

# The role of pharmacists in the comprehensive care of patients with hepatitis C: a systematic review

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## OPEN ACCESS

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## Abstract

**Objective:** To identify and characterize the actions/interventions carried out by pharmaceutical services to approach patients with Hepatitis C and propose a clinical pathway for managing the disease that involves pharmacists. **Methodology:** A systematic review was conducted in PubMed and EMBASE using the terms “Hepatitis C,” “Pharmaceutical Services,” “Community Pharmacy Services,” and “Pharmacies.” Articles published until March 31, 2019, whose central topic was the activities carried out by the pharmaceutical services in the care of patients with Hepatitis C, were included. Information on the activity performed, the person in charge, whether the intervention was individual or collective, and the implementation environment was collected. The activities were grouped into promotion and prevention, administrative management, pharmaceutical care, research, and other support services. Based on the above, a clinical pathway for the management of Hepatitis C involving pharmacists was proposed. **Results:** Sixty articles were included, mainly descriptive studies. Most publications reported interventions in the United States and Spain. Pharmaceutical staff involvement was identified at each stage of the care process, including the provision of harm reduction services, Hepatitis C virus screening, enrolling patients to treatment, medication prescription, and laboratory orders. **Conclusions:** The actions/interventions carried out by the pharmaceutical service for Hepatitis C management were identified and characterized. A clinical pathway has been proposed to integrate professional pharmaceutical services with other patient care activities.

## Keywords

Pharmacy Services; Patient Care Management; Hepatitis C; Antivirals; Comprehensive Health Care.

## INTRODUCTION

In the last decade, significant progress has been made in the treatment of hepatitis C virus (HCV) infection due to the development of direct-acting antivirals (DAD), which allow simpler, shorter, more effective and better tolerated treatments compared to conventional pharmacological therapies (interferon and ribavirin) (1, 2). DADs have been shown to increase patient adherence and minimize treatment discontinuation. However, there are still barriers to access this therapy and to achieve treatment continuity, especially among vulnerable populations facing access

barriers associated with low educational levels, socioeconomic status, health education, and psychoactive substance abuse (1).

In this sense, as nonphysician practitioners, pharmacists may assist hepatitis C patients with their health care (3, 4), considering that they can improve patients' access to treatment and health care services (5, 6) by working as part of multidisciplinary teams and by providing close and continuous clinical follow-up to ensure adherence to pharmacotherapy (1).

Although several authors have described the activities carried out by pharmaceutical providers in the prevention,

screening and management of hepatitis C, they have been published separately and there is no consolidated information on the subject. Therefore, the aim of this study was to identify and describe the activities and procedures performed by pharmaceutical providers in relation to the management of hepatitis C patients and, as a result, suggest a clinical pathway for the comprehensive management of this disease that considers the participation of pharmacists.

## METHODS

### Identification and selection of articles

A review was performed in PubMed/Medline and EMBASE using the following search strategies: (“Hepatitis C”[Mesh]) AND ((((((“Pharmaceutical Services”[Mesh]) OR “Pharmaceutical Services, Online”[Mesh]) OR “Pharmacy Service, Hospital”[Mesh]) OR “Community Pharmacy Services”[Mesh]) OR “Pharmacies”[Mesh]), and ‘hepatitis c’/exp AND ‘pharmaceutical care’/exp, respectively. Search filters: Full text access articles describing studies conducted in human beings and published in English or Spanish before March 31, 2019. Editorials, notes, pieces of news, opinions, abstracts presented in congresses, and original papers describing activities and procedures performed by pharmaceutical services aimed at the provision of care to hepatitis C patients were included.

The publications identified in the search were subjected to a paired analysis. Initially, the title and abstract of each record were reviewed for eligibility purposes. Subsequently, the full text of the preselected articles was read and those related to articles previously included or that did not provide new information were excluded. The search was complemented with other studies appearing in the reference list of the articles included for analysis and that were considered relevant for the purposes of the review (Figure 1).

### Data extraction and categorization of information

Data gathered from each article were inserted into a database that included the following variables: action/intervention, description of the activity, type of intervention (individual or collective), person in charge (professional pharmacist, technician or other), setting in which the activity was carried out (outpatient service, hospital, community or prison), health care categories (public health management, health promotion, diagnosis, treatment, rehabilitation or palliation) and references of the studies describing the intervention.

Actions and interventions identified were classified into categories based on the functions of the pharmaceutical service: promotion and prevention, administrative management, pharmaceutical care, research, and other support services.

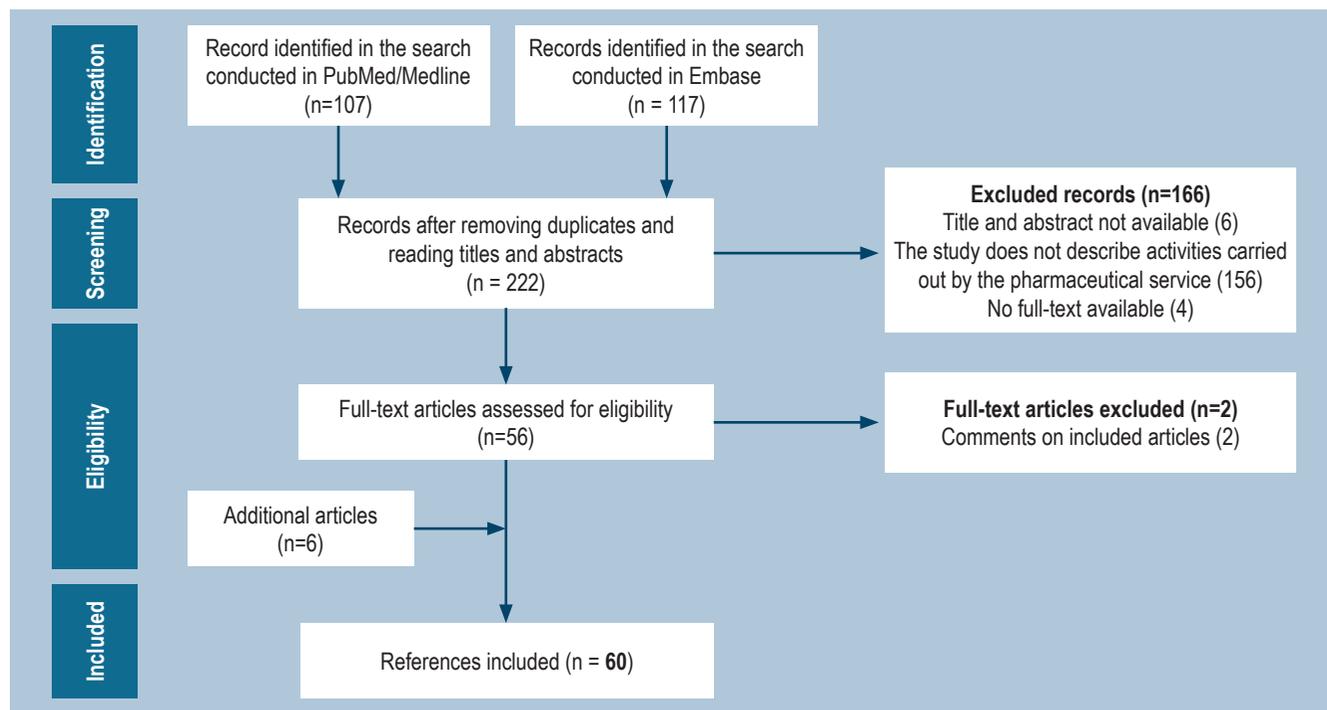


Figure 1. Flow diagram of the records included in the review.

To understand the results, the information retrieved from all articles included in the review was consolidated according to the actions and interventions described by them. Information on the strategies used to assess the quality of the interventions retrieved was also identified.

## RESULTS

### Identified studies

In total, 60 articles were included in the review (**Figure 1**); of these, 83% reported pharmaceutical activities carried out mainly in the United States (USA) and Spain. In addition, 45% were published between 2016 and 2019 (**Table 1**).

### Actions and interventions carried out by the Pharmaceutical Service for the management of chronic hepatitis C infection

**Table 2** lists the actions/interventions, the personnel in charge of them, the settings where they were performed, and the references of the articles describing them.

Four classifications were used to describe the setting:

1. Community, if the activities were carried out in pharmacies or drugstores, since they are usually located in neighborhoods and offer a service that is not related to other health care facilities.
2. Outpatient, if the activities were performed by pharmaceutical services and institutions providing outpatient services, that is, providing health services to patients who do not need hospitalization.
3. In-patient, when activities were developed during the provision of care to in-patients.
4. Prison, when activities were carried out during the provision of care to patients in the prison health system.

### Promotion and prevention

#### Patient information and education (7-11)

- Educational activities aimed at increasing public and individual awareness on the transmission mechanism of hepatitis B and C and how to prevent their infection.
- Provision of educational material on hepatitis C and visible posters in the pharmacy encouraging patients to ask for medical advice about their health problems.

#### Vaccine supply (8)

Provision of vaccination service including vaccines against hepatitis A and B and other vaccines that may be necessary in patients with chronic liver disease.

**Table 1.** Characteristics of the articles included in the review (n=60)

Characteristics	n	%
Type of publication		
- Original article	44	73.3
- Opinion	7	11.7
- Abstract or poster presented in a conference	6	10.0
- Piece of news	2	3.3
- Editorial	1	1.7
Type of study		
- Observational		
Descriptive	29	48.3
- Analytical Observational		
Cohorts	9	15.0
- Intervention analysis		
Quasi-experimental	2	3.3
Randomized clinical trial	1	1.7
Open-label trial	1	1.7
Pilot study	2	3.3
- Reviews		
Narrative review	3	5.0
Systematic review	1	1.7
Economic studies	1	1.7
Not applicable	11	18.3
Country where the study or publication was conducted		
- USA	36	60.0
- Spain	14	23.3
- Brazil	2	3.3
- Other	8	13.3
Year of publication		
- 2000-2005	5	8.3
- 2006-2010	11	18.3
- 2011-2015	17	28.3
- 2016-2019	27	45.0

### Harm reduction services (9, 12-16)

Key services to prevent sexually transmitted infections in at-risk population groups such as injecting drug users (IDUs). They may include:

- Education interventions and delivery of educational materials on human immunodeficiency virus (HIV), HCV, and the provision of sterile syringes, either over-the-counter or in syringe exchange programs.
- Provision of sharps containers for needle disposal.
- Provision of sterile items such as syringes, needles, water, and metal lids.
- Disposal of used syringes.
- Initiation of Naloxone administration by the pharmacist (according to the protocols established for the management of opioid overdose).
- Training or information on how to inject safely and prevent overdose.

**Table 2.** Actions and interventions carried out by the Pharmaceutical Service for the management of chronic hepatitis C infection: results of the review.

Category/Activity	Type of intervention	Person in charge	Setting	Categoría	Category
Promotion and prevention					
- Patient information and education	Individual and collective	Pharmacist	Community	Public health management	(7-11)
- Vaccine supply	Collective	Pharmacist	Community	Public health management	(8)
- Harm reduction services	Collective	Pharmaceutical personnel (professional, technician)	Community	Public health management	(9, 12-16)
- HCV screening	Collective	Pharmacist	Community	Diagnosis	(7-10, 17-21)
Administrative management					
- Administrative support (treatment authorization)	Individual	Pharmaceutical staff (professional, technician or pharmacy students); nurse specialized in liver disease	Outpatient Community	Treatment	(1, 6, 20, 22-26)
- Procurement and distribution of drugs	Individual	Pharmacist	Outpatient In-patient	Treatment	(8)
Pharmaceutical care					
- Drug dispensing	Individual	Pharmaceutical staff (professional, technician or pharmacy students)	Outpatient Community	Treatment	(1, 22, 25, 27-31)
- Pharmacotherapy-related follow-up (face-to-face or by telephone)	Individual	Pharmacist	Outpatient In-patient Community	Treatment	(1, 3, 5, 8, 10, 20, 25, 27-30, 32-48)
- Patient education and promotion of adherence to treatment	Individual	Pharmaceutical staff (professional, technician or pharmacy students)	Outpatient In-patient Community	Treatment	(8, 11, 20, 23, 27, 30, 32-36, 38, 40, 46, 49-51)
- Pharmacovigilance: detection, evaluation, notification of adverse drug reactions and recommendations for their management	Individual	Pharmacist	Outpatient In-patient Community	Treatment	(1, 8, 11, 22, 29, 33, 35, 36, 38, 45, 47, 52, 53)
Research					
- Clinical research	Collective	Pharmacist	Outpatient In-patient	Public health management	(8)
Other support services					
- Development of information and clinical decision support systems	Collective	Pharmacist, medical specialists, computer expert	Outpatient In-patient Prison	Public health management	(20, 33, 44, 45, 54)
- Participation in multidisciplinary teams	Individual	Pharmacist	Outpatient In-patient	Treatment	(33)
- Support and activities during the transition of patients from one level of care to another	Individual	Pharmacist	Outpatient In-patient	Treatment	(3, 8, 33)
- Support Group	Collective	Multidisciplinary team	Community	Health promotion	(55)
- Sending motivational letters and emails	Individual	Pharmaceutical staff (professional, technician or pharmacy students)	Outpatient	Treatment	(56)
- Provision of training to health professionals	Collective	Pharmacist	Outpatient In-patient	Public health management	(8, 47)

- Provision of condoms for free and referral to social services, referral centers or medical care services for treatment.

### **HCV screening (7-10, 17-21)**

Provision of rapid HCV tests followed by a counselling or referral to a physician process depending on the test result.

## **Administrative management**

### **Administrative support (1, 6, 20, 22-26)**

Collecting information on the patient's baseline clinical parameters (laboratory results, fibrosis staging, clinical notes made by the medical staff) and sociodemographic data to complete pre-authorization records required by insurance companies, the health system or health care providers. This information can be recorded in the patient's medical record. If a comprehensive program is available, pharmacists can request the delivery of the medication in the patient's pharmacy of choice and schedule a visit to initiate treatment.

### **Procurement and distribution of drugs (8)**

Besides the usual medication procurement and dispensing process, pharmacists can identify patients at risk of non-adherence based on their medication refill history. They can also ensure that patients get their prescribed medications on time, speed up the pre-authorization process, and make sure all drugs are updated in the pharmacy system to check for possible drug interactions.

## **Pharmaceutical care**

### **Drug dispensing (1, 22, 25, 27-31)**

The drug dispensing process may be carried out during the follow-up consultation with the pharmacist by arranging with the patient whether the medications will be dispensed at the nearest pharmacy, delivered to their home, or directly provided in observed therapy. In some contexts, pharmacy students may be available to check with the patient over the telephone if their prescribed drug has been delivered to the pharmacy.

### **Pharmacotherapy-related follow-up (face-to-face or by telephone) (1, 3, 5, 8, 10, 20, 25, 27-30, 32-48)**

This process aims at improving adherence to treatment and, therefore, at having a higher probability of achieving sustained virologic response and preventing the development of resistance. It allows for the early detection and resolution of drug-related issues that may arise during treatment.

It is usually performed monthly in person or via telepharmacy, depending on the needs of the patient needs and available resources. Follow-up can be complemented with

periodic phone calls, especially in patients in whom risk factors for non-adherence have been identified.

This type of follow-up involves:

- Initial assessment by the pharmacist (a pharmaceutical interview aimed at collecting sociodemographic and social history [alcohol consumption, drug abuse] data), of health conditions, history of allergies, outpatient pharmacotherapy (active ingredients, dosage regimen and route of administration), prescription type and use of alternative therapies.
- Pharmacotherapy validation.
- Immunization history review.
- Verification of laboratory tests orders and drug prescriptions.
- Evaluation of adherence to treatment and its effectiveness.
- Pharmaceutical intervention (if applicable).
- In the event the patient consumes alcohol or psychoactive substances, the pharmacist can provide information on the importance of alcohol withdrawal and recommend places to support the abandonment of such substances.

### **Patient education and promotion of adherence to treatment (8, 11, 20, 23, 27, 30, 32-36, 38, 40, 46, 49-51)**

This is an ongoing process that takes place during the follow-up visits; however, the first visit is key, since this is where basic information about hepatitis C and its treatment is discussed, therapy goals are established, and the importance of adherence to medication and follow-up is stressed to the patient. This process allows for the tailoring of management strategies to the individual needs of the patient, thus optimizing the treatment outcomes.

Topics to be addressed:

- Hepatitis C (HCV genotype, its association with treatment duration and likelihood of cure, severity of the disease, measures to reduce the risk of transmission).
- Treatment (route of administration and how to store the drug, what to do if a dose is missed, drug interactions).
- Adverse drug reactions and how to manage them. The patient may be instructed to take note of any uncomfortable experience during treatment and may be advised to adopt, preferably, non-pharmacological strategies to improve drug tolerance. In this way, pharmacists can dissuade the patient from abandoning treatment.
- Lifestyle changes to limit disease progression, such as avoiding alcohol use.
- Indications about that, in case of visiting the emergency room or requiring hospital admission, patients should bring antiviral drugs with them since treatment may not be available in those facilities.

Providing written information (physical or digital) and using tools to improve adherence to treatment, such as pill organizers, reminders, and medication taking schedules is recommended. Refill reminders may also be used to remind patients to pick their medications on time or have them delivered to their home. Alarms may also be created on patients' mobile devices to remind them when to take their medications.

### **Pharmacovigilance (1, 8, 11, 22, 29, 33, 35, 36, 38, 45, 47, 52, 53)**

Since DAAs are mainly characterized by symptomatic adverse drug reactions, timely review by pharmacists and consultation with physicians may result in interventions such as monitoring, dose reduction, change or prescription of medications, and recommendation of non-pharmacological measures for symptomatic management, to avoid early treatment discontinuation or lack of patient adherence.

Pharmacists conduct this review usually during follow-up visits or at the time of dispensing the drugs, when patients are asked about the adverse effects commonly associated with antiviral treatment, and lab tests are reviewed to monitor the occurrence of adverse drug reactions. Then, any detected reaction is reported to pharmacovigilance systems with complete information of the drug.

Similarly, the pharmacovigilance process should include the review of safety reports prepared by agencies for drug regulation and the notification of other health professionals.

### **Research (8)**

This item includes taking part in the development of clinical trials on novel therapies and writing research articles on the use of antiviral drugs in different patient populations. Pharmacists may actively collaborate with other health care providers in several types of research, such as efficacy and safety, pharmacokinetics, and pharmacoeconomics studies.

### **Other support services**

#### ***Development of information and clinical decision support systems (20, 33, 44, 45, 54)***

This item comprises the development of information and clinical decision support systems that can help promote the quality and efficiency of the health care process. They can be as complex as institutions want to make them. The simplest ones could be clinical guidelines that set standard criteria for the selection of patients that will undergo treatment, treatment protocols for special population groups (elderly, chronic kidney disease, children, among others), details of the health care process and indications for the management

of drug interactions, all in compliance with clinical practice guidelines implemented in each country.

More complex systems allow recording patients' clinical information using their medical records, assessing patients' adherence to antiviral therapy, and even generating automated pharmaceutical events and warnings regarding the efficacy and safety of the pharmacological therapy. These systems can ease pharmacotherapy-related follow-up by automatically incorporating hematological, biochemical, and microbiological analyzes from laboratory databases, and providing real-time data for statistical processing and analysis.

#### ***Participation in multidisciplinary teams (33)***

This involves the creation of working groups with various health professionals responsible for the provision of health care to patients with hepatitis C, including pharmacists, to discuss individual cases in order to reach a consensus on the most suitable and cost-effective treatments.

#### ***Support activities during the transition of patients from one level of care to another (3, 8, 33)***

Clinical pharmacists' involvement in patient transfers from one level of care to another between health care institutions (for example, from a hospital to an outpatient clinic or vice versa). Clinical pharmacists have the possibility to train medical and health care staff on the importance of the continuity of treatment of hepatitis C, adverse events, and drug interactions. Some of these processes include medications reconciliation, coordination, and procurement.

#### ***Support group (55)***

These groups aim at offering support to hepatitis C patients, as well as their friends and relatives. In this context, educational sessions discussing general symptoms of the disease, treatment, adverse drug reactions, diet, liver effects, the emotional impact of being diagnosed with hepatitis C infection, alternative treatments, access to health services, personal experiences, and other topics may be arranged for each month of the year.

#### ***Provision of training to health care professionals (8, 47)***

This item refers to the provision of training to health care professionals on disease complications, treatment criteria, and proper use of medications in accordance with clinical practice guidelines. Depending on the context, these training sessions can be done either face-to-face or through online conferences. This action may encourage the creation of clinical discussion boards.

#### ***Sending motivational letters and emails (56)***

This is a strategy to encourage adherence to treatment by sending motivational letters to patients, as well as responding to their requests for information.

## Assessment of the activities carried out by pharmaceutical services in the provision of health care process

Pharmaceutical providers should offer more than just health services; they should also provide quality assurance processes. As a result, metrics must be built to assess the effects of pharmaceutical professionals' practices and to record information about patients who have been treated (3).

Patient compliance rates, usage habits, adherence to treatment recommendations, treatment efficacy, incidence rate and severity of drug-related problems and adverse drug reactions, degree of avoidable drug-related problems, costs, and patient satisfaction are some of the metrics that can be considered (29, 44, 45, 47).

Management indicators should be presented periodically to the work team (33) and other health professionals, using presentations, live online broadcasts, web publishing or e-mail distribution (47).

### Cost assessment

The role of pharmacists in the care of hepatitis C patients is critical in cost containment, mainly by preventing unnecessary medical expenses through therapy optimization (8, 44, 57). For this reason, they should participate in health care-related costs (54), costs saved due to pharmaceutical interventions (28, 32), and return on investment (32) analyses, since this information contributes to justifying the implementation or expansion of pharmaceutical care services (58).

Lavitas et al. analyzed cost saving following a comprehensive HCV drug treatment program in cooperation with the Clinical Pharmacy Services of the University of Massachusetts and the Massachusetts Medicaid program in USA, finding that optimizing treatment regimens avoided spending more than \$3.7 million in patients who completed treatment (32).

In addition, Radley et al., in a study comparing the costs of conventional HCV care (in hospitals) to pharmacist-led care (in primary care clinics), found that the latter could reduce costs by up to 74.4% (£ 933 vs. £ 238), since this type of care require less expensive facilities and simplified testing and monitoring requirements. Also, a comprehensive care program may increase the number of people who can access treatment and shorten the time it takes for people with HCV infection to be cured (10).

### Patient satisfaction assessment

Pharmaceutical services have been introduced in a variety of settings; however, there are few studies assessing patient satisfaction with the services provided, especially in the field of hepatology (23). Robustillo et al. reported the need

to measure patient satisfaction as it allows knowing their opinion on the services and therapies they receive, as they consider it *a measure of outcome in direct health care* (39).

The most common period to assess patient satisfaction is when the care process ends, although some studies, such as the one conducted by Menchen et al., have evaluated the difference in satisfaction levels of patients with HCV with the intervention carried out prior to the implementation of the comprehensive care model for these patients and 6 months later (59).

In addition to service satisfaction, clinical satisfaction can also be assessed (39). Key aspects to be evaluated may include satisfaction with treatment (effectiveness, adverse reactions, and treatment modifications) (39), satisfaction with the information received (lifestyle and vaccination recommendations, and education interventions about hepatitis C management and treatment), and satisfaction with service (waiting times, accessibility to the health care provider, ability of the health care provider to handle questions and complaints, and referral to other services, if required) (23, 40, 59).

### Assessment of HCV knowledge

A questionnaire may be administered before and after a training session to determine the impact of the pharmacist's instruction on the awareness of the patient or health practitioners in topics such as transmission process, treatment, and adverse reactions, in order to find out about the initial and final state of HCV knowledge (7, 17).

### Use of technologies in pharmaceutical practice

The inclusion of information and communication technologies (ICTs) in pharmaceutical practice (telepharmacy) has resulted in shorter treatment times and increased patient access to health care services (5) because it facilitates the training and assistance provided by pharmaceutical staff even after hours (hotline 24/7), when the pharmacist is out of the workplace, or when patients reside in rural areas and travel distances must be reduced (5, 8, 22, 48, 49, 56).

Likewise, telepharmacy allows pharmacotherapy-related follow-up in patients living in remote areas and who cannot travel to hospitals for face-to-face visits (5, 22), monitoring the incidence of adverse events, providing guidance on over-the-counter medications for their management, and, if necessary, referring patients to a doctor (60). Grisheau et al. described a model in which telephone contact with the patient was arranged two weeks after starting the treatment. Calls were made every four weeks to assess adverse effects, adherence to the treatment plan, the need for drugs refills, and ensure that patient health details and appropriate tests were followed up on. All of these calls were entered into

each patient's electronic medical record and sent to their attending physician. It is worth noting that follow-up calls were alternated with follow-up visits at the hospital, so that patients had at least some kind of contact with the medical staff every two weeks during treatment (27).

Similarly, ICTs can be used to remind patients using emails, mobile messages, or calls, about their paperwork, appointments, or medical check-ups and routine laboratory tests, or to assess the hepatitis C-related quality of life in these patients (25, 30).

### Proposal of a clinical pathway for the management of hepatitis C that considers the participation of the pharmacist

This proposal, which includes the perspective of pharmaceutical services (Figure 2), is based on the guidelines suggested by the Colombian Ministry of Health and Social Protection



**Figure 2.** General flow diagram of the proposed clinical pathway for the management of hepatitis C with the involvement of the pharmacist. Adapted from: Colombian Ministry of Health and Social Protection - Instituto de Evaluación Tecnológica en Salud. Vía clínica para el tratamiento de hepatitis C (Clinical pathway for the treatment of hepatitis C). Bogotá, D.C: Ministerio de Salud y Protección Social; 2017.

for the management of hepatitis C (61). The findings of this review were incorporated into the Ministry's proposal.

When applying this model in specific contexts, the regulations that govern the practices of pharmacists, the practices they are authorized to perform, the available services, and the degree of interconnection between health care professionals, health care provision environments, and the different health care provision processes should be considered.

The general treatment flow diagram is shown in Figure 2.

### Promotion, prevention, screening, and diagnosis

People infected with HCV can be screened in three settings: community, outpatient, and inpatient, either by pharmaceutical or nursing staff (Figure 3). Initially, carrying out educational talks about the disease and risk factors for infection is suggested. Afterwards, a checklist may be administered to those who agree to identify behaviors or risk factors for infection. People with risk factors may be screened with rapid anti-HCV tests, depending on their availability. Any positive result must be confirmed by performing an HCV RNA test.

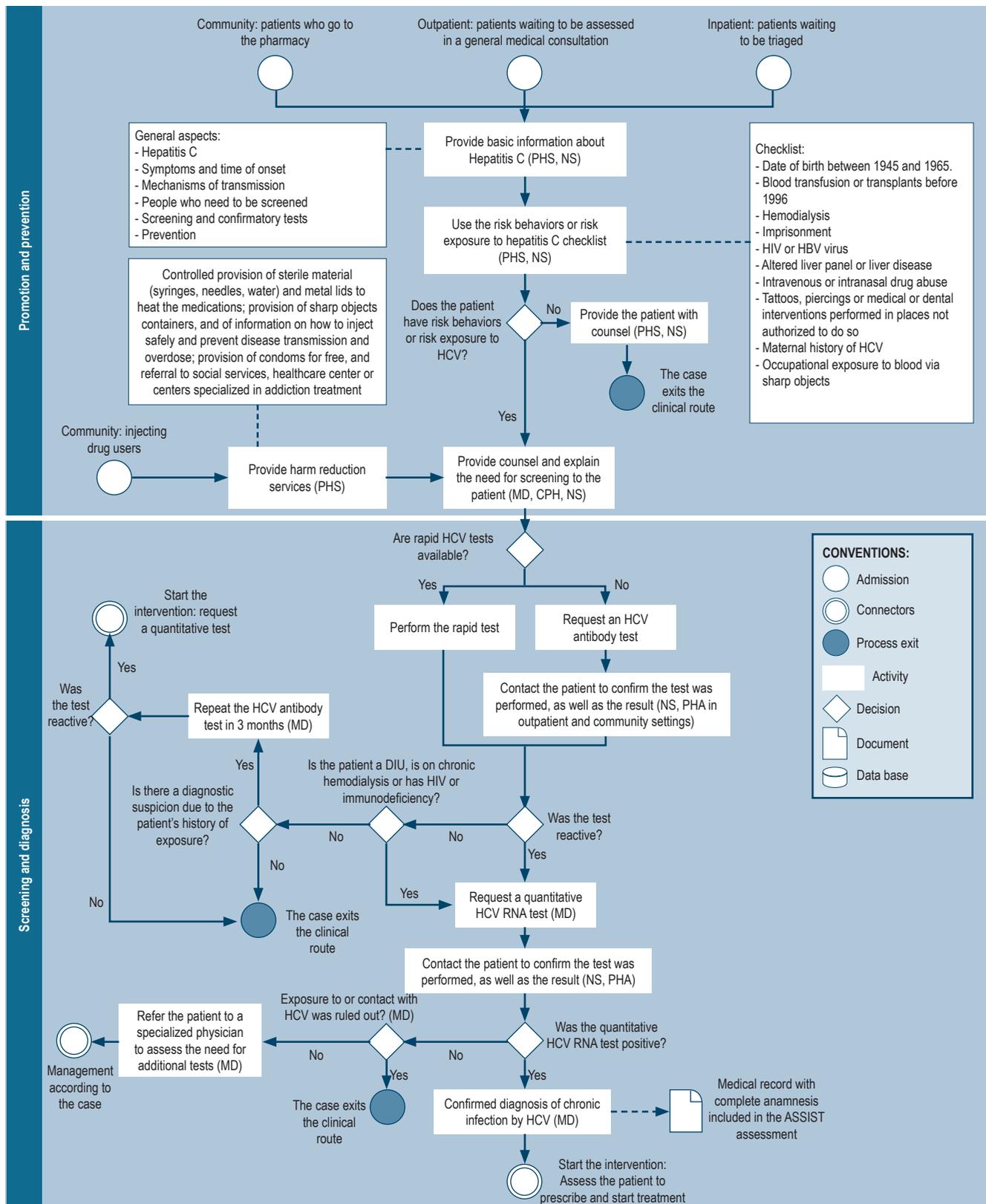
The role of community pharmacists in the detection of HCV patients is crucial because people who are not linked to the health system and who are at risk of HCV infection initially seek assistance from community pharmacies. Therefore, rapid HCV testing, as well as pharmaceutical staff trained to use these tests should be available at this level of care, since this could favor the identification of people with undiagnosed HCV (21). In this way, the community pharmacy may serve as an HCV patients recruitment node, in particular the most vulnerable population groups, such as low-income people and IDU, as well as provide support in the prevention of this disease and its transmission and in connecting the patient to health care centers.

### Assessment of patients for the prescription and initiation of treatment

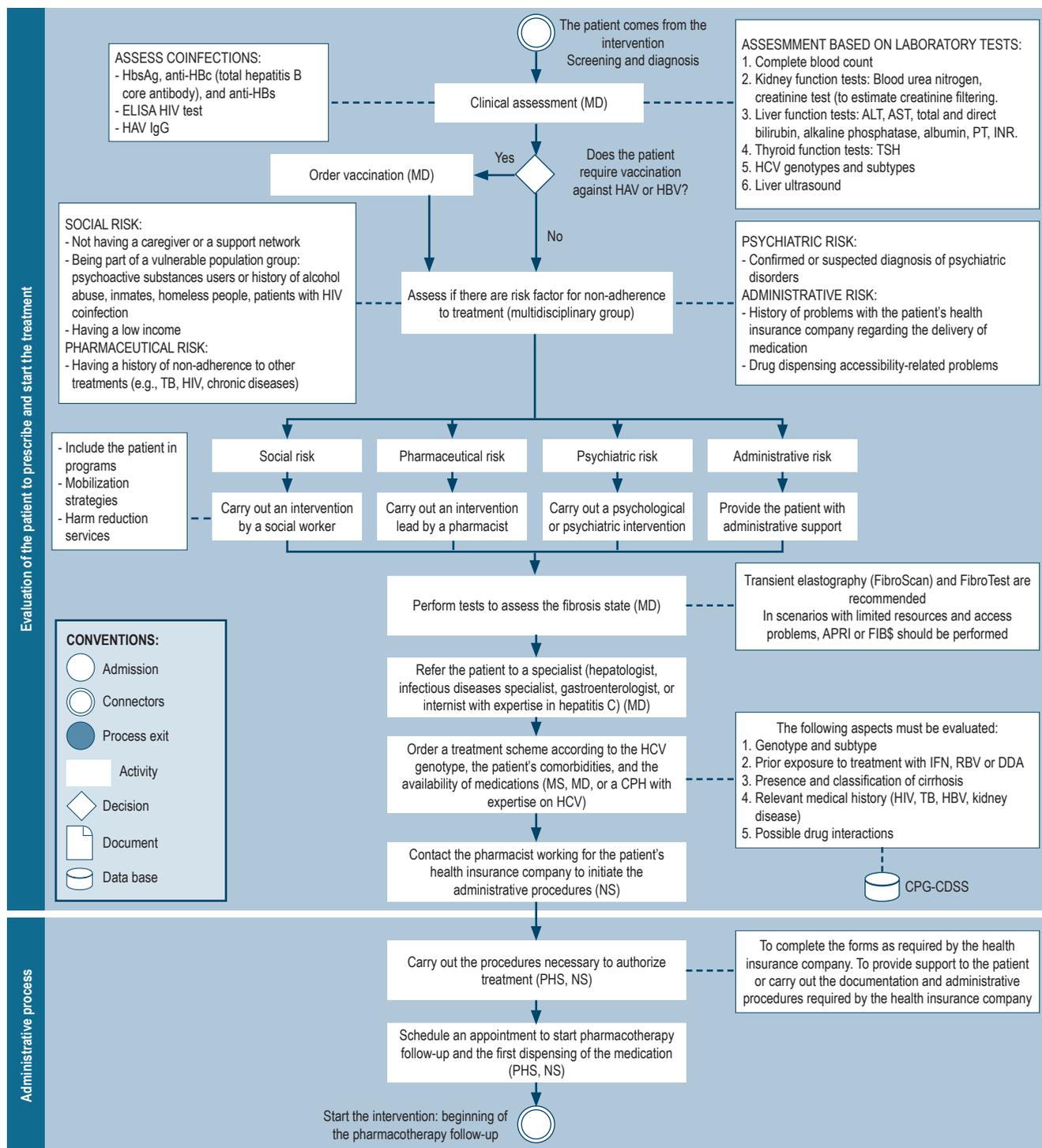
Patients with a confirmed diagnosis of chronic hepatitis C must be evaluated by medical staff in order to initiate treatment. Furthermore, the support of a multidisciplinary team (53), which could be composed of medical, nursing, social care, psychology, and pharmaceutical professionals, is recommended to assess potential risks of non-adherence to treatment and to timely reduce any access barriers and achieve the therapeutic goals (Figure 4).

### Administrative process

Due to the high costs of DAAs, strategies such as the pre-authorization process have been required to control spen-



**Figure 3.** Pharmaceutical promotion and prevention, screening, and diagnosis. NS: nursing staff; CPH: clinical pharmacist; MD: medical doctor; PHS: pharmacy staff (including technicians, professionals, or support students); PHA: pharmacy assistant; IDU: injecting drug user; HCV: hepatitis C virus, HIV: human immunodeficiency virus.



**Figure 4.** Evaluation of patients for the prescription and initiation of treatment; administrative process. \*Depending on the circumstances, general practitioners or clinical pharmacists who have expertise in hepatitis C may prescribe DAAs after having consulted with a specialist and assessing the patient's clinical parameters, medical record, comorbidities, and potential contraindications to the therapy, in accordance with the country's clinical practice guidelines. HBsAg: hepatitis B surface antigen; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ELISA: enzyme-linked immunosorbent assay ; NS: nursing staff; CPH: clinical pharmacist; HB: Hepatitis B; Hb: Hemoglobin; IFN: interferon; CPG: clinical practice guideline; INR: international normalized ratio; MD: medical doctor; MS: medical specialist (hepatologist, gastroenterologist, infectologist, or internist with experience in the treatment of hepatitis C); PHS: pharmacy staff (including technicians, professionals, or support students); PT: prothrombin time; RBV: ribavirin; CDSS: clinical decision support system; TB: tuberculosis; TSH: thyrotropin; HBV: hepatitis B virus; HCV: hepatitis C virus.

ding within health systems. Insurance providers use this procedure to assess whether care is medically necessary and sufficient based on the patient's diagnosis and condition (6). Pharmacists have assisted in the coordination of this process by working in medication acquisition and dispensing (2, 6, 22, 23, 25-27, 36), therapy optimization, and expenditure control (Figure 4) (44).

### Pharmacotherapy follow-up

Due to the recent commercialization of new DAAs, intensive pharmacotherapy-related follow-up programs are expected to track the safety and efficacy of these drugs in clinical practice (28). This is an active process in which the pharmacist works as part of a multidisciplinary team in order to make a comprehensive assessment of the patient, their diseases, and treatments, allowing for the timely identification of potential and actual drug-related problems (8).

Pharmacotherapy follow-up begins before treatment is started (Figure 5) and continues throughout the course of treatment. It consists of several activities:

- Initial assessment by the pharmacist (pharmaceutical interview): this is the first encounter of the patient with the pharmacist. Its aim is to establish a relationship of trust based on active listening and empathy. The patient's concerns regarding their condition and care are addressed in this initial meeting, which is focused on recognizing their expectations (36).
- Validation of pharmacotherapy: the pharmacist reviews the medical prescriptions and verifies their suitability, as well as that of the antiviral scheme selected in compliance with clinical practice guidelines, by using the details obtained during the pharmaceutical interview and the patient's medical record (considering the genotype, staging of cirrhosis status, and history of previous treatment). Also, the pharmacist considers other conditions resulting in contraindications to the therapy (1, 3, 8, 10, 25, 27, 29, 30, 32, 33, 35, 37, 41, 42, 44-48). It should be noted that in countries where no pangenotypic schemes are available, viral genotype evaluation is necessary to personalize therapy and offer cost-effective treatments (57). The validation of pharmacotherapy is a strategy for the prevention, identification and resolution of medication errors (28) or drug-related complications (8, 29), which may include the use of alternative drugs or therapies that may interfere with antiviral treatment, drug-disease interactions, or the need to improve the management of conditions other than hepatitis C in these patients (8). In some contexts, the pharmacist must ensure that the prescribed treatments are in accordance with the pharmaceutical benefit plans

established by the institution or country, as is the case with the Veterans Health Administration in the United States of America (3).

### Review of immunization history

It comprises the evaluation of the patient's immunization history and the need for vaccines against hepatitis A and B viruses, influenza, and pneumococcal disease (8, 48).

### Verification of laboratory tests orders and drug prescriptions

The pharmacist verifies that the medication prescriptions are appropriate for the length of treatment, as well as the laboratory tests orders required for follow-up (3). In certain countries, the pharmacist has the authority to prescribe or modify, in accordance with the treatment protocol and with the physician's signature, the medications and laboratory tests required to determine the safety and efficacy of therapy (3, 34, 48).

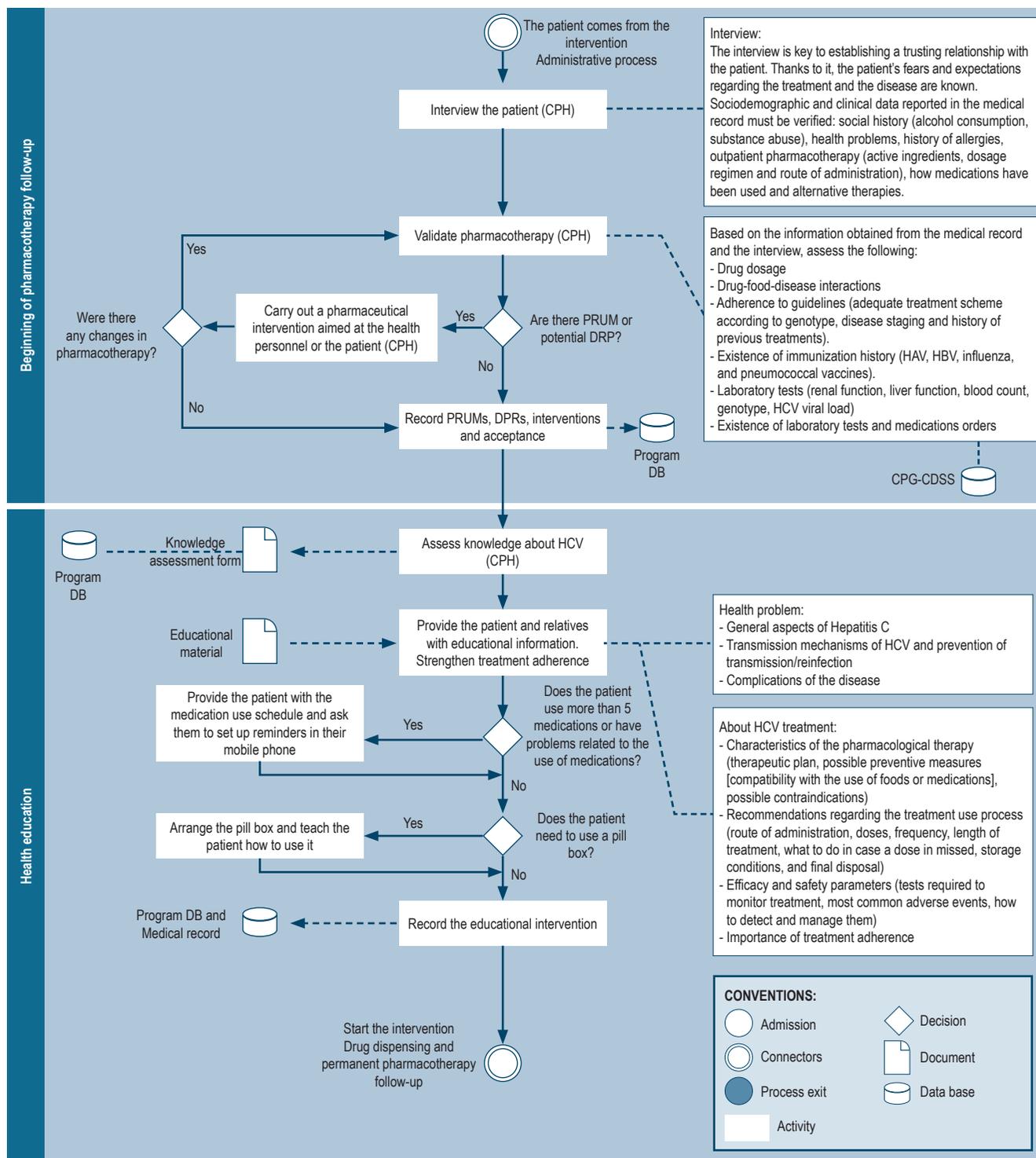
### Health education

The pharmacist's participation in health education may solve the limited time availability that medical providers must advise patients on disease status and proper use of medications. This can positively impact the patient's adherence to hepatitis C treatment and increase cure rates (8).

In addition to the individual educational phase, support groups may be formed to provide support to patients with hepatitis C (Table 2), which improves their awareness and perspective on the disease, as well as the visibility and perception of the role of the pharmacist as a community health care provider (55).

**Table 3.** Types of pharmaceutical interventions

Oriented to the pharmacological strategy or quantity of the drug	- Provide recommendations for therapy and dosage adjustments
Oriented to treatment monitoring	- Recommendations for issuing or modifying laboratory tests orders
Oriented to the health care process	- Refer the patient to specialists or other services - Renew drugs prescriptions - Request vaccination - Modify the route of administration
Oriented to patient education	- Promote adherence (decrease voluntary non-compliance by changing the patient's attitudes about treatment)



**Figure 5.** Beginning pharmacotherapy-related follow-up and health education. DB: database; CPH: clinical pharmacist; CPG: clinical practice guideline; PRUM: problems related to the use of medications; DRP: drug-related problems; CDSS: clinical decision support system.

## Drug dispensing

Drug dispensing can occur during the pharmacotherapy-related follow-up consultation with the pharmacist (28,

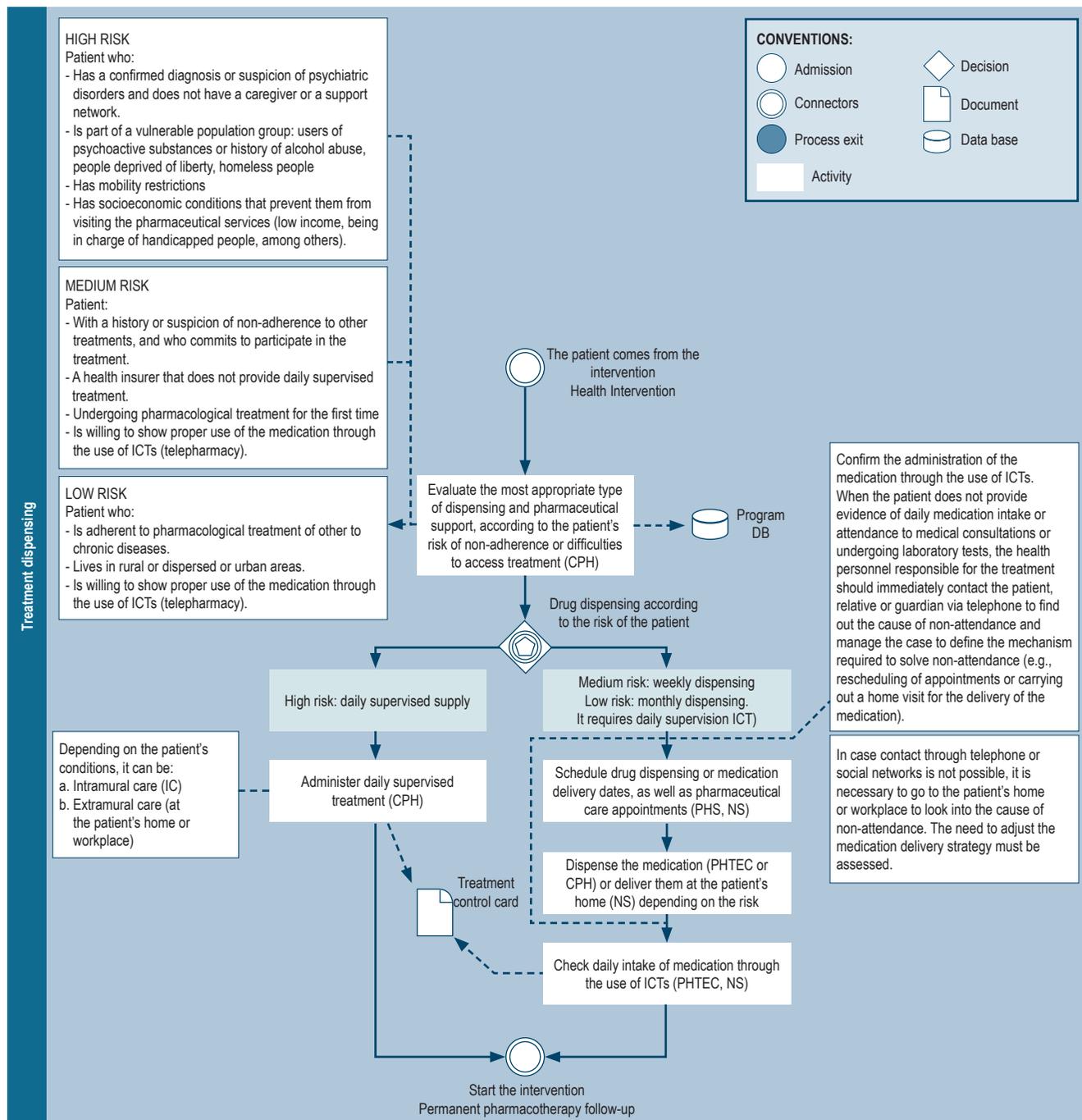
29) by coordinating with the patient if medications will be dispensed at the nearest pharmacy (25, 27), delivered at their home (1, 22, 30), or through directly observed therapy (also known as *daily controlled supply*), where patients

receive daily treatment, and in the case of doses to be used during the weekend (i.e. when the drug administration is in charge of the patient), the pharmacist and the patient can develop an action plan to perform this activity (31).

The dispensing modality depends on the context, the available services, and the patient's needs. Thus, assessing

the adherence of the patient adherence, as well as data on sociodemographic factors and clinical conditions is suggested to establish the most appropriate dispensing modality and frequency (Figure 6).

To monitor adherence to treatment, a record of the dispensation of medications should be kept and, if directly



**Figure 6.** Treatment dispensing. DB: database; NS: nursing staff; CPH: clinical pharmacist; PHS: pharmacy staff (includes technicians, professionals, or support students); PHSE: pharmaceutical service; CDSS: clinical decision support system; PHTEC: pharmacy technician; ICT: information and communication technologies; HCV: hepatitis C virus.

observed therapy is not used, checking the drug intake using ICTs is suggested.

### Permanent pharmacotherapy follow-up

In-person pharmacotherapy follow-up visits may be conducted every 28-30 days and include, besides the activities described in the initial phase of pharmacotherapy follow-up (Figure 7), the following actions:

- Verification of medications introduced or excluded from the patient's pharmacotherapy (35).
- Evaluation of treatment efficacy by reviewing laboratory findings such as viral load and liver function tests.
- Detection, evaluation and notification of adverse drug reactions and recommendations for their management: treatment safety is assessed by means of the patient interview and the review of lab test results (blood count, thyroid tests [for ribavirin or interferon therapy] and kidney function) (8, 19, 22, 30, 35, 36, 42, 47).
- Assessment of patient adherence: this assessment can be made by asking questions about medication use (36), inspecting the packaging of the tablets dispensed to the patient (49), analyzing drug dispensing dates reported in information systems (1, 8, 23, 33, 41, 44, 47), and keeping records of medication use (10). Adherence measurement questionnaires such as Morisky-Green (40, 43), Haynes-Sackett (38), or a visual analogue scale (VAS) on which the patient assesses compliance (40) may also be used.
- Support actions during the transition of the patient from one level of care to another: If the patient is to be treated at a hospital, whether for the treatment of an adverse reaction or complications cause by their diseases, the pharmacist must provide support to ensure medication reconciliation and therapy continuity in said situation.

### Pharmaceutical care

Medication errors or problems related to actual or potential medications may be detected in pharmaceutical practice, or patient therapy may need to be optimized, leading to interventions to the medical or nursing staff or the patient, depending on the circumstances (Table 3) (1, 3, 8, 19, 22, 23, 28-34, 37, 41, 42, 45, 58, 60). All interventions and suggestions made by the pharmacist, including appointments, phone calls, pharmacotherapy evaluations, and all activities related to patient counseling and adherence, should be recorded in the patient's medical record or in the information systems (8, 60).

### Case closure

The case may be closed when the patient completes treatment and is cured (sustained virological response:

undetectable viral load 12 weeks after the end of treatment), when the patient dies, or when the patient wishes to discontinue the treatment (Figure 8). A follow-up consultation is suggested between 6 and 12 months after achieving sustained virological response, especially in patients susceptible to reinfection (IDU, people living with HIV, men who have sex with men, patients on hemodialysis, sex workers). Additionally, patients with advanced stage cirrhosis or hepatocarcinoma should continue to see their specialist physician as usual (hepatologist or gastroenterologist). The quality of the care provided should be measured at the end of the care process using satisfaction questionnaires.

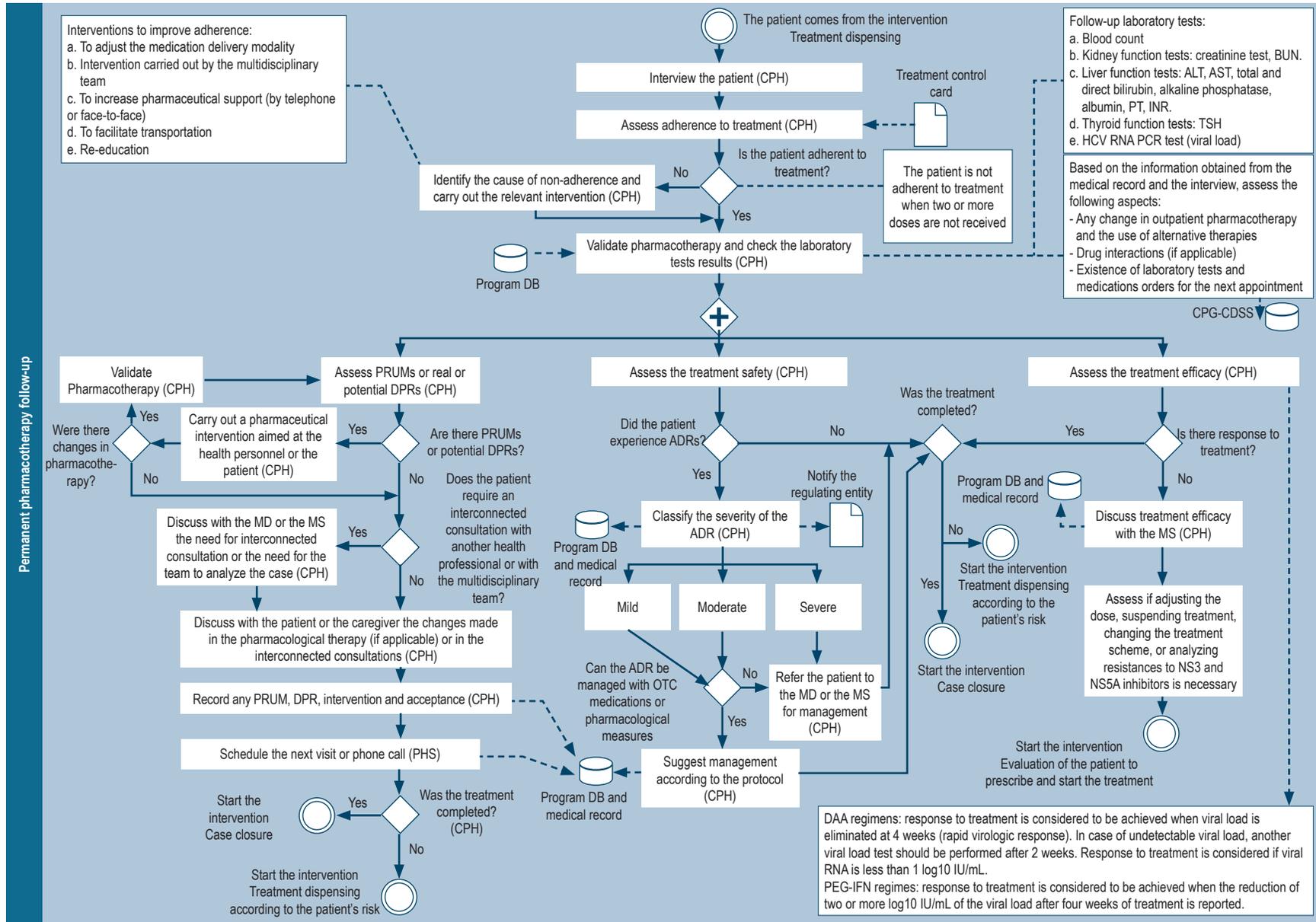
## DISCUSSION

The involvement of pharmaceutical services in the care of patients with hepatitis C, besides promoting adherence and improving clinical outcomes, may minimize treatment costs by promoting therapy optimization (44). Their participation in outpatient, community and inpatient settings is not only essential to the population enrolled in health systems but is also critical for individuals who do not usually use the health care system, either due to insecurity or non-affiliation, since they often use this form of pharmaceutical services to receive some kind of assistance. In this sense, implementing the procedures outlined in this review could expand care coverage to the affiliated population, while also promoting prompt diagnosis and treatment in vulnerable population groups and non-users of the health system. In addition, a comprehensive provision of health care services to these patients enhances cooperation between pharmacists and other health professionals, which would allow assessing the safety of DAAs.

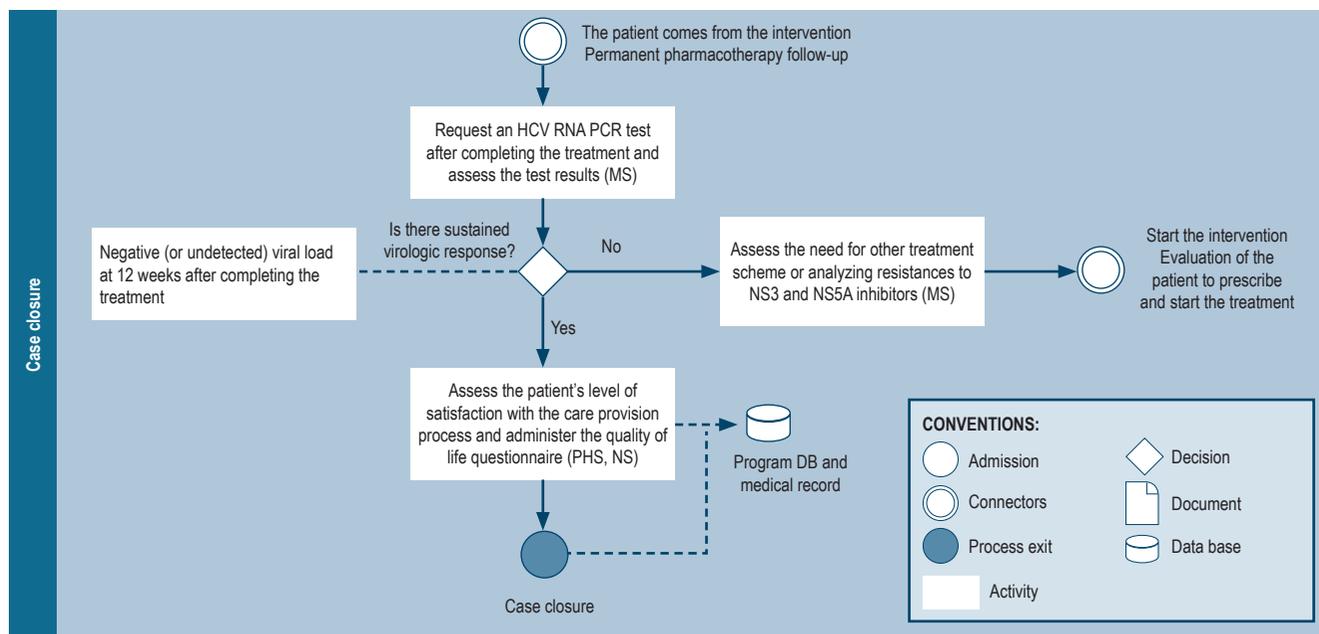
Consequently, a clinical pathway for the treatment of patients with hepatitis C complemented by pharmacy service actions/interventions is presented here. Depending on the context of each country, the existing legislation, the available resources, and the degree of interconnection between health professionals, and health care settings, this strategy may be adapted for its implementation. It may also be used to treat other sexually transmitted diseases and other costly chronic diseases.

### More relevant findings

This review identified the activities carried out by pharmaceutical services in the management of hepatitis C, which allowed proposing a clinical pathway for the management of hepatitis C management complemented by the actions/interventions of pharmaceutical services. It is important to note the actions of the pharmaceutical staff actions at each point of the care process, in which their role is extended



**Figure 7.** Permanent pharmacotherapy follow-up. DB: database; BUN: blood urea nitrogen; CPH: clinical pharmacist; MD: medical doctor; MS: medical specialist (hepatologist, gastroenterologist, infectologist or internist with experience in hepatitis C); NS3: non-structural protein 3; NS5A: non-structural protein 5A; OTC: over-the-counter drugs; PEG-IFN: Pegylated interferon; PHS: pharmacy staff (includes technicians, professionals or support students); PRUM: problems related to the use of medications; DPR: Drug-related problems; ADR: adverse drug reaction; CDSS: clinical decision support system.



**Figure 8.** Closing the case. RNA: Ribonucleic acid; DB: database; NS: nursing staff; MS: medical specialist (hepatologist, gastroenterologist, infectologist, or internist with experience in hepatitis C treatment); PHS: pharmacy staff (including technicians, professionals, or support students); HCV: hepatitis C virus.

beyond pharmacotherapy follow-up and is given an active participation in key processes such as HCV screening and the linking of patients to treatment. In this regard, Radley et al. and Dong et al. highlighted the importance of community pharmacies and opioid replacement services as potential places for performing HCV screening, particularly in people who are not enrolled in the health care system to promote timely detection of HCV and achieve an early onset of treatment (9, 10). Similarly, the provision of harm reduction services is of great importance to prevent HCV transmission, especially in high-risk populations such as IDUs (9, 12-16).

The participation of pharmacists in promotion and prevention activities should be considered, especially in the Colombian and Latin American contexts. To facilitate these services, a formal training plan is needed to enhance acceptability and foster positive attitudes among pharmacy workers (9, 12). Furthermore, public relations and marketing strategies are needed to increase the visibility of community pharmacists (pharmacies and drug stores) in this expanded role of patient care, as well as the establishment an operational model that allows pharmacist to receiving remuneration for their activity and the services offered (9).

Another process to consider is drug prescription, in which pharmacists have not played any significant role to date. However, since DAAs are easier to implement, as Galewitz et al. (4) and Radley et al. (10) have noted, clinical pharmacists specialized in hepatitis C may be able to

prescribe these antivirals (prior the approval by specialists, the review of clinical practice guidelines, the review of the patient's medical record, and the assessment of clinical parameters, comorbidities, and potential contraindications of antiviral therapy).

Pharmaceutical care can also support primary health care by shortening patients' waiting times to see a doctor. In the United States, for example, the training of clinical pharmacists in treating patients with hepatitis C has enabled them to prescribe drugs, request laboratory tests, refer patients to specialists, and perform physical examinations (4), so specialists are consulted only when necessary. With this type of adjustment, the agenda of specialists could be freed up to provide treatment to more chronic patients or to focus on patients with more specific needs.

Similarly, patient education by the pharmacist or a multidisciplinary team is highlighted as one of the most relevant practices to promote patient and family empowerment, as well as active involvement in health-related decision-making (8, 34).

Moreover, the use of ICTs in pharmaceutical practice has been shown to increase access to treatment in patients with hepatitis C and other chronic diseases (5).

### Similarities and differences between publications

During the search, no systemic reviews addressing our objective were found. Editorials such as the one authored

by Briggs (20) summarize the role of pharmaceutical staff in the management of hepatitis C; however, it only refers to the processes they are involved in, without detailing the activities these processes imply and the times required to carry them out. The *Joint Opinion of the GI/Liver/Nutrition and Infectious Diseases Practice and Research Networks* of the American College of Clinical Pharmacy (8) details all the roles that a clinical pharmacist may have, but it does not describe the activities that can be performed with the support of other pharmaceutical service staff such as pharmacy technicians or support students. This review, in addition to summarizing and describing each of the activities that were identified and the environment in which they are carried out, proposes a clinical approach for the management of HCV in which pharmaceutical staff (professionals, technicians and support personnel) are included within the care process and their interrelationship with other health professionals is considered.

Some of the interventions described in this review are restricted by Colombia's current regulatory framework, especially those related to treatment decision-making and treatment modifications, or the referral of patients to be vaccinated against other types of hepatitis. Therefore, the generation of evidence of the effectiveness of this type of intervention in cooperation with the health care team in the treatment of these patients, especially with treating physicians, is essential. In this regard, Briggs (20) states that the role of pharmaceutical workers as health care providers must be made clear, particularly for public policy makers, so that the latter consider these health workers as key players within the health care team, since they can contribute to meeting the health needs of patients and the community.

## Limitations of the review

The assessment of the quality of the studies was not considered as a criterion for the inclusion for full analysis of the articles, since the main objective of the review was to classify all the actions and procedures carried out by pharmaceutical services in the treatment of patients with hepatitis C setting and the contexts in which they were implemented.

## Indications and guidelines for future research

Real-life studies are needed to generate objective evidence of the impact that the clinical pathway proposed in this review might have on the improvement of access to treatment, on clinical outcomes, and on the costs associated with the provision of health care to these patients.

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