

# Point-of-care testing for hepatitis C virus infection at alternative and high-risk sites: an Italian pilot study in a dental clinic

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## SUMMARY

The Infectious Diseases Department and the Department of Dentistry of San Raffaele Scientific Institute in Milan conducted a screening and prevention program, the "EASY HCV-test Program," at a dental clinic to increase the identification of unrecognized infections. Using a cross-sectional community-based study design, hygienists in the dental clinic offered patients a hepatitis C virus (HCV) rapid salivary test (Oral-Quick ADVANCE® Rapid HCV Antibody Test) with pre- and post-test counseling prior to initiation of their oral hygiene routine.

From April 2015 to November 2015, the EASY HCV test was offered to 2650 patients visiting the Center of Oral Health and Prevention at the Department of Dentistry at San Raffaele Hospital in Milan. Among them, 2077 eligible volunteers were tested. The test showed positive reactivity in 22 cases; of these, 21 subjects were known to suffer from HCV, and the test confirmed their status. One subject was newly diagnosed with HCV infection.

The results of this study suggest EASY HCV test screening conducted in dental clinics may constitute an effective strategy for increasing HCV testing among people at risk for infection.

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## INTRODUCTION

Hepatitis C affects 170 million people worldwide (four times more than HIV infection), 1.5 million of whom are in Italy (2% of the affected population). However, these data may not accurately represent the true global epidemiological picture of hepatitis C, as the infection is often asymptomatic. Indeed, the signs and symptoms of those who have contracted the hepatitis C virus (HCV) may not occur for many years, and thus may escape diagnosis. Italy has the highest prevalence of liver diseases leading to liver cirrhosis in Europe (World Health Organization (WHO), July 2015).

In April 2014, the WHO launched "Guidelines for the screening, care and treatment of persons with hepatitis C." These were the first guidelines produced by the WHO for dealing with hepatitis C treatment and complement existing

guidelines on preventing the transmission of blood-borne viruses, including HCV. The guidelines were intended for policy-makers, government officials, and others working in low- and middle-income countries that are developing programs for the screening, care, and treatment of people with HCV infection. The guidelines will help expand treatment services to patients with HCV infection, as they provide key recommendations and discuss considerations for implementation. The guidelines recommend that serology screening be used to identify persons with HCV infection and be offered to members of populations with a high HCV prevalence and to individuals with a history of HCV risk exposure/behavior.

Many cases of viral hepatitis remain asymptomatic until decades after infection, allowing the disease to slowly destroy the liver and eventually present severe and deadly complications like liver cirrhosis, liver cancer, and liver failure. In most countries in the region, the majority of people living with viral hepatitis do not know about their infection (in some countries, this is more than 75%). Many became infected through blood transfusions or other medical procedures performed years earlier, when no tests were available. More than 20% of those infected will develop liver cirrhosis or cancer if these diseases are not diagnosed in time (WHO, July 2015).

Early diagnosis is unusual, and identification of the carrier

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is rare in most individuals. Although the blood safety and injecting practices in healthcare settings have improved in recent years, HCV continues to spread. The level of awareness in the general public remains very low.

Recent revolutionary treatments for chronic hepatitis C, such as direct-acting antivirals (DAAs), have made it possible to cure more than 90% of infections in just 3 months and without the severe adverse effects often seen with previous treatment regimens. The WHO is now working on a global strategy to combat viral hepatitis C, with the ambitious goal of eliminating the disease as a serious public health threat, potentially saving millions of people from chronic liver disease-related mortality. The strategy will include a comprehensive package of prevention measures and calls for better access to treatment and improved global awareness about viral hepatitis, the so-called “silent killer”.

The therapeutic prospects for this strategy continue to be encouraging. Indeed, the new generation of drugs renders the eradication of the virus a possibility in the majority of chronic HCV cases, which may also reduce the global dimension of the epidemiology of this infection.

Several vulnerable population groups, particularly people who inject drugs, are at greater risk of infection. However, everyone is potentially at risk, as unsafe injections and other invasive procedures, both within and outside the healthcare sector, can potentially expose individuals to HCV. Several initiatives are needed to identify hitherto undiagnosed patients with chronic viral hepatitis, to propose staged responses to the disease, and to develop antiviral treatments to avoid progression of liver diseases. These initiatives should be targeted not only at the known at-risk populations but also at the general population, particularly those in lower socioeconomic groups.

The dental clinic is one promising venue for efforts to prevent HCV infection and to test for HCV-positive cases. The confidential relationship created between patient and doctor, particularly with regard to HCV infection, is noted in the patient’s clinical database. The need for screening and prevention of infection during operating and consulting sessions facilitate dialogue between dentists and patients about this kind of initiative, thus spreading awareness of the EASY Program among the public (Garbin *et al.*, 2014; Jones *et al.*, 2014).

Participation by dentists and/or dental hygienists in the field of preventive dentistry could improve the quality of the results of HCV screening and prevention. The idea that hygienists and dentists should promote the prevention of not only stomatognathic pathologies but also of systemic diseases, including HCV infection, has become increasingly accepted (Genco and Genco, 2014).

Prevention and treatment are not separate entities when providing care over a long period of time, and the line between these are necessarily blurred (Sim *et al.*, 2006; Gherlone *et al.*, 2015). Dental practices can increase preventive care by introducing small interventions and making use of the practice team. Prevention is also increasingly focused on preventing disease by correcting unhealthy lifestyles that could predispose individuals to develop various diseases. Most current prevention initiatives aim to enhance the relationship between doctor and patient and provide education on a healthy lifestyle (Jones *et al.*, 2014).

Since January 2011, the Infectious Diseases Department of San Raffaele Scientific Institute in Milan has been conducting a prevention program, the “EASY HCV-test Pro-

gram,” which relies on a new oral salivary test (Parisi *et al.*, 2013). The program has been available at STD prevention clinics, general practitioner clinics, and points of care. The aim of the initiative was to encourage people to be tested by facilitating their access to testing. The non-invasiveness of this rapid test (which operates through collection of a saliva sample) and its immediate response makes the offer of testing more attractive to patients (Parisi *et al.*, 2013).

A 10-year collaboration between the Department of Infectious Diseases and the Department of Dentistry of San Raffaele Scientific Institute in Milan resulted in the development of the EASY HCV-test Program for HCV screening and prevention at the first dental clinic in Italy. The aim of the project was to evaluate the feasibility and acceptability of an initiative addressing issues that involve widespread discrimination and social stigma. Measures such as the use of personal protective equipment (gloves, goggles, masks), instrument sterilization, and disinfection of surfaces are aimed specifically at infection control. In addition, measures are implemented to educate the general population on the prevention of hepatitis C and to reduce the transmission of infection by increasing the opportunity to identify unrecognized cases thereof. A number of patient groups (EPAC, Association of People with Hepatitis C, and ANLAIDS-Lombardia Association) have promoted the initiative as an opportunity to develop a protocol of “best practices” with regard to how dentists and hygienists should approach patients with HCV to improve their dental care.

## MATERIALS AND METHODS

This cross-sectional community-based study was sponsored by the Department of Infectious Diseases and the Department of Dentistry of San Raffaele Scientific Institute in Milan and supported by the EpaC Onlus and ANLAIDS-Lombardia associations. The project was implemented in the Unit of Oral Health and Prevention at the Department of Dentistry, where a pool of hygienists offered the HCV rapid test before starting routine professional oral hygiene procedures. Dentists and hygienists who participated in the program were trained on how to propose the test to patients, communicate the HCV test results, and discuss treatment options.

Brochures were distributed in the waiting room to provide patients with information on the prevention of HCV infection. To guarantee the privacy of the subjects, hygienists performed pre-test counseling and provided subjects with an informed consent form (ICF). After signing the ICF, subjects underwent the test free of charge (Parisi *et al.*, 2014).

The subjects who were tested were asked to complete an anonymous questionnaire soliciting data on demographic characteristics, risk-related behaviors, and previous HCV/HIV testing experiences. Specifically, information on sex, drug use, educational level, nationality, general behaviors, use of HIV/HCV prevention services, previous surgical practices, invasive diagnostic practices, dental care, tattoos, and STDs was collected. Those who did not agree to testing were provided with personal counseling about the prevention of HCV and other sexually transmitted infections.

People eligible for inclusion in the study were aged >18 years, unaware of their HCV serological status, and able to complete the questionnaire in Italian or English. The

subjects were informed that they could refuse testing at any time. Post-test counseling was provided to all HCV-reactive and non-reactive subjects by the skilled hygienists involved in the study.

### Testing

The test was performed by a skilled hygienist following the manufacturer's procedures. The prevention program was performed using the new OraQuick ADVANCE® Rapid HCV Antibody Test (OraSure Technologies, Bethlehem, PA, USA) (<http://www.orasure.com/products-infectious/products-infectious-oraquick-hcv.asp>). The test is a single-use immunoassay for the qualitative detection of antibodies to HCV (anti-HCV) in oral fluid, fingerstick whole blood, venipuncture whole blood, and plasma specimens. The clinical sensitivity and specificity of the OraQuick HCV test using oral fluid were 97.8% (95% confidence interval [CI]) and 100% (95% CI, 98.4-100%), respectively. It is very important to follow the manufacturer's sampling procedure (saliva collection), because this step can affect the proper performance of the test, resulting in false positive test results.

An initial, free-of-charge dedicated appointment was offered to all those with preliminary HCV-reactive test results. This appointment was fixed within 24-72 hours (counting working days only) of the regular appointment and involved regular screening, confirmation of test results, other diagnostic procedures to determine the status of the liver disease, and, following identification of the HCV viral load and genotype, the initiation of treatment according to the guidelines.

### Ethics committee and data collection

The project protocol was approved by the Institutional Review Board of the Ethics Committee of San Raffaele Hospital in Milan. An ICF was prepared explaining the details of the study, the HCV testing procedure, and the interventions available for each individual who adhered to the program.

The HCV test results were immediately added to a personal electronic file by the person responsible. Study data, including the questionnaires, were conveyed to the Department of Infectious Diseases of San Raffaele Hospital and analyzed anonymously under the control of the Head of the project and the Department.

### RESULTS

From April 13, 2015 to November 13, 2015, 2377 dental patients visiting the Dental Unit of San Raffaele Hospital in Milan were approached to discuss HCV transmission, risk of HCV infection, disease progression to cirrhosis or hepatocellular carcinoma, and participation in the EASY

HCV-test Program. Due to promotional efforts among the general population, the total number of subjects tested during the period increased gradually over time, with a mean value of ~87 subjects/week. In total, 2097 (78.4% of contacted subjects) of 2377 eligible volunteers underwent HCV tests and completed the interview. Of these, 1426 subjects (68%) completed the anonymous questionnaire on the initiative (Table 1). Usable and complete questionnaires were obtained from 1388 subjects, whereas 38 were invalidated due to missing responses. The data extracted from the valid questionnaires revealed the following about the population responding to the EASY test initiative:

- In total, 65% of the subjects (905 of 1388 subjects, 45% male and 55% female) reported they had never been tested for HCV.
- Seven tests were initially invalid due to migration issues with the immunoassay. These tests were repeated using a new kit that yielded valid results.
- Details of the examined population (not shown here) will be define elsewhere.

Positive reactivity was found in 22 cases; of these, 21 (about 1% of the total tested sample) were known to have HCV, and the test confirmed their status (positive reactivity) with no false positives. They were asked to undergo the new test for research purposes, and, as they were already receiving treatment, were not referred to the infectious diseases specialist. Only one subject was newly diagnosed with HCV infection: a 65 year old housewife with a high level of education who had never been tested for HCV. She had no history of blood transfusions, piercings, surgical interventions, or alcohol or drug abuse. She was asymptomatic, with no history of HCV-related symptoms or pathology. She was immediately referred to the Department of Infectious Diseases of San Raffaele Hospital, where the diagnosis was confirmed, and she had the opportunity to start treatment promptly (fast-track entry, which was arranged by the EASY HCV-test Program).

### DISCUSSION

Our results suggest that the promotion of EASY HCV screening at dental clinics should be further developed as a strategy to increase HCV testing, particularly among those who have never been tested (65% in this sample). Of the young adults (aged 18-25 years) in the study, 71% (134 of 187 subjects) had never been tested for HCV.

A dental clinic serves a heterogeneous population, including individuals who would never have thought of undergoing the tests if they had not been invited to do so by their dental hygienist. For example, such an approach could reach adolescents or young adults, including those with a high educational level who do not consider themselves

**Table 1** - Details on the numbers of tested subjects for each month.

	from 13 to 30 April 2015	May 2015	June 2015	July 2015	September 2015	October 2015	from 1 to 13 November 2015	Total
Contacted and informed subjects	241 (*)	329 (*)	408	395	473	365	166	2377*
Tested subjects	223	306	366	337	411	305	149	2097
Invalid and repeated test	0 (*)	2 (*)	3	1	1	0	0	7
Negative test	219 (*)	300 (**)	338	322	383	305	140	2075
Positive Test	4 (*)	6 (**)	3	3	5	0	1	22

at risk or would not think that testing would be so easy. Moreover, many patients at a dental clinic may be exposed to HCV risk factors. After HCV infection, progression to cirrhosis is more rapid in the following groups: males, those aged >50 years, individuals who consume >50 g/day of alcohol, and those with diabetes and HIV infection (Poynard *et al.*, 1997). This profile also fits subjects at risk of periodontal disease, many of whom are often seen in dental clinics for reasons related to prevention. Consequently, residents of the catchment area of an Oral Health Prevention Center (e.g., the center at the I.R.C.S.S. San Raffaele Hospital) may constitute an appropriate target population for efforts to diagnose and identify individuals with HCV infection.

A satisfactory response rate (2650, 78.4% of the sample) was achieved over the 6-month period. Due to the high socioeconomic status of patients who normally attend a dental clinic specializing in prevention, the subjects expressed great interest in the project.

The use of a rapid diagnostic test that is also extremely easy and comfortable was considered a key determinant of the success of this initiative. The use of oral fluid is an attractive alternative for a patient given the fact that the collection of plasma or serum samples requires equipment and training and is more time-consuming. Therefore, patients appeared to be more willing to undergo this test.

All patients answered questions about HCV infection and transmission modes, and those with positive results were provided with information on the next steps to be taken by healthcare professionals (in this case, dental hygienists). Patients felt reassured by the guarantee that if the EASY HCV test were positive, immediate and preferential referral to the specialist clinic for a first visit would be provided, at which time a complete diagnostic process would be started. Indeed, patients who were newly diagnosed with HCV infection were seen by the specialist department of the same hospital within 2 working days. The Working Group also decided, in accordance with wishes of the affected patients, to test the 21 subjects already diagnosed with HCV infection to publicize this new and alternative screening method (which had been previously unknown to all) and assess the possible presence of false negatives. Efforts to increase awareness of these alternative tests among dental patients and providers may be an appropriate approach to increasing the number of people with awareness of their serological status. The recent introduction of the rapid oral HCV antibody test facilitates the process of testing at facilities providing ambulatory dental care.

In this study, 65% of subjects (905 of 1388 subjects, 45% male and 55% female) reported that they had never been tested for HCV. The majority of the subjects were >40 years of age; 423 subjects (31%) were >50 years of age and 182 subjects (13%) were 41-50 years of age. This is probably due to the fact that tests for HCV were not assiduously prescribed during pregnancy or in medical practice in general until a few years ago. This suggests that the promotion of EASY HCV screening at a dental clinic can increase HCV testing among the general population, especially those who have never been tested.

Patient groups (supported by EpaC Onlus and AN-LAIDS-Lombardia associations) promoted this initiative

as an opportunity to develop a protocol of "best practices" for how to approach patients with HCV visiting dental clinics, how to train dentists on communicating with patients about tests for HCV, and, especially, how to treat such patients in a non-discriminatory manner. This overall philosophy is consistent with that underpinning the "humanization" of medical care, which considers not only the diseases but also the patients' general well-being.

The dental clinic of the I.R.C.C.S. of San Raffaele Hospital, Milan follows the best practices, which are outlined in the document attached to this paper. These include comprehensive professional oral hygiene services, rapid screening for HCV infection, pre- and post-test counseling, non-discriminatory dental care for patients suffering from HCV, and overall support for patients with systemic diseases such as HCV. This initiative was developed in response to the global progress in hepatitis testing, the remaining challenges in this domain, and the future directions for such testing recently outlined in the new 2016-2020 WHO guidelines.

These challenges include how to better focus testing and reach those still undiagnosed and most at risk, especially key populations, such as men, adolescents, and children. The key challenges in hepatitis testing include the lack of simple, reliable, and low-cost diagnostic tests and testing facilities. Additionally, data regarding country-specific hepatitis testing approaches, who to screen, and the stigmatization and social marginalization of those with or at risk of viral hepatitis are lacking. Moreover, there are no international or national guidelines on hepatitis testing in resource-limited settings.

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