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FULL PAPER

# Barriers to HCV micro-elimination in a cohort of people living with HIV (PLWH)

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SUMMARY

To achieve the World Health Organization goal of hepatitis C virus (HCV) eradication, barriers to treatment should be investigated and overcome. The aim of this study was to identify those barriers and describe the strategies adopted to achieve HCV micro-elimination in a cohort of coinfected people living with HIV (PLWH-HCV). Adult PLWH-HCV followed at our hospital with detectable serum HCV-RNA in 2018 were enrolled. After a three-year follow-up, barriers to HCV treatment were investigated and strategies to overcome them were described. Of 492 PLWH-HCV seen in 2018, 29 (5.9%) had detectable serum HCV-RNA. Eight out of 29 (27.6%) were excluded because they were already under treatment, while 2 others were excluded because they moved to other outpatient clinics. Among the remaining 19 study participants, the most common barriers to treatment were poor adherence to therapies and follow-up visits (n=9, 47%), recent HCV diagnosis awaiting proper staging (n=3, 16%) and treatment hesitancy (n=2, 10%). During the following three years, direct-acting antivirals (DAAs) treatment was completed in 11/19 (58%) cases, with achievement of sustained virological response in 100% of cases. For the remaining cases, 2/19 (10.5%) were lost to follow-up, 2/19 (10.5%) died before treatment initiation and 4/19 (21.0%) are still awaiting treatment. Despite 3 years of effort, HCV micro-elimination has not been achieved at our center. We observed that poor adherence and treatment hesitancy were the main barriers to treatment. Strategies addressing these issues need to be implemented.

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## INTRODUCTION

Chronic hepatitis C virus (HCV) infection is a major public health concern. According to World Health Organization (WHO) estimates, 71 million people worldwide were living with HCV infection in 2015 (World Health Organization, 2017). Because of these impressive data, the WHO developed a global strategy to eliminate viral hepatitis by 2030. The goals of this strategy include a 90% reduction of new HCV infections, 90% increase in HCV diagnosis, and 80% increase in treatment rates together with a 65% reduction in mortality (Mangia *et al*., 2021).

Among HCV chronically infected patients, about 2 million are living with HIV (PLWH), and the odds of HCV infection are estimated six times higher in PLWH than in the general population (World Health Organization, 2017) (Platt *et al*., 2016). HIV co-infection accelerates liver damage and is linked to higher rates of hepatic fibrosis, progression to liver failure, and liver-related mortality (Kirk *et al*., 2013). Additionally, intravenous drug use, psychiatric disorders and socio-economic difficulties may be present in PLWH and may represent perceived patient-related barriers to treatment uptake (Taylor *et al*., 2013) (Degenhardt *et al*., 2017).

Direct-acting antivirals (DAAs) are highly effective against HCV, with rates of sustained virological response (SVR) higher than 90%. On the other hand, a few side effects have been reported, even in the case of PLWH (Milazzo *et al*., 2017) (Navarro *et al*., 2017). Drug-drug interactions can occur between DAAs and antiretroviral therapy (ART), but are usually manageable and do not represent an obstacle to HCV treatment (Degenhardt *et al*., 2017).

Several barriers to HCV treatment initiation have been identified so far, including both patient-related barriers – such as treatment refusal or lack of access to treatment – and healthcare-related barriers – such

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as polypharmacy and management of active drug and alcohol use (Lazarus *et al.*, 2018).
In this context, different populations living with chronic HCV require dedicated programs (Day *et al.*, 2019) (Bruggmann & Litwin, 2013).
Since 2017, the European Association for the Study of the Liver (EASL) has adopted the micro-elimination strategy as a stepwise approach in the fight against HCV (Lazarus *et al.*, 2018), especially in defined subgroups of people, such as PLWH, prisoners, and people who inject drugs (PWID) (Stöver *et al.*, 2019) (Lazarus *et al.*, 2017).
The aim of the present study is to identify HCV treatment barriers and describe strategies adopted in a 3-year period to achieve HCV micro-elimination in a cohort of PLWH living with HCV (PLWH-HCV).

## METHODS

### *Study cohort*

This is a retrospective, single-center study. PLWH-HCV aged ≥18 years followed at the Infectious Diseases outpatient department of the San Martino Hospital in Genoa (Italy) were included if they had at least one detectable serum HCV-RNA. The study period for inclusion was from January 1, 2018 to December 31, 2018, after which patients included were followed up until January 31, 2022.
PLWH-HCV were excluded if they were already on treatment with DAAs at the time of positive HCV-RNA sampling or they were followed by other outpatient clinics.

### *Study procedures*

Demographic, clinical and laboratory characteristics were collected for all study participants at every scheduled visit, as well as the AST/platelet ratio index (APRI) (Lin *et al.*, 2011) (Chou *et al.*, 2012). In case of liver cirrhosis, the Child-Pugh score was reported (Matta *et al.*, 2016) (Yongpisarn *et al.*, 2021). Survival status was described as well as response to DAAs in case of HCV treatment initiation and strategies adopted to engage patients to treatment.
At our center, PLWH are expected to attend follow-up visits at least every six months. According to international guidelines (European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu *et al.*, 2020), PLWH previously successfully treated for HCV are screened for HCV-RNA every 12 months. In case of detectable HCV-RNA, HCV treatment initiation is discussed before the scheduled visit at the staff meeting to evaluate the need for further pre-treatment tests, adherence to medications, and possible obstacles to HCV treatment. At the scheduled visit, PLWH receive counseling for HCV treatment. In case of treatment deferral, reasons for treatment are rediscussed at every subsequent visit.
Serum HCV RNA levels were assessed by polymerase chain reaction (PCR) with a lower detection limit of 10 UI/mL (*Roche Taqman®* method).
The primary aim of the present study was to identify barriers to the treatment of HCV in our PLWH-HCV cohort. A secondary endpoint was to describe strategies adopted to engage patient to care and to achieve HCV micro-elimination during the follow-up period.

### *Definitions*

Poor compliance was defined as scarce adherence to treatments (both ART and co-medications) and unwillingness to retention in care (more than one missed appointment for clinical evaluation and/or blood tests during the last year). Treatment hesitancy is defined as the refusal to start a new treatment despite attempts by the clinician to convince the patient of its importance.
Adherence to ART was verified by means of the hospital pharmacy's electronic records.
Reasons for deferring HCV treatment were defined as patient-related in case of treatment refusal or poor compliance and healthcare-related in case of ongoing diagnostic workup (Lazarus *et al.*, 2018).
Sustained virological response (SVR) was defined as undetectable HCV RNA at least 12 months after the end of treatment, according to current guidelines (European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu *et al.*, 2020).

### *Statistics*

Continuous variables were described by median and range or interquartile range (IQR). Categorical variables were described by numbers and percentages.
The rate of HCV treatment initiation during a 3-year follow-up and reasons for treatment delay were reported. Follow-up strategies and efforts to achieve the goal of micro-elimination of HCV were also reported.

### *Ethics*

IRCCS Polyclinic San Martino Hospital participates in the Rete Ligure HIV cohort, a large regional clinical network in which PLWH are anonymously and prospectively included after acquisition of a dedicated informed consent. The use of clinical and laboratory data collected in the Rete Ligure HIV cohort for research purposes was approved by the Ethical Committee of the Ligurian Region on August 28, 2013 (*MEDINFO, https://www.reteligurehiv.it. Date last access: August 1, 2022.*, s.d.). Data of the study participants were automatically and anonymously extracted by the Rete Ligure HIV platform.

## RESULTS

At the beginning of the observational period, 1,070 PLWH attended our infectious Disease Outpatient

service, of whom 492 (46%) had positive HCV serology and 29/492 (5.8%) had detectable serum HCV-RNA. Eight were excluded because they were already on treatment with DAAs and 2 others were excluded because they were being followed by other outpatient clinics.

Nineteen patients were included in the study. Of these, 16/19 (84%) were Caucasian and 9/19 (47%) were female. The median age was 49.4 years (IQR 45-56 years). Injection drug use was the most common risk factor for HCV infection (15/19, 79%), and 8/15 (53%) were receiving opioid substitution treatment with methadone or buprenorphine. The most common comorbidity in our cohort was the presence of psychiatric disorder (7/19, 37%).

Five (5/19, 26%) patients had liver cirrhosis (1 with Child-Pugh score C and 4 with Child-Pugh score B); 2 of them had APRI score >1.5 and 2 had clinical signs of cirrhosis and portal hypertension.

With regard to HIV-infection, CDC stages in the cohort were represented as follows: A for 4/19 (21%), B for 4/19 (21%), C for 11/19 (58%). The median CD4+ cell count was 406/mm$^3$ (IQR 133-509) and 8/19 (42%) had a CD4+ cell count under 200/mm$^3$. Seven study participants (37%) had HIV-RNA higher than 50 copies/mL. Further characterization of study participants is outlined in *Table 1*.

Patient-related barriers led to HCV treatment deferral in 14/19 (74%) cases, while healthcare-related barriers accounted for the remaining 5/19 (26%) cases. Among patient-related reasons, 9/19 (47%) were due to poor compliance and 2/19 (10%) to treatment hesitancy. Of note, 3 study participants had already received treatment for HCV infection: 1 interrupted treatment before completion, 1 experienced virological relapse after a complete course of treatment taken with low adherence and 1 experienced HCV reinfection.

Among healthcare-related barriers, the need to complete liver disease staging in recent HCV infection diagnosis delayed treatment in 3/19 (16%) cases, in 1 case treatment was delayed because of pregnancy,

**Table 1** - *Clinical and laboratory characteristics of the study participants.*

| *ID* | *Risk factor for HIV infection* | *APRI score* | *CHILD score* | *Main comorbidities* | *Perceived barrier in 2018* | *Treatment related status in 2022* | *Type of HCV treatment* | *SVR* |
|---|---|---|---|---|---|---|---|---|
| #1 | IVDU | 2.78 | B | Psychiatric | Treatment failure | Dead | NA | NA |
| #2 | IVDU | 0.33 | NA | Psychiatric | Poor compliance | Treated | glecaprevir/ pibrentasvir | Yes |
| #3 | IVDU | 0.46 | NA | None | Treatment hesitancy | Not treated yet | NA | NA |
| #4 | IVDU | 0.43 | NA | None | Poor compliance | Dead | NA | NA |
| #5 | IVDU | 0.22 | NA | Thyroiditis | Poor compliance | Treated | glecaprevir/ pibrentasvir | Yes |
| #6 | IVDU | 0.64 | NA | None | Poor compliance | Treated | glecaprevir/ pibrentasvir | Yes |
| #7 | IVDU | 0.19 | NA | Tubercolosis | DDI and poor compliance | Not treated yet | NA | NA |
| #8 | IVDU | 0.31 | NA | Psychiatric | Uncompleted treatment | Not treated yet | NA | NA |
| #9 | IVDU | 1.21 | C | Psychiatric | Poor compliance | Lost to follow-up | NA | NA |
| #10 | IVDU | 0.30 | NA | Cardiologic | Poor compliance | Treated | glecaprevir/ pibrentasvir | Yes |
| #11 | IVDU | 0.59 | NA | Psychiatric | Treatment hesitancy | Not treated yet | NA | NA |
| #12 | Sexual | 1.21 | B | None | Pregnancy | Treated | sofosbuvir/ velpatasvir | Yes |
| #13 | IVDU | 0.14 | NA | None | Reinfection | Treated | sofosbuvir/ velpatasvir | Yes |
| #14 | IVDU | 0.54 | NA | None | Poor compliance | Treated | sofosbuvir/ velpatasvir | Yes |
| #15 | IVDU | 0.75 | NA | None | Poor compliance | Treated | sofosbuvir/ velpatasvir/ voxilaprevir | Yes |
| #16 | IVDU | 0.39 | NA | Psychiatric | Poor compliance | Lost to follow-up | NA | NA |
| #17 | Sexual | 0.93 | NA | None | Recent HCV diagnosis | Treated | sofosbuvir/ velpatasvir | Yes |
| #18 | Sexual | 0.84 | B | Pulmonary | Recent HCV diagnosis | Treated | sofosbuvir/ velpatasvir/ voxilaprevir | Yes |

**Table 2** - *Perceived barriers to treatment initiation at the beginning of the observational period and treatment related status after three-years follow-up.*

| *Perceived barriers to treatment initiation (N=19)* | *Treatment related status after three-years follow-up* |
|---|---|
| Poor compliance (N=9, 47%) | Treated (N=6) |
| | Dead before treatment initiation (N=1) |
| | Lost to follow-up (N=2) |
| Treatment hesitancy (N=2, 11%) | Not yet treated yet (N=2) |
| Reinfection following HCV eradication (N=1, 5%) | Treated (N=1) |
| Previous DAAs treatment failure (N=1, 5%) | Dead before treatment initiation* (N=1) |
| Uncompleted treatment (N=1, 5%) | Not yet treated yet (N=1) |
| Recent diagnosis of HCV infection (N=3, 16%) | Treated (N=3) |
| Drug-drug interactions (N=1, 5%) | Not yet treated yet (N=1) |
| Pregnancy and breastfeeding (N=1, 5%) | Treated (N=1) |

and the last case was a poorly compliant patient with major drug-drug interactions between DAAs and ongoing treatment for pulmonary tuberculosis. Barriers to treatment initiation are summarized in *Table 2*.
During the three years of follow-up, all the 11/19 (58%) study participants who started DAAs completed treatment schedule and achieved SVR.
Of the 11 patients treated, the following barriers to treatment initiation were overcome: previous poor compliance in 6 cases; recent diagnosis of HCV infection in 3 cases; pregnant status in 1 case and reinfection in the last case.
On the other hand, 8/19 (42%) study participants did not start DAAs during the follow-up. Of these, 2 poorly compliant patients were lost to follow-up, 2 patients died before treatment initiation, and 4 patients are still waiting to start DAAs treatment.
Of the two patients who died before treatment, one died for hepatocellular carcinoma and the other for community-acquired pneumonia.
For the four PLWH still waiting for treatment, the same barriers at the beginning of the observational period were found after three years of follow-up. Two of them have continued to refuse the treatment proposal at all the scheduled visits that they attended for HIV infection, despite counseling, while the remaining two did not attend regular follow-up visits (median of follow-up visits 0.75/year).
To overcome those barriers, especially regarding poor compliance or irregularity at follow-up visits, the main strategy adopted was a close follow-up, with monthly visits to consolidate taking charge and treatment adherence. A treatment proposal was made at every follow-up visit for all those not yet treated, in order to begin the treatment as soon as possible, regardless of the clinical/radiological stage of the hepatitis, and to explain the importance and the efficacy of the HCV eradication treatment.
Moreover, we offered the possibility to have blood tests without a reservation in our outpatient clinic, or we performed out-of-appointment follow-up visits at the time of direct ART distribution.
In one case, directly observed treatment with a day hospital service was adopted in a patient with Child-Pugh B score for liver cirrhosis with esophageal varices and low adherence to ART therapy due to socio-economic difficulties.
Regarding hesitancy to treatment, clinicians at our clinic explained the benefit of treatment for personal and public health at every follow-up visit, and they considered it a priority to start treatment with DAAs even in patients with an unknown fibrosis status who did not show regularity in performing the required checkups.

## DISCUSSION

In the present study, we found that 5.8% of PLWH-HCV at our center were still HCV viremic in 2018, despite the availability of safe and effective drugs against HCV and despite the fact that they were already chronically followed for HIV infection at our outpatient clinic.
The main barriers to treatment initiation and completion were poor adherence to cures and treatment hesitancy. Strategies adopted to overcome those barriers with implemented counseling and frequent scheduled visits were effective for treatment initiation in 58% of cases, with 100% of SVR reached, as expected.
We observed a high prevalence of psychiatric comorbidity and of opioid substitution treatment in our cohort, indicating a subgroup of people with complex medical and socio-economical needs who are at high risk of low adherence due to the fragile medical care link between the hospital and territorial medical services (Taylor *et al.*, 2013) (Degenhardt *et al.*, 2017) (Bruggmann & Litwin, 2013).
Only a minority of PLWH-HCV in our cohort had an active HCV infection with detectable HCV-RNA, and a third of them were under treatment with DAAs at the beginning of the observational period, not presenting with any treatment initiation barrier.
Barriers to treatment initiation were patient-related in most cases, especially linked to poor compliance

both to ART and follow-up visit and hesitancy in starting new treatments. In a minority of cases treatment deferral was a clinical decision due to ongoing acute treatment with documented drug-drug interaction and pregnancy.

Three of participants in the study were newly diagnosed HCV infected or newly linked to care by our center, so they had just started the liver disease staging pathway.

In our analysis, we considered the loss-to-follow-up rate of 10% widely expected. The outbreak of COVID-19 pandemic during the three-year observation period represented an additional obstacle to starting treatment due to the disruption of essential health services, with difficult accessibility to hospital care and continuity of care. This global emergency may have played a role in decreased patient follow-up and poor compliance with follow-up visits, as 43% of countries reported discontinuation in hepatitis B and C diagnosis and treatment services worldwide (World Health Organization, 2021).

During the observation period, we failed in our micro-elimination mission in 8 PLWH-HCV.

We found that the most difficult barrier to deal with was treatment hesitancy, having failed to overcome it in 100% of cases. This represents the most important teaching of the study, as we realized that the clinician's capabilities are limited when it comes to managing fear of a new treatment. Non-routine collaboration with specific professional figures such as psychologists and social workers was probably the main limiting factor of our intervention, making us aware of the need to implement collaboration with all stakeholders involved in the treatment process, as recommended in other micro-elimination reports (AASLD/IDSA HCV Guidance Panel, 2015) (Kondili *et al.*, 2022). On the other hand, we were able to overcome the poor compliance barrier in 66.6% of cases, which represented our second most difficult challenge. We found that our approach in engaging patients to HCV eradicating treatment by frequent scheduled visits (>2/years) and proposing the start of treatment as soon as possible, at every visit, regardless of the clinical/radiological stage of the hepatitis, was partially effective. In the case of people who were already showing poor compliance with ART and HIV infection checkups, the option of starting DAAs therapy on the same day as the medical checkup was provided, considering each visit an opportunity to start treatment.

Micro-elimination strategies must be stakeholder-oriented, and it is not possible to define a universal strategy of effectiveness. Several approaches are reported in the literature, but it has not been shown that proposing frequent follow-up is always effective in all cases.

The main limitations of our study are the retrospective, single center nature and the limited number of participants included, who could not be representative of other PLWH-HCV cohorts.

In addition, description of treatment barriers and monitoring of intervention strategies are not standardized and therefore are subject to interpretation, with difficult reproducibility in other settings.

In conclusion, the goal of HCV micro-elimination could be achievable, although barriers to treatment initiation due mainly to patient hesitation and accessibility to care are still present. A greater effort to overcome those barriers needs to be made by means of a continuous analysis of people's environment and a more integrated and multidisciplinary approach that involves all stakeholders.

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