

Hepatitis C diagnosis and treatment in people who use drugs: mind the gap in the linkage to care

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Abstract. – OBJECTIVE: The objective of this study is to identify a simplified rapid screening and linkage-to-care model for HCV among PWUD.

PATIENTS AND METHODS: The study stems from a collaborative project bringing together two local Italian Centers for Drug Addiction and the Hepatology-Infectious Diseases Department of Lazzaro Spallanzani. A research physician analyzed the available medical records seeking to identify HCV and HIV infected patients in care in the addiction centers. Between March 2018 and January 2020 subjects were selected from among a cohort of 720 PWUD in the two Centers' care. The study comprises three steps: first, screening for HCVAb; second, the linkage to care; third, clinical assessment to treatment. The research physician recruited patients for the first two steps directly in their local addiction center. The third step was conducted in the Spallanzani. The characteristics of those subjects who adhered to the three-step study program were then compared to those of the non-adhering PWUD.

RESULTS: 194 were known HCVAb positive patients. Of the 505 PWUD in the care of the two Centers eligible for screening, 364 were enrolled in the study. 144 resulted HCVAb positive. 269 were tested for HCVRNA. 101 underwent a full assessment. 96 patients started antiviral therapy with DAA. Patients who refused first step screening were older patients and mainly heroin users; in the second step, almost all the HIV/HCV co-infected patients agreed to a viremia test; in the third step all the HIV/HCV co-infected patients refused HCV treatment.

CONCLUSIONS: The study suggests an on-site specialist approach conducted directly in

the addiction centers themselves starting from screening; it can bring the goal of HCV PWUD microelimination closer.

Key Words:

Hepatitis C, Drug users, Linkage to care, Facilitation, Decentralisation, Microelimination.

Introduction

In May 2016, the World Health Organization (WHO) released its first global strategy for the elimination of HCV infection and to halt the global spread of HCV by 2030. The WHO's two targets are to treat 80% of the HCV epidemic patients and to reduce new infections by 90% by 2030¹.

Italy is the country with the highest prevalence of HCV in Western Europe. In 2019 the Polaris Observatory reported that, out of the region's 12 nations, Italy is set to achieve WHO targets by 2025-2035^{2,3}.

The limitations to HCV therapy are no longer efficacy of, or adherence to, treatment but rather identification of the available patients to treat⁴. Since March 2017 Italy's national health system provides the new direct antiviral agents (DAA) free of charge to all HCV infected patients⁵.

Recent studies^{6,7} report that between 20% and 80% of HCV positive individuals are themselves aware of their status. The main approach then is implementation of case-finding strategies, seeking to identify those people at a high risk of infec-

tion. The European Association for the Study of the Liver (EASL) calls for the eradication of HCV in sub-populations at high risk of infection (e.g., people living with HIV, prisoners, people who use drugs) in their own settings (hospitals, places of detention, addiction centers). This approach is called microelimination⁸.

The burden of HCV infection is considerable among injecting drug users (estimated prevalence 39%), representing approximately 6.1 million people living with hepatitis C infection^{9,10}. In 2012 an Italian observational study of drug users showed high levels of HCV antibody positivity (prevalence 63.9%) with a detectable HCVRNA rate of 68.3%. However, only 19.3% of those positive were receiving antiviral treatment¹¹. In Italy, people who use drugs (PWUD) receive substitutive therapy in the National Centers for Drug Addiction (Italian abbreviation: SerDs).

SerDs are local drug addiction centers providing the National Health System's public services for pathological addictions and the addicted. These centers are responsible for the prevention of drug-related diseases, the rehabilitation, treatment, social reintegration and employment of drug addicts. Staffing includes both qualified and specialized professionals: doctors, psychologists, social workers, educators, nurses, as well as administrative staff. The centers provide diagnostic services, guidance, psychological support and treatment related to the degree of addiction and to the possible presence of psychiatric disorders.

These centers operate nationwide, patients being referred to the one closest to where they live. They serve a largely marginalized population that is often difficult to diagnose and to link to care.

The complexity of each individual situation makes it very unlikely that public services can reach them using a "one-size-fits-all"¹². Several countries have, however, already put in place effective strategies of HCV micro-elimination in PWUD populations¹³⁻¹⁶.

A facilitation model of screening with appropriate linkage-to-care programs is required to attain HCV eradication in high prevalence settings such as the PWUD population^{13,15,17}.

Achievement of a high level of screening is complex however, as close collaboration between the infectious disease specialists and the physicians prescribing opioid agonist therapy is critical¹⁷. Many general practitioners and addiction specialists have yet to receive clinical management support to engage in HCV care^{18,19}. A further significant problem in the management of screening in PWUD

populations is the need to reduce the time required for the screening and to identify the setting in which the patient is most likely to encounter and contact HCV diagnosis and treatment^{20,21}.

Several countries have undertaken studies to evaluate different strategies for more rapid and effective HCV screening and linkage-to-care among these patients^{10,13,22}.

In addition, certain of the characteristics of addicted people, and their lack of knowledge of viral infection transmission, represent a significant barrier to achievement of HCV eradication among PWUD.

This study's aims are to propose a simplified, rapid screening and linkage-to-care model for diagnosis and treatment of HCV infection among PWUD, to determine the prevalence of HCV infection in this population and to identify the specific characteristics of those PWUD who will adhere to the study program as opposed to those who will not.

Patients and Methods

A collaborative project was launched between the clinical staff of two local Italian Centers for Drug Addiction in Rome (one center serving a suburban area with social problems, the other a satellite district with high levels of drug related crime on the coast) and the Hepatology and Infectious Diseases Department of the National Institute of Infectious Diseases – Lazzaro Spallanzani, a major research institute and specialized hospital also located in the capital.

A research physician, an expert in Infectious Diseases of the Liver and appointed by the Institute, recruited patients directly from the two Drug Addiction Centers' cohorts of people who use drugs (PWUD). The physician reviewed the existing Medical Records in order to identify the clinical features of PWUD in the care of the two centers, especially data on the most commonly abused drug and its preferred route of administration and data relating to the virological features associated with HCV and HIV.

The study comprised three steps: first, screening for HCVAb; second, linkage-to-care; third, clinical assessment to treatment.

Step 1 – Screening

Initially the clinical staff of the two local Drug Addiction Centers did the screening; subsequently, the hospital commissioned a research physician to undertake this.

Inclusion criteria for Step 1 were: no indication in the data of HCV infection; a previous negative HCV antibody (HCVAb) test more than 6 months earlier; recent exposure to possible infection.

PWUD satisfying one or more of the inclusion criteria were enrolled after provision of written informed consent. Reasons for declining enrollment were recorded.

At screening, all enrolled PWUD patients had a rapid capillary HCV test in their regular local addiction center. The finger stick capillary test was performed with a fast HCVAb test (Ora-Quick, OraSure Technologies, Inc, Bethlehem, PA, USA), an indirect immunoassay with proven high sensibility and specificity to identify HCV-Ab in a small blood sample²³⁻²⁵.

Step 2 – Linkage-to-care

Every HCVAb positive patient entered Step 2: the linkage-to-care. In order to keep timelines as short as possible, these patients were directed to the center's clinical unit to take the HCVRNA test that same week. The research physician directly enrolled PWUD previously aware of their HCVAb positivity; these patients too were given an HCVRNA test the same week they consented to the study.

Step 3 – Full Assessment and Treatment

Each viremic patient were offered the opportunity to undergo further diagnostic procedures and to begin antiviral treatment. Patients agreeing underwent – in a single day – blood tests, fibroscan and a complete examination. Specifically, this involved HCV genotyping, laboratory assessment, a transient elastography and consultation with a specialist in order to identify the most appropriate treatment for the individual patient according to Italian and European guidelines^{26,27}. In addition, serum samples were collected for future virological study.

Reasons given for declining clinical evaluation and treatment were recorded.

As part of the consultation all patients were scheduled a liver ultrasonography appointment and received a detailed timetable for blood tests, drug withdrawals and follow-up clinical controls (at the end of treatment and at 12-weeks post-treatment, as indicated in Italian guidelines)²⁷.

Furthermore, patients could contact the study research physician by telephone or by e-mail or in person at their local addiction center, this both during treatment and after its completion for counseling and for answers to any clinical matter.

Throughout the study, should a patient not attend an appointment, the research physician made contact to schedule a new appointment within the week. Contact and rescheduling also continued during Covid emergency in order to ensure follow-up of all patients.

Data Collection and Statistical Analysis

All data were collected in three separate databases, respectively Medical Records information; screening and diagnosis; clinical and treatment details.

The personal, anamnestic, clinical and virological characteristics of patients were analyzed in respect of the execution or rejection of each step of the study.

Statistical analysis was performed using the Chi-squared test. Statistically significant were declared at a *p*-value of < 0.05. The statistical methods adopted in this study were reviewed by a biomedical statistician.

Ethical Considerations

The study protocol was approved by the Ethics Committee of the National Institute for Infectious Diseases – Lazzaro Spallanzani, and conducted in conformity with the 1975 Declaration of Helsinki.

Results

Seven hundred and twenty clinical files were reviewed (Figure 1). The most important route of drug administration was intravenous (58.7%) followed by inhalation (20.3%). Forty patients (5.6%) resulted HIV positive, with thirty patients co-infected HIV-HCV. No HCV data was available for seven patients.

Medical records reported 194 HCVAb positive patients.

Step 1

Five hundred and five PWUD in the care of the two addiction centers were eligible for screening.

Two hundred and fifteen subjects were ineligible for HCVAb screening, either because they were already aware of HCVAb positivity or because they had had an HCVAb negative test in the last 6 months (194 and 21 subjects, respectively). Only 7 HIV positive patients were eligible.

In the period March 2018 to January 2020, 72.1% (n=364/505) of subjects were enrolled

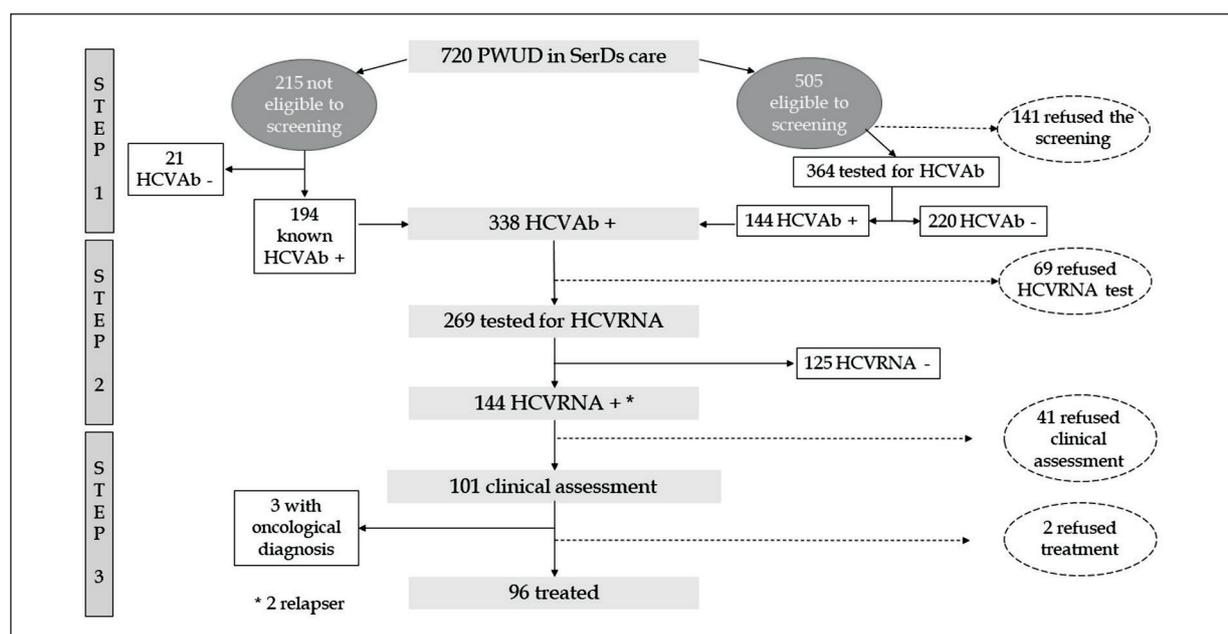


Figure 1. Genotype distribution of PWUD enrolled in step 3.

in the screening study. The remaining 27.9% (n=141/505) of PWUD refused screening (for details see Table I).

The mean age of screened patients was 45 years (range 22-71) of those who refused screening 50 years (range 24-73). Table II records the epidemiological characteristics of eligible subjects and the differences between those who accepted and those who refused screening.

The different kinds of addiction were to heroin, cocaine, THC and alcohol; the routes of drug administration were endovenous, inhalation, smoked and oral.

The data shows that those refusing screening were older patients and mainly heroin users.

144 subjects were HCVAb positive at an OraQuick capillary screening test (39.6%). With these, a total of 338 PWUD participating (46.9%) were HCVAb positive.

Step 2

An HCV RNA blood test was offered to all 338 HCVAb positive patients.

Patients tested numbered 269. Some 69 patients refused testing more than once; their characteristics are reported in Table III.

Almost all the co-infected HIV/HCV patients (n=39/42; 92.9%) underwent a viremia test.

PWUD resulting viremic numbered 144 (53.5%), including two patients who had relapsed after recent antiviral treatment.

Step 3

A complete clinical assessment was offered to all viremic patients. One hundred and one underwent the blood test, fibroscan and clinical assessment.

Forty-one patients refused to attend the proposed centralised medical care in the hospital,

Table I. Reported PWUD reasons of HCV OraQuick test denial.

Reported reasons	PWID	Not PWID	Tot.
Refused	19 (21.8%)	15 (27.8%)	34 (24.1%)
Refused, HCVAb neg. aware	18 (20.7%)	20 (20%)	38 (26.9%)
Refused, HCVAb pos. aware	10 (11.5%)	0	10 (7.1%)
Refused, HCV treated	17 (19.5%)	2 (3.7%)	19 (13.5%)
Refused, HCV RNA neg.	2 (2.3%)	0	2 (1.4%)
ND	21 (24.1%)	17 (31.5%)	38 (27%)
Tot.	87	54	141

Table II. Epidemiological characteristics of eligible subjects.

Characteristics		Screened	Not screened	p-value
Age	< 50	223 (61.3%)	56 (39.7%)	.009
	≥ 50	141 (38.7%)	85 (60.3%)	
Sex	M	291 (79.9%)	120 (85.1%)	.12
	F	73 (20.1%)	21 (14.9%)	
Addiction	Heroin	246 (67.6%)	124 (87.9%)	.013
	Other	118 (32.4%)	17 (12.1%)	
Route of drug administration	IV	187 (51.4%)	87 (61.7%)	.89
	Other	177 (48.6%)	54 (38.3%)	
HIV infection	Neg	361 (99.2%)	137 (97.2%)	.85
	Pos	3 (0.8%)	4 (2.8%)	
Tot.		364	141	

Table III. Characteristics of HCVAAb positive patients.

Characteristics		HCVRNA tested	HCVRNA refused	p-value
Age	< 50	105 (39.0%)	23 (33.3%)	.21
	≥ 50	164 (61.0%)	46 (66.7%)	
Sex	M	208 (77.3%)	53 (76.8%)	.99
	F	61 (22.7%)	16 (23.2%)	
Addiction	Heroin	257 (95.5%)	69 (100.0%)	.13
	Other	12 (4.5%)	0	
Route of drug administration	IV	244 (90.7%)	68 (98.6%)	.04
	Other	25 (9.3%)	1 (1.4%)	
HIV infection	Neg	230 (85.5%)	66 (95.7%)	.016
	Pos	39 (14.5%)	3 (4.3%)	
Tot.		269	69	

four of whom enrolled in the study from the beginning. The remaining thirty-seven patients were already aware of their chronic HCV infection but refused specialist care. In Table IV their characteristics are reported. The only characteristic shared was that all co-infected patients (n=11) in Step 3 refused HCV treatment, specifically 7 of them were also non-compliant with HIV therapy.

Ninety-six subjects started antiviral therapy with DAA. Three patients never attended therapy after diagnosis advanced cancer at clinical assessment: one with a multifocal hepatocellular carcinoma (HCC), one with rectal cancer and one with metastatic lung cancer. Two patients dropped out after clinical assessment, refusing second-level imaging and never starting therapy.

Table IV. Characteristics of HCVRNA positive patients.

Characteristics		HCV treated	HCV treatment refused	p-value
Age	< 50	39 (38.6%)	17 (41.5%)	.92
	≥ 50	62 (61.4%)	24 (58.5%)	
Sex	M	84 (83.2%)	30 (73.2%)	.52
	F	17 (16.8%)	11 (26.8%)	
Addiction	Heroin	99 (98.0%)	38 (92.7%)	.39
	Cocaine	2 (2.0%)	3 (7.3%)	
Route of drug administration	IV	92 (91.1%)	37 (90.2%)	.88
	Other	9 (48.6%)	4 (9.8%)	
HIV infection	Neg	101 (100.0%)	30 (73.2%)	.0005
	Pos	0	11 (26.8%)	
Tot.		101	41	

More than one-third of patients (34.7%, n= 45/101) showed significant fibrosis (F3-F4), the remaining 65.3% (n= 66/101) patients mild or no-fibrosis (F0-F2).

During the treatment or the follow-up, a renal carcinoma was diagnosed in one patient, an HCC in another (who then underwent hepatic resection). One patient had acute bleeding from esophageal varices and was treated with ligation.

Figure 2 represents HCV Genotype distribution. The most frequent HCV genotypes were 1a and 3 (44.6% and 34.7%, respectively). Only one patient had HCV co-infection (genotype 3+4).

All patients (n= 82) who had blood sampled twelve weeks after the end of therapy achieved a sustained virologic response, these including the four patients who had discontinued therapy (2 after 4 weeks of treatment, 2 after 8 weeks).

Fourteen patients were lost at follow-up and 3 of them discontinued therapy after 4 weeks.

Discussion

Five hundred and five PWUD in care at two local addiction centers had not been screened for HCVAb in the past 6-12 months. This confirms that the medical care available to PWUD is inadequate, despite the fact that this population has many comorbidities. They frequently refuse blood tests, specialist examination and hospitalization when proposed by addiction center staff.

Thanks to the introduction of rapid on-site screening, 364 PWUD subjects were screened. In spite of the ease of this procedure 27.9% of

subjects refused screening, of whom almost 60% using drugs by injection (PWID). Analyzing the reasons PWID gave for refusal, 42.5% referred to HCV negativity. Thus, in a population at high risk of HCV infection (such as PWID), 50 patients remain a possible unknown reservoir for HCV infection and, again, these are particularly the older patients and the heroin users. The reason may be because a – silent – HCV infection, widespread among PWUD, is not perceived by them as a health problem.

Several studies have demonstrated the existence of multiple barriers to HCV screening and testing as perceived by patients. In the C-SCOPE, the most commonly perceived barriers include: poor attendance or missed appointments, little knowledge of HCV and its treatment, fear of treatment side effects, the asymptomatic nature of HCV infection, difficulties encountered in navigating through the healthcare system, stigma, mistrust of the healthcare system¹⁹. Our study proposed on-site screening and testing, the local addiction centers as the point of care, a research physician offering counseling and information about HCV infection as well as continuous care throughout the steps.

The Enhance study¹⁶ highlighted that a flexible approach facilitates and improves a relationship based on trust between the patient and the specialist clinician which can help to remove some of these barriers.

Our study revealed differences based on who introduced the test to the target-group. In fact, comparing the initial period when it was the addiction centers' staff who offered the HCV rapid test, to the second period when it was the research physician who proposed the study as well as the rapid test. In particular, patients were almost six times more likely to agree to be tested when asked by the research physician than when asked by the center staff over the same span of time and in the same facility.

This was probably due to the perceived removal of two of the barriers: the research physician, a specialist hepatologist, increased patient awareness of, and knowledge about, HCV (ways of transmission, natural history of infection, treatment) and assured a continuous presence during opening hours.

The study demonstrates a high prevalence of HCVAb positivity (46.9%), confirming that PWUD are an important reservoir of HCV infection. Indeed, PWUD are the focus of global attention in terms of HCV eradication strategies.

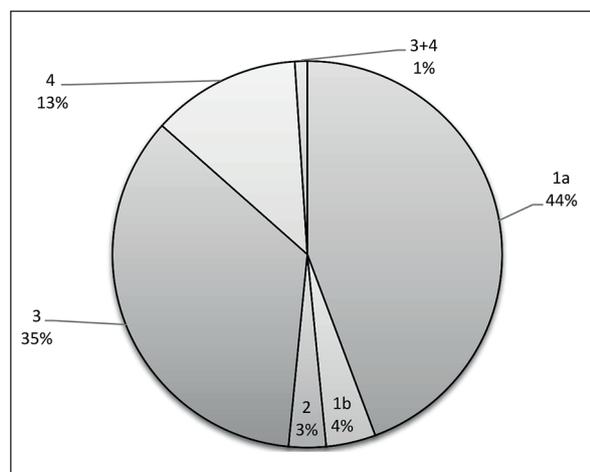


Figure 2. Genotype distribution of PWUD enrolled in step 3.

Several studies on the microelimination of HCV infection in PWUD have shown the importance of close interaction between Infection Disease Units and the local addiction center staff. Messina, Persico and their collaborators demonstrated that the cooperation and decentralisation model of HCV eradication in PWUD is effective in terms of diagnosis, linkage-to-care and treatment adherence respectively, through consultant periodic prospective audits and the creation of a network model^{13,28}.

Our study proposes on-site collaboration between local addiction centers and a specialist hospital. This model picked up the patients who had never attended HCV treatment. An integrated approach on-site - in the centers where PWUD are used to taking their opioid substitutive therapy - demonstrated a high rate of linkage to care (n=269/338).

Also in the CLEO study the locally-based model emerged as the best approach to this marginalized, difficult-to-treat population. In this study Rinaldi and co-authors created a locally based SerD model in which the management of PWUD was carried out through interdisciplinary cooperation between the specialist hospital hepatologist working in the center and the centers themselves. The CLEO study also showed that the SerD-based model is the best approach to this marginalized and difficult-to-treat population²⁹.

In our study, almost all co-infected HIV/HCV patients agreed to HCVRNA testing. This is probably due to greater experience in providing centralized care. Yet we also established that the PWUD continue to evade medical care, which may be because they need full decentralisation, a micro-local approach, as considered in the Oru et al³⁰.

Of the viremic patients, 70.1% underwent clinical assessment in the Lazzaro Spallanzani Department for Infectious Diseases and almost all were treated (n=96/101). This implies a decreasing dropout at Step 3, following diagnosis of chronic hepatitis C. 90.2% of those who declined specialist care were patients who had been aware of their HCV diagnosis for several years. This would again confirm PWUD are a difficult-to-treat population, especially in centralized models.

Among the 101 patients who underwent clinical assessment we found a high percentage of advanced fibrosis (34.7%) at risk of HCC and gastrointestinal bleeding^{31,32}, and a high percentage of patients with advanced tumors (n= 4/101;

4%), again confirming that this is a target group reluctant to accepting medical care.

DAAs enable treatment of the patients non-adherent to medication regimes and to follow-up due to their elevated level of SVR. Most of the patients who discontinued HCV treatment had attained SVR. In fact, in the adherence study: the non-adherent population had 94% SVR^{33,34}. In our study these non-adherent patients were identified as heroin addicts.

Subjects who refused care represent the most important study limitation. Subjects who refused screening (n=141/505), completed diagnosis (n= 69/338), underwent clinical assessment (n=41/144) or attended treatment (n=2/101) still represent a potential reservoir of HCV infection among PWUD. Statistical analysis showed that those who refused screening are older patients (above 50 years old) and heroin addicted, while those who are intentionally not following HIV therapy are also refusing HCV treatment. It is in order to reduce this reservoir that we are promoting HCV counseling in this particular setting.

One other study limitation is the absence of a suitable control group. In addition, these SerD centers had no previous experience about clinical trial on HCV diagnosis and treatment.

Conclusions

Our study and its on-site specialist approach starting from screening could get us closer to the goal of HCV PWUD microelimination. The main gap still to be bridged is the scale of patient dropout occurring at Step 3 when centralisation of care becomes necessary.

Efforts should be made to adapt subsequent models in order to minimise dropout rates among these patients. Specifically, these patients should no longer have to navigate their way through a complex health system and for that their pathway from diagnosis to treatment has to be significantly shortened.

A new project is under way that focuses on achieving full on-site, rapid approach and treatment.

Meanwhile the virological samples collected are to be analyzed in order to evaluate the possible presence of molecular clusters that could be associated with possible epidemiological links.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Informed Consent

Written informed consent was provided by all study participants.

Acknowledgements

Supported by Fellowship Program 2017 Gilead Sciences S.r.l., n° 99d17f6d989. Institutional Review Board: National Institute for Infectious Diseases "Lazzaro Spallanzani" IRCCS, Rome, trial registry (n. 49/2017).

Authors' Contribution

The authors thank the Fellowship Program 2017 Gilead. We thank Paola Paci for reviewing the statistical analyses. We thank Mariana Badescu and James Ruscoe for reviewing the English. We thank all the SerDs and Hepatology and Infectious Disease Department of Lazzaro Spallanzani staff: Paola Carabini, Adelaide Equizi, Angela Martino, Luciano Pavoni, Claudia Boro, Elisa D'Anzieri, Danilo Del Prete, Loredana Ferraro, Fabio Patrino, Mauro Neri, Tiziana Mereu, Daniela Nesticò, Catia Salvi, Cristina Tilotta.

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