Infect Dis Trop Med 2021; 7: e685

HCV eradication in people living with HIV: the final countdown?

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ABSTRACT:

— ***Background:*** HCV coinfection is present in 15-30% of people with HIV (PWH). This population shows a rapid progression of hepatic fibrosis and high morbidity and mortality. This study aimed to follow PWH with an active HCV infection after 2018 and investigate the critical barriers to eradicating these patients.

— ***Patients and methods:*** We performed a prospective study on PWH with a positive HCV-RNA after 1st January, 2018. The participants' main characteristics at baseline were compared between those treated or not, using Chi-square or Mann-Whitney U test, as appropriate. Furthermore, data about HCV and liver disease were collected. We collected clinical data after 2, 4, 8, 12, 24, and 48 weeks after the DAA started treating PWH.

— ***Results:*** Seventy-three PWH had a detectable HCV-RNA. Of these, 61 (83.6%) were eligible to receive DAA treatment, but only 53 (72.6%) were treated. On 1st September, 2020, 50 (94.3%) reached a sustained virologic response (SVR), and three (5.7%) patients failed the therapy. Two of these have been retreated with sofosbuvir/velpatasvir/voxilaprevir. One of them showed a second failure, whereas the other finished the therapy, and the SVR result is pending. Over these two years of follow-up, three (4.1%) people died.

On September 1st, 2020, 20 patients have not been treated. In 8 cases, the treatment has not been started due to the patient's choice. In the other 8 cases, an important psychiatric condition that implicates poor adherence to HIV treatment was present. The other 4 patients were difficult to reach and had poor compliance.

— ***Conclusions:*** In the last two years, we have treated 53 PWH, meaning that only 8.2% (20 PWH) still have a detectable HCV-RNA. To treat this kind of patient (psychiatric, poorly adherent, and difficult to reach) we need to implement new strategies, such as directly observed treatment with the addiction of centers' tight synergy with home caring staff assistance.

— ***Keywords:*** HIV, HCV, Coinfection, DAA.

INTRODUCTION

Among people with HIV (PWH), HCV coinfection represents an important cause of morbidity and mortality. The percentage of coinfected PWH is estimated to be around 15-30%. This percentage is high because the two viruses share the same transmission route[1]. Of note, coinfected patients have a more rapid hepatic fibrosis progression if compared with HCV monoinfected with an increased risk of cirrhosis and hepatocellular cancer[2-4]. Furthermore, PLWH with hepatitis C coinfection have an increased risk of hospitalization and mortality[5].

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The introduction of direct-acting antiviral (DAA) represented a revolution in hepatology, making HCV infection curable with an efficacy above 95% and very low toxicity if compared with the previously available treatments[6-9].

This study aimed to follow PWH with an active HCV infection after 2018 and investigate the critical barriers to eradicating HCV in these patients.

PATIENTS AND METHODS

We performed a prospective study, enrolling all PWH with positive HCV-RNA referring to our outpatient clinic in Sassari from January 1st, 2018 to September 1st, 2020.

Demographic data, medical history (smoking, alcohol abuse, methadone intake, HCV previous treatment), and HIV history (Nadir CD4 cells/mL, route of transmission) were extracted by patients' medical records. We performed blood tests to evaluate HIV disease status (HIV-RNA and CD4 cells count), liver function (AST, ALT, platelets, gamma-glutamyltransferase, and bilirubin), HCV-RNA, and HCV genotype. In all patients eligible for DAA treatment, we performed fibroscan, and in patients with evidence of advanced fibrosis or cirrhosis, we performed a liver ultrasound examination to exclude the presence of hepatocellular carcinoma. Sustained Virological Response (SVR) was defined as a the presence of an undetectable HCV-RNA at 12 weeks after the end of treatment. We collected clinical data after 2, 4, 8, 12, 24, and 48 weeks after the DAA start.

Statistical Analysis

Before performing the statistical analysis, data distribution was evaluated with the Kolmogorov-Smirnov test. Data were elaborated as numbers on total (percentages), means ± standard deviation or median with interquartile range (IQR), when appropriate. Continuous variables with parametric distribution were compared with Student's *t*-test or

Table 1. Demographic and clinical patients' characteristics.

	Total (73)	Treated (53)	Not-treated (20)	*p*-value*
Sex				< 0.001
Male, n (%)	53 (72.6%)	44 (83%)	9 (45%)	
Female, n (%)	20 (27.4%)	9 (17%)	11 (55%)	
Risk Factors				0.554
Heterosexual, n (%)	1 (1.4%)	1 (1.9%)	0	
MSM, n (%)	2 (2.8%)	2 (3.8%)	0	
PWID, n (%)	70 (95.8%)	50 (94.3%)	20 (100%)	
Smoking				0.062
Yes, n (%)	60 (82.2%)	43 (81.1%)	20 (100%)	
No, n (%)	10 (17.8%)	10 (18.9%)	0	
Alcohol abuse				0.039
Yes, n (%)	35 (47.9%)	21 (39.6%)	14 (70%)	
No, n (%)	38 (52.1%)	32 (60.4%)	6 (30%)	
Methadone intake				<0.001
Yes, n (%)	39 (53.4%)	21 (39.6%)	18 (90%)	
No, n (%)	34 (46.6%)	32 (60.4%)	2 (10%)	
Age, median (IQR)	54 (49-56)	54 (50.5-58)	55 (48-56)	0.672
Cirrhosis				0.028
Yes, n (%)	21 (28.7%)	12 (22.6%)	9 (45%)	
No, n (%)	50 (68.5%)	41 (77.4%)	9 (45%)	
Unknown, n (%)	2 (2.8%)	0	2 (10%)	
HCV treatment before 2018				0.700
Yes	60 (82.2%)	43 (81.1%)	17 (85%)	
No	13 (17.8%)	10 (18.9%)	3 (15%)	
FIB4, median (IQR)	2.01 (1.41-3.38)	1.93(1.38-2.64)	2.45 (1.69-4.71)	0.070
Nadir CD4 cells/mm³, median (IQR)	189.5 (112 -283.25)	202 (135-287)	108 (25 – 271)	0.025
CD4 cells/mm³ baseline, median (IQR)	660 (412-987)	719 (557-1061)	411 (244.5-633.5)	0.001
Viral load <50 copies/ml				<0.001
Yes, n (%)	58 (79.4%)	48 (90.6%)	10 (50%)	
No, n (%)	15 (20.6%)	5 (9.4%)	10 (50%)	
Deaths	3 (4.1%)	1 (1.9%)	2 (10%)	0.124

*Chi-square or Mann-Whitney U test as appropriate. MSM: man who have sex with man; PWID: people who inject drugs; IQR: interquartile range.

Mann-Whitney U test, when appropriate. Categorical data were evaluated with the Pearson chi-squared test. *p*-value was considered significative if <0.05. Statistical analysis was performed using STATA/IC 16.1.

RESULTS

Overall, 650 PWH are followed by our Unit, and 200 have a positive HCV-screening. During the study timeline, we tested all PWH, and we found 73 people with a detectable HCV-RNA. Therefore, more than 60% of coinfected PWH were previously treated or had spontaneous clearance.

Among them, 53 (72.6%) patients were male, with a median age of 54 (IQR 49-56) years. The main patients' characteristics have been summarized in Table 1.

After the medical evaluation, 63 (83.6%) received DAA's treatment eligibility, but only 53 (72.6%) were treated. Among treated patients, 30 (56.6%) were treated with the combination sofosbuvir/velpatasvir, 16 (30.2%) with glecaprevir/pibrentasvir, 4 (7.5%) with sofosbuvir/velpatasvir/voxilaprevir, and 3 (5.7%) with elbasvir/grazoprevir.

On September 1st, 2020, 50 (94.3%) patients reached the SVR, and three (5.7%) had a virological failure. Regarding the patients who failed, two of them were retreated with sofosbuvir/velpatasvir/voxilaprevir. One of them shoed a second virological failure; the other finished the treatment, but the SVR result is pending (Figure 1).

During these two years of follow-up, three (4.1%) patients died. Two PWH, not treated for HCV, died for acute liver failure and encephalopathy, respectively. For the other patient, the cause of death is unknown.

On September 1st, 2020, 20 patients were not still treated. In 8 cases, the treatment was not started due to the patient's choice. In the other 8 cases, there was a major psychiatric disorder, which has already resulted in poor adherence to HIV treatment. The other four patients were difficult to reach and had poor compliance.

Whe comparing PWH treated and untreatedwith DAAs, those not treated were more frequently females (17% *vs.* 55%, p <0.001), alcohol abusers (39.6& *vs.* 70%, p= 0.039), and were receiving methadone (39.6% *vs.* 90%, p <0.001). Regarding HIV infection, treated patients had a significantly higher CD4 cell count (cells/mm^3) median (719 (IQR557-1061) *vs.* 411 (IQR244,5-633.5); p=0.001). Only 5 (9.4%) PWH receiving antiretroviral therapy had a detectable viral load compared with 10 (50%) among untreated patients (p<0.001).

DISCUSSION

In our center, we currently look after 645 PWH, of whom 200 are HCV-antibody positive. Most of them have already been treated or spontaneously cleared the virus over the years. In the last two years, we treated 53 PWH, and only 8.2% (20 PWH) still have a detectable HCV-RNA.

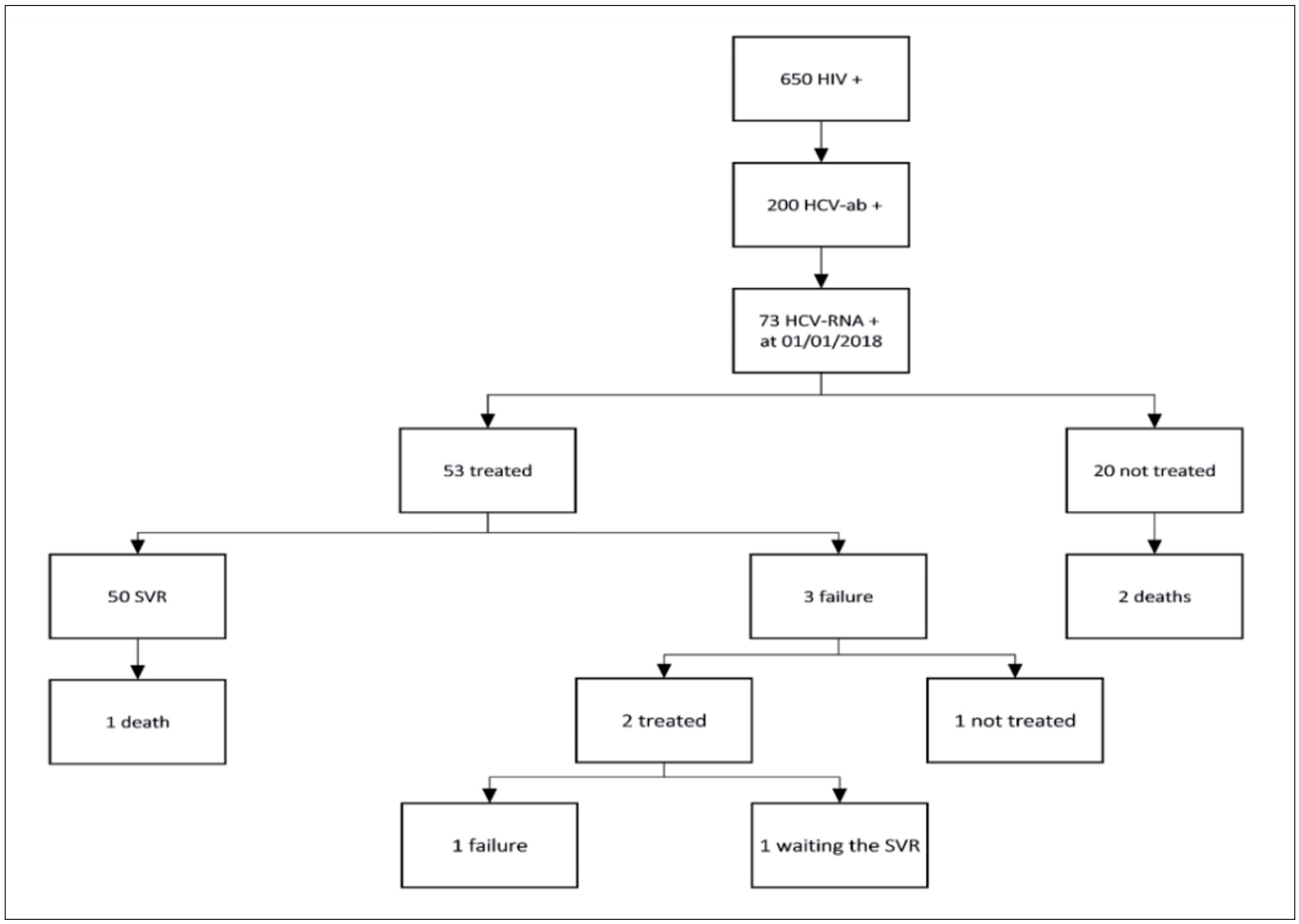

Figure 1. Patients' disposition of 650 PLWH followed in our outpatients' clinic.

Among treated PWH, only 3 (5.6%) failures occurred, supporting DAA's high efficacy also in in this population[10]. Furthermore, no adverse events have been reported by the patients, confirming the safety of the regimens.

One of the main differences between treated and untreated PWH was alcohol abuse. This datum confirms the previous literature in the field. Indeed, different studies showed how adherence decreased in people assuming alcohol. Furthermore, liver damage is quicker in such patients, and morbidity and mortality are higher[11,12].

The percentage of females was significantly higher in untreated than in treated. However, they were all PWIDs with a lack of compliance. This was the reason for not treatment initiation.

Another relevant datum highlighted by our survey was related to immune and virological status. As expected, untreated PWH had a lower CD4 count and a detectable viral load. Although previously published studies suggested an association between HCV-coinfection and the failure of HIV viral control[11]. In our cohort, the lack of patients' compliance to HIV-treatment and discontinuing the clinic appointments were the most important reasons not to start the treatment.

CONCLUSIONS

In conclusion, eradicating HCV in PWH is feasible, giving high efficacy and low adverse reaction incidence that characterize the available HCV direct-acting drugs. However, we need to implement new strategies, such as directly observed treatment with the addiction centers' support or synergy with home caring staff assistance, creating new tailored micro elimination paths.

Conflict of Interest:
The authors declare that they have no conflict of interest.

REFERENCES

1. Alter MJ. Epidemiology of viral hepatitis and HIV coinfection. J Hepatol 2006; 44 (Suppl 1).
2. Behzadpour D, Ahmadi Vasmehjani A, Mousavi Nasab SD, Ahmadi NA, Baharlou R. Impact of HIV infection in patients infected with chronic HCV (genotypes 1a and 3a): virological and clinical changes. Pathog Glob Health 2016; 110: 310-315.
3. Fabrizi F, Dixit V, Martin P, Messa P. Hepatitis C virus increases the risk of kidney disease among HIV-positive patients: Systematic review and meta-analysis. J Med Virol 2016; 88: 487-497.
4. Puoti M, Moioli M, Travi G, Rossotti R. The Burden of Liver Disease in Human Immunodeficiency Virus-Infected Patients. Semin Liver Dis 2012; 32: 103-113.
5. Cenderello G, Tittle V, Pasa A, Dentone C, Artioli S, Barbour A, Setti M, Giacomini M, Fraccaro P, Viscoli C, Cassola G, Nelson M, Di Biagio A. The impact of liver disease: a leading cause of hospital admissions in people living with HIV. Infect Dis Trop Med 2015; 1: e167.
6. Ferenci P, Bernstein D, Lalezari J, Cohen D, Luo Y, Cooper C, Tam E, Marinho RT, Tsai N, Nyberg A, Box TD, Younes Z, Enayati P, Green S, Baruch Y, Bhandari BR, Caruntu FA, Sepe T, Chulanov V, Janczewska E, Rizzardini G, Gervain J, Planas R, Moreno C, Hassanein T, Xie W, King M, Podsadecki T, Reddy KR. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. N Engl J Med 2014; 370: 1983-1992.
7. Afdhal N, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, Nahass R, Ghalib R, Gitlin N, Herring R, Lalezari J, Younes ZH, Pockros PJ, Di Bisceglie AM, Arora S, Subramanian GM, Zhu Y, Dvory-Sobol H, Yang JC, Pang PS, Symonds WT, McHutchison JG, Muir AJ, Sulkowski M, Kwo P. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med 2014; 370: 1483-1493.
8. Sharafi H, Alavian SH, Behnava B, Rezaee-Zavareh MS, Nikbin M, Alavian SM. Real-life efficacy of generic sofosbuvir/ledipasvir for treatment of Iranian patients with chronic hepatitis C: A cohort study. Casp J Intern Med 2020; 11: 41-46.
9. Brindicci G, Santoro C, Mazzola, Giannelli A, Infante G, Fiorella C, Lagioia A, Punzi G, Volpe A, Fontana T, Losappio R. Efficacy evaluation of new anti-HCV treatments after a two-year use - Infectious Diseases & Tropical Medicine. Infect Dis Trop Med 2017; 3: e368.
10. Alavian SM, Dolatimehr F, Sharafi H, Safi-Abadi M, Rezaee-Zavareh MS, Ehsan Bayatpour M, Karimi-Sari H, Mohazzab-Torabi S. Treatment of HCV Infection with Direct-acting Antiviral Agents in Patients with HIV/HCV Co-infection: A Systematic Review 2018; 18: 82971.
11. Sims OT, Chiu CY, Chandler R, Melton P, Wang K, Richey C, Odlum M. Alcohol Use and Ethnicity Independently Predict Antiretroviral Therapy Nonadherence Among Patients Living with HIV/HCV Coinfection. J Racial Ethn Health Disparities 2020; 7: 28-35
12. Shuper PA, Joharchi N, Irving H, Fletcher D, Kovacs C, Loutfy M, Walmsley SL, Wong DK, Rehm J. Differential predictors of ART adherence among HIV-monoinfected versus HIV/HCV-coinfected individuals. AIDS Care 2016; 28: 954-962.