refrigeration.
- Do not use blood samples stored for more than 3 days, as a non-specific reaction may occur.
- Before testing, the blood sample should be at room temperature (between 15°C and 30°C).

[Lancet collection]

- Clean the area where you will use the lancet with an alcohol swab.
- Squeeze the tip of your finger and then prick the side of your finger with the lancet provided. Wipe away the first drop of blood. Immediately afterwards, dispose of the lancet safely.
- Dip the open end of a new capillary pipette (10 µL) into the next drop of blood and relieve the pressure to draw blood into the capillary pipette until the fill line is reached.

Plasma or serum

[Plasma] Using venipuncture, introduce the blood into the collection tube (containing anticoagulants, such as heparin, EDTA, and sodium citrate), then centrifuge to obtain the plasma sample.

[Serum] Using venipuncture, introduce the blood into the collection tube (which DOES NOT contain anticoagulants) and let it rest for 30 minutes for coagulation to occur. Centrifuge the tube to obtain a serum sample.

If plasma or serum samples will not be used immediately, they should be refrigerated at 2°C to 8°C. If it is necessary to store them for more than 2 weeks, they must be frozen (Less than -20 °C). Before testing, the plasma or serum sample should be at room temperature (between 15°C and 30°C).

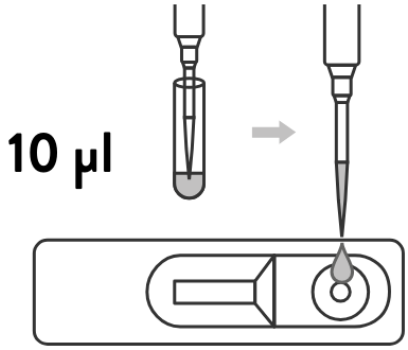
Plasma or serum samples containing precipitate may give inconsistent test results. It is necessary to clarify the samples by centrifugation before testing.

Test procedure

1. Before testing, bring all kit components and samples to a room temperature between 15°C and 30°C.

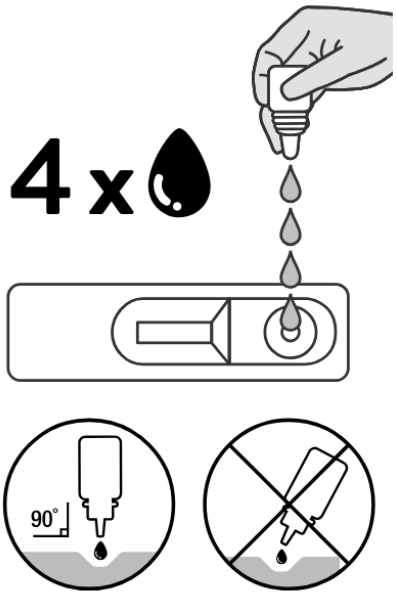
2. Remove the test device from the bag and place it on a flat, dry surface. Label the test device with a patient identifier.

3. [Using a micropipette] Place 10 µl of the plasma, serum or blood sample into the sample well marked “S”. Or [Using a capillary pipette] Place 10 µl of the drawn blood sample into the sample well marked “S”.



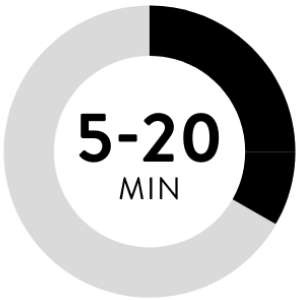
4. Place 4 drops of assay diluent into the “S” sample wells.

Caution: If the bottle is not held vertically, inadequate results may be obtained. Add exactly 4 drops. Adding more than 4 drops may cause the background to turn reddish or cause an erroneous result. Do not allow the tip of the bottle to come into contact with the device to avoid cross contamination.



5. When the test starts running, you will see a purple color scrolling across the results window located in the center of the test device.

6. 5 to 20 minutes after adding the assay diluent, interpret the results. Do not read the results after 20 minutes.

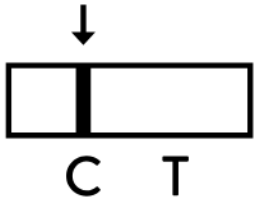


Caution: If the test result is not readable after 5 minutes due to the intense color of the background, read it again later, within 20 minutes of adding the diluent. Reading the result outside of that time frame (before 5 minutes or after 20 minutes) may give false results.

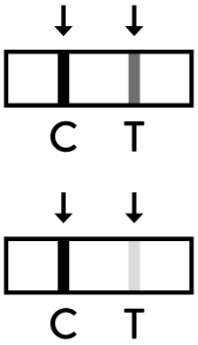
Test interpretation

1. A control line will appear in the "C" section of the results window indicating that the test is working correctly. 2. In the "T" section of the results window, the test results are displayed.

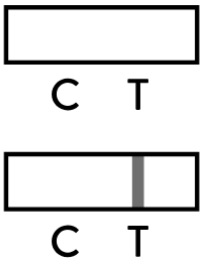
Non-reactive result: If only the control line (C) appears in the result window, the result is non-reactive.



Reactive Result: If the test line (T) and the control line (C) appear in the result window, regardless of the order of appearance, the result is reactive. Caution: The presence of any test line, even a faint color, indicates that the result is reactive.



Invalid result: If the control line (C) is not visible in the results window after running the test, it is considered that there is no valid result. This situation may be because the instructions were not followed correctly or because the test has deteriorated. It is recommended that the sample be retested with a new test device.



Internal quality control

The Bioline™ HCV Test Device has two pre-coated lines on the test surface: “T” (test line) and “C” (control line). The test line and control line are not visible in the results window

before sample application. The control line is used as a reference in the procedure and only indicates that the diluent was applied correctly and that the active ingredients of the main components of the test strip work but does not ensure correct application of the sample; It is not a reactive sample control.

Performance characteristics

The Bioline™ HCV Test Kit is designed to have 99.3% (95% CI: 96.1 - 99.9%) sensitivity and 98.1% (95% CI: 94.5 - 99.4%) sensitivity. %) specificity.

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