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ORIGINAL ARTICLE

# Implementation of a re-linkage to care strategy in patients with chronic hepatitis C who were lost to follow-up in Latin America

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**Abbreviations:** DAA, direct-acting antivirals; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LTFU, lost to follow-up; SVR, sustained virological response; WHO, World Health Organization.

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## Abstract

To achieve WHO's goal of eliminating hepatitis C virus (HCV), innovative strategies must be designed to diagnose and treat more patients. Therefore, we aimed to describe an implementation strategy to identify patients with HCV who were lost to follow-up (LTFU) and offer them re-linkage to HCV care. We conducted an implementation study utilizing a strategy to contact patients with HCV who were not under regular follow-up in 13 countries from Latin America. Patients with HCV were identified by the international classification of diseases (ICD-9/10) or equivalent. Medical records were then reviewed to confirm the diagnosis of chronic HCV infection defined by anti-HCV+ and detectable HCV-RNA. Identified patients who were not under follow-up by a liver specialist were contacted by telephone or email, and offered a medical reevaluation. A total of 10,364 patients were classified to have HCV. After reviewing their medical charts, 1349 (13%) had undetectable HCV-RNA or were wrongly coded. Overall, 9015 (86.9%) individuals were identified with chronic HCV infection. A total of 5096 (56.5%) patients were under routine HCV care and 3919 (43.5%) had been LTFU. We were able to contact 1617 (41.3%) of the 3919 patients who were LTFU at the primary medical institution, of which 427 (26.4%) were cured at a different institutions or were dead. Of the remaining patients, 906 (76.1%) were candidates for retrieval. In our cohort, about one out of four patients with chronic HCV who were LTFU were candidates to receive treatment. This strategy has the potential to be effective, accessible and significantly impacts on the HCV care cascade.

**KEYWORDS**
care cascade, elimination, hepatitis C virus, Latin America, retrieval

## 1 | INTRODUCTION

Latin America is constituted by 20 countries with a population of more than 626 million people and an estimated hepatitis C virus (HCV) prevalence rate <1%.[1] Approximately only 14% of the people with chronic HCV are estimated to be diagnosed with this infection,[2] making the World Health Organization's (WHO) ambitious goal of eliminating HCV by 2030 difficult to attain.[3] In order to achieve this target, implementation of innovative strategies to diagnose and treat more patients is needed. In this sense, several factors must be organized for the HCV care cascade, including a high HCV infection diagnosis rate, successful linkage to care, treatment maintenance, ability to scale up treatment, and prevention strategies of new infections and reinfection.[4] Currently, most efforts are focused on diagnosing new patients or addressing high-risk groups. Developing strategies to identify HCV patients have been challenging. Some high-risk groups are relatively easy to reach and screen, such as patients with end-stage renal disease needing haemodialysis or those who have previously used intravenous drugs.

Little attention has been paid to the challenge of maintaining patients with HCV infection and how to re-link those who were lost to follow-up (LTFU) back to HCV care. LTFU occurs in all steps of the care cascade and may severely affect clinical outcomes. Studies from different countries have shown that approximately 14%–61% of patients diagnosed with HCV infection are LTFU.[5–9] This is likely the consequence of the slow, silent and asymptomatic progression of the disease, and prior experience with interferon (IFN)-based therapy that had considerable side effects and low sustained virological response (SVR) rates. The high amount of LTFU observed at outpatient's clinics urges further action. Thus, re-linkage of those

LTFU back into the HCV care cascade is an important step on the road towards HCV elimination. Several strategies have been performed, which have shown to be successful at retrieving a significant proportion of these patients to HCV care and proved to be a cost-effective approach.[5–10]

In this study, we aimed to evaluate the implementation of a strategy to identify patients with chronic HCV who were LTFU in 13 different countries in Latin America. Additionally, we evaluated their candidacy for reengagement and compared their characteristics with those who were under routine HCV care.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design, setting and participating centres

We conducted a multicentre and multinational implementation study utilizing a strategy to identify and reengage individuals with chronic HCV infection who were lost to medical follow-up in 45 centres from 13 Latin American countries. The enrolment period was from 1 December 2020 to 31 October 2021. The study was supported and coordinated by the Latin American Association for the Study of the Liver (ALEH) and registered in an open public registry (clinicaltrials.gov: NCT04470271). Each Ethical Committee from all participating centres approved the study protocols. All data were processed confidentially in an anonymous database accessible only to the coordinating centre. The protocol was in accordance with the Strengthening the Reporting of Observation Studies in Epidemiology guidelines.[11] The study followed ethical standards (institutional and national) and those mandated by the Helsinki Declaration of 1975, as revised in 2008. All authors had access to the study data, reviewed and approved the final version of this manuscript.

### 2.2 | Target population and retrieval strategy

The target population for re-linkage to care was defined as subjects 18 years old or greater with diagnosis of chronic HCV infection defined as having anti-HCV antibody and positive HCV-RNA. Patient LTFU was defined as those individuals with chronic HCV who did not have routine follow-up by a specialist. Based on previous studies and considering the restrictions due to the COVID-19 pandemic, more than 365 days from the last HCV-related visit with the treating medical institution was considered sufficient to define LTFU in patients with HCV.[12]

The reengagement strategy consisted of two phases. In the first phase, patients with HCV were identified by the international classification of diseases (ICD-9/10) or equivalent. In those institutions with no access to electronic medical records, information regarding HCV status was obtained according to the resources of each centre (i.e. HCV databases). Medical and laboratory records were then reviewed to confirm the diagnosis of chronic HCV infection. All patients with chronic HCV were enrolled at each site, and data were collected and managed using REDCap® hosted by the Austral University Hospital.[13] Variables collected included patients' age, sex, comorbidities, HCV genotype, history of hepatocellular carcinoma, liver transplantation status, extrahepatic manifestations of HCV infection and HCV treatment history. Liver fibrosis stage was recorded according to the last evaluation method by liver elastography, liver biopsy, serum markers or the presence of clinical significant portal hypertension as previously described.[14] Those who spontaneously cleared HCV infection, had short life expectancy at presentation, had been referred to another centre or who were deceased were excluded from the study. The resulting list consisted of patients with chronic HCV infection who were LTFU and a second group of patients who were under routine HCV care at their medical institution.

In the second phase, we assessed HCV status in patients who were under routine HCV care. Reason for no treatment was recorded, as well those who were cured or were non-responders to antiviral therapies. Patients who were LTFU were contacted by telephone or e-mail by a research investigator at each institution to assess their HCV status. Up to two e-mails were sent and/or three phone calls were made, on different days, including weekends. From those patients who were finally contacted, reason for LTFU was identified, and patients classified as candidates to be treated according to local guidelines, cured at a different institution, unwilling to be treated, or deceased.

### 2.3 | Statistical analysis

Continuous variables were reported with a mean (±standard deviation, SD) or median (Interquartile ranges 25%–75%, IQR). Proportions were calculated with corresponding 95% confidence intervals (95% CI). All statistical data were analysed with STATA 13.0 (StataCorp).

## 3 | RESULT

### 3.1 | Identification of patients eligible for retrieval

A total of 10,364 individuals were identified with a previous positive anti-HCV test, as illustrated in Figure 1. The list of the contribution of each participating centre is described in Table S1. We excluded 1349 (13%) patients as they were wrongly coded, presented missing data or had undetectable HCV-RNA on further chart review. Of the remaining 9015 individuals with confirmed chronic HCV infection, a total of 5096 (56.5%, 95% CI 55.5–57.5) patients were under routine HCV care and 3919 (43.5%, 95% CI 42.4–44.5) had been LTFU. Figure 2 describes the proportion of patients who were LTFU in each participating country.

Demographic and clinical characteristics of patients with HCV attending and those LTFU are presented in Table 1. Overall, patients

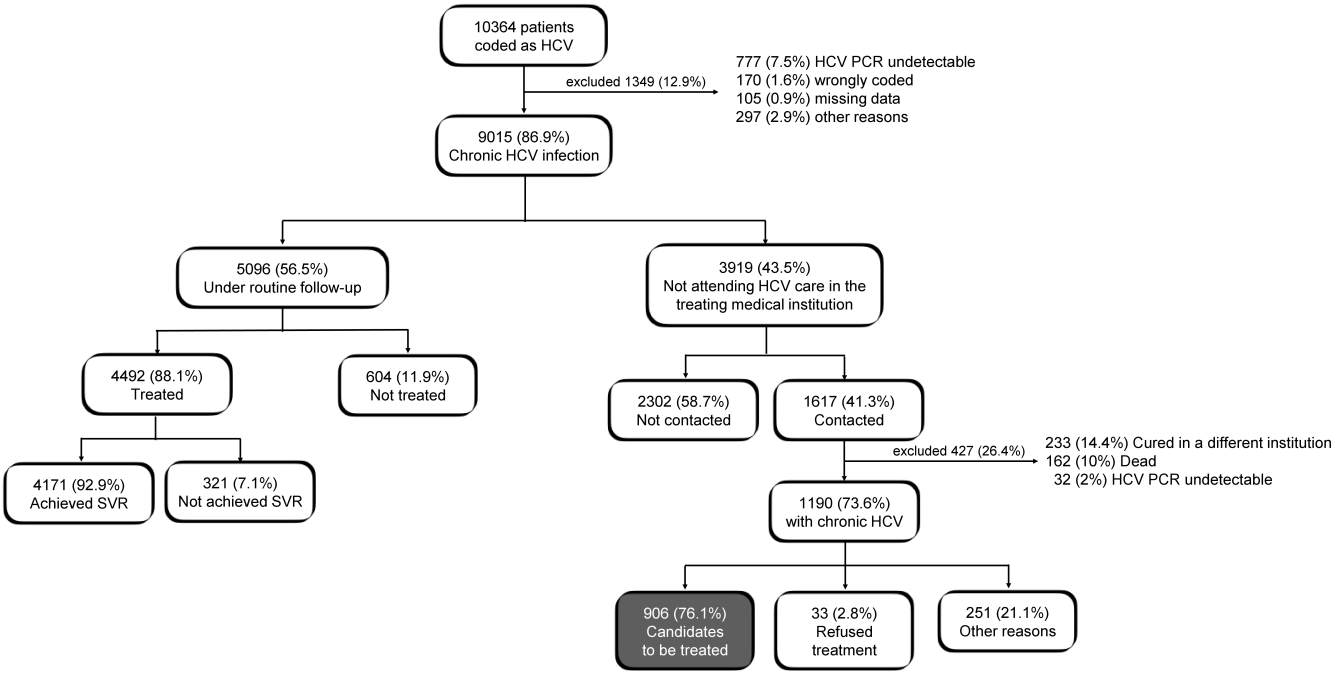
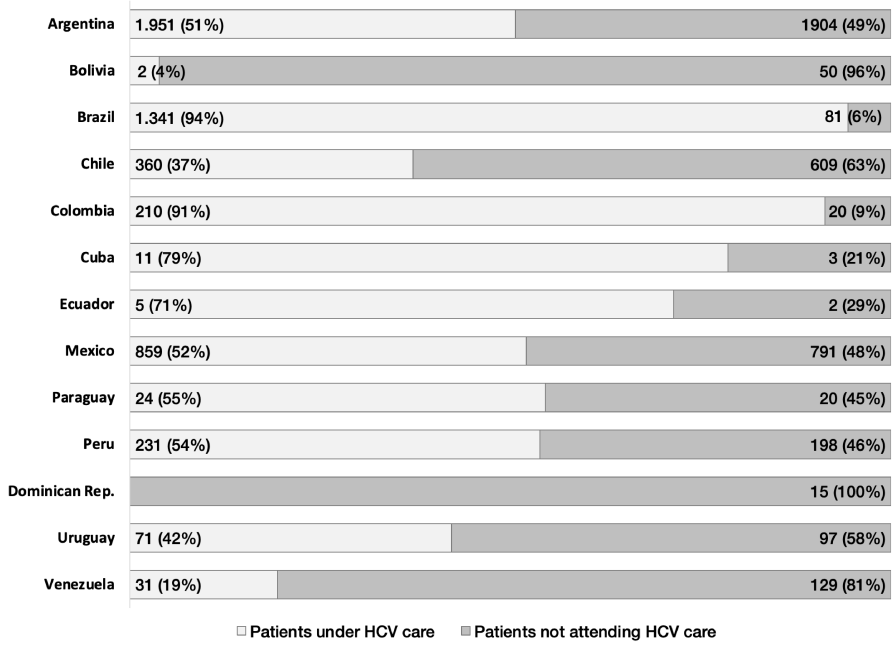



**FIGURE 1** Identification and classification of patients who were lost to follow-up and those undergoing routine HCV care.

**FIGURE 2** Proportion of patients who were lost to follow-up in each participating country.




who were LTFU were younger (58.7 years vs. 61.1 years; $p < .001$), were more likely to be men (57.4% vs. 49.5; $p < .001$) and to have a concomitant infection with human immunodeficiency virus (HIV) (13.8% vs. 7.3%; $p < .001$) and hepatitis B virus (3.1% vs. 1.7%; $p < .001$).

## 3.2 | Patients lost to follow-up

Of the patients who were LFTU at their primary medical institution, 41.3% (1617/3919) were contacted, and 23.1% (906/3919) met criteria for reengagement (Figure 1). Out of the patients who were contacted, 14.4% (233/1617) were already treated and cured at a different institution and 10% (162/1617) were deceased (Figure 1). Thus, 73.6% (1190/1617) of the patients who were contacted had chronic HCV infection and 76.1% (906/1190) were candidates for medical reevaluation at the outpatient clinic. As shown by the clinical characteristics of individuals with active HCV infection in Table 2, patients who were candidates for reengagement had a median age of 57 ± 14.4 years and were mostly male (53.3%), 15.6% of them had a concomitant HIV infection, 3.6% had a past history

**TABLE 1** Baseline characteristics of patients with chronic hepatitis C virus undergoing routine HCV care and of patients who were lost to follow-up.

| | Patients not attending HCV care, *N* = 3919 | Patients under HCV care, *N* = 5096 |
|---|---|---|
| Age (median, SD) | 58.7 (13.8) | 61.1 (12.7) |
| Gender (*n*, %) | | |
| Male | 2250 (57.4) | 2523 (49.5) |
| Female | 1667 (42.5) | 2562 (50.3) |
| Transgender | 2 (0) | 10 (0.2) |
| Race (*n*, %) | | |
| Caucasian/Hispanic | 3.617 (92.3) | 4.350 (85.7) |
| African American | 73 (1.9) | 265 (5.2) |
| Amerindian | 77 (2.0) | 98 (1.9) |
| Asian | 18 (0.5) | 22 (0.4) |
| Other | 134 (3.4) | 361 (7.1) |
| HCV genotype (*n*, %) | | |
| 1 | 1.599 (73.9) | 3.321 (73.4) |
| 2 | 241 (11.1) | 461 (10.2) |
| 3 | 265 (12.2) | 651 (14.4) |
| 4 | 60 (2.8) | 90 (2.0) |
| 5 | 0 (0) | 3 (0.1) |
| Unknown HCV genotype (*n*, %) | 1754 (44.8) | 570 (11.2) |
| Comorbidities (*n*, %) | | |
| Hypertension | 892 (22.8) | 1.577 (30.6) |
| Diabetes | 481 (12.3) | 917 (17.8) |
| Body mass index >30 | 261 (6.7) | 545 (10.7) |
| Chronic kidney disease | 240 (6.1) | 356 (7.0) |
| History of cardiac disease | 146 (3.7) | 321 (6.3) |
| Cerebrovascular disease | 33 (0.8) | 37 (0.7) |
| Coinfection (*n*, %) | | |
| Human immunodeficiency virus | 540 (13.8) | 374 (7.3) |
| Hepatitis B virus | 124 (3.1) | 85 (1.7) |
| Extraheptic manifestations (*n*, %) | | |
| Non-Hodgkin lymphoma | 19 (0.5) | 55 (1.1) |
| Cryoglobulinemia | 22 (0.6) | 101 (2.0) |
| Porphyria cutanea tarda | 22 (0.6) | 22 (0.4) |
| Immune thrombocytopenia | 25 (0.6) | 21 (0.4) |
| Lichen planus | 5 (0.1) | 14 (0.3) |
| Sjögren disease | 3 (0.1) | 14 (0.3) |
| Other | 52 (1.3) | 101 (2.0) |
| Liver fibrosis stage (*n*, %) | | |
| Mild (F0–F2) | 882 (22.5) | 1964 (38.5) |
| Advanced (F3–F4) | 1261 (32.2) | 2573 (50.5) |
| Not evaluated | 1776 (45.3) | 559 (11.0) |
| History of hepatocellular carcinoma (*n*, %) | 212 (5.4) | 399 (7.8) |
| Liver transplant (*n*, %) | 63 (1.6) | 387 (7.6) |

of hepatocellular carcinoma and 0.6% underwent liver transplantation. In those patients with prior liver fibrosis assessment, 39.1% had already progressed to advanced fibrosis (F3-4). The main identified reasons for LTFU, as expressed by patients, included (1) having lack of information regarding liver disease progression (25%), (2) loss of health insurance (13%), and (3) lack of information about new antiviral treatments (9%) and having moved to a different location (8%).

**TABLE 2** Baseline characteristics of patients lost to follow-up who are candidates to receive treatment with direct-acting antivirals.

| | Total, N = 906 |
|---|---|
| Age (media, SD) | 57 (14.4) |
| Gender (*n*, %) | |
| Male | 528 (58.3) |
| Female | 377 (41.6) |
| Transgender | 1 (0.1) |
| Race (*n*, %) | |
| Caucasian/Hispanic | 867 (96.0) |
| African American | 4 (0.4) |
| Amerindian | 15 (1.7) |
| Asian | 4 (0.4) |
| Other | 13 (1.4) |
| HCV genotype (*n*, %) | |
| 1 | 297 (32.8) |
| 2 | 51 (5.6) |
| 3 | 43 (4.8) |
| 4 | 28 (3.1) |
| 5 | 0 (0) |
| Unknown | 487 (53.4) |
| Comorbidities (*n*, %) | |
| Hypertension | 251 (27.7) |
| Diabetes | 128 (14.1) |
| Body mass index >30 | 43 (4.8) |
| Chronic kidney disease | 51 (5.6) |
| History of cardiac disease | 29 (3.2) |
| Cerebrovascular disease | 6 (0.7) |
| Coinfection (*n*, %) | |
| Human immunodeficiency virus | 141 (15.6) |
| Hepatitis B virus | 20 (2.2) |
| Liver fibrosis stage (*n*, %) | |
| Mild (F0–F2) | 201 (22.2) |
| Advanced (F3–F4) | 129 (14.2) |
| Not evaluated | 576 (63.6) |
| History of hepatocellular carcinoma (*n*, %) | 33 (3.6) |
| Liver transplant (*n*, %) | 5 (0.6) |

### 3.3 | Patients who were under regular hepatitis C care

After chart review, 5096 (56.5%) patients were under routine HCV care (Figure 1). A total of 4492 (88.1%) individuals had undergone at least one antiviral treatment and 4171 (92.9%) achieved SVR. Treatment regimens are described in Table S2, and response to the different antiviral schemes is presented in Figure S1 Overall, 604 (11.9%) individuals were under HCV care but did not receive any antiviral treatment. The main identified reasons for not being treated were barriers to access direct-acting antiviral (DAA) regimens (37%), patients being unwilling to receive antiviral therapies (18%) and having short life expectancy determined by their treating physician (16%).

## 4 | DISCUSSION

This large Latin American multicentre cohort study includes more than 9000 patients with chronic HCV infection and shows that almost one out of four patients who were LTFU are candidates to receive antiviral treatment and cure. Moreover, we found a substantial proportion of patients who were routinely followed by a physician still did not have access to DAA therapies. These findings represent a significant barrier to achieve HCV elimination goal by 2030.

The high percentage of patients LTFU in our study was unfortunately not unexpected given that Latin American countries have a segmented and fragmented healthcare system, with many countries lacking integrated public policies and systematic approaches that address viral hepatitis. These countries often suffer from a vulnerable and fluctuating economy where many individuals can lose their health insurance affecting patient's adherence to access to clinical visit and subsequently to medications. Difficulties to access DAA regimens are dissimilar around Latin American. In our study, a significant number of patients with HCV who were under routine care did not have insurance approval for therapy. The current DAA costs in some Latin American countries constitute an obstacle to the access to treatment after diagnosis, despite decreasing prices or the use of generic compounds. Some countries of the region have unrestricted access to universal coverage of DAAs such as Argentina, Brazil, Chile and Mexico. Other countries such as Peru have restricted access to DAAs based on fibrosis stages, while some other countries including Cuba, Bolivia and Ecuador have access to antiviral therapies only through donations. Different strategies aimed at increasing a large-scale implementation of HCV treatment in each country need an in-depth evaluation to address their own limitations. This includes resource sharing by countries with unrestricted access to DAAs. Experience has shown that expansion of treatment indications to non-specialized healthcare settings has provided very good results,[15–17] which can be modelled by resource-rich settings.

In our study, we identified poor understanding and awareness of the risk of serious liver complications from discontinuing HCV care. Education programs that raise awareness about HCV care among patients and physicians are needed to enhance treatment adherence and treatment outcomes. This can also include targeting vulnerable populations such as those co-infected with HIV based on our findings that a high proportion of them were LTFU. Coinfection with HIV has also being described as a factor associated with inability to contact patients after using a digital case-finding algorithm for untreated patients with HCV.[18] Previous studies investigating patients LTFU during the IFN-era have described strikingly high rates of LTFU ranging from 63% to 96%.[8,19] The IFN-based therapies were

associated with low cure rates and considerable side effects reducing patients' interest on remaining on the HCV care continuum. In the new DAA regimen era, reengagement studies have reported better results. Kracht et al.[9] designed a retrieval project through screening prior HCV positive tests in Utrecht, Netherlands, where authors found that 14% of chronic HCV were LTFU but only 43% of the patients were re-linked to HCV care. A study from Seville, Spain, analysed the anti-HCV positive test results at the Microbiology Unit.[5] Of the total anti-HCV-positive patients, 21% were never referred to a specialist, and of those who were referred, 23.1% were LTFU. In this study, authors were able to contact 45.3% of the non-referred and 54% of the referred patients. These results are in line with our findings where we contacted 41% of LTFU patients of which 56% were potential candidates for re-linkage to care.

In order to achieve a complete HCV elimination, high reengagement rates are necessary to prevent infection spread and development of HCV-related complications. In our study, we described a high proportion of patients LTFU with advanced fibrosis. Similar results were described by a nationwide retrieval project, CELINE study, were 27% of the retrieved patients presented advanced liver fibrosis.[20] These findings highlight the importance of retrieving patients with chronic HCV to prevent liver-related complications such as cirrhosis and hepatocellular carcinoma. National and regional authorities should commit to this task by providing contact details to enhance case-finding and implementing methods to contact individuals who are LTFU. For example, in the Netherlands, asylum seekers were identified as an important group in the LTFU population.[21]

When evaluating different case-finding strategies, retrieval seems more efficient in comparison with screening projects performed in high-risk groups and in the general population. This can be partly explained by the high number needed to screen in a low-prevalence territory like Latin America.[1] Screening studies performed in the general population are needed, but they can be expensive, time consuming and logistically challenging. This strategy can become frustrating when it is associated with a low proportion of newly identified HCV patients. Alternatively, van Dijk et al.[22] proposes micro-elimination through retrieval to become a standard of care and to include this concept in HCV clinical practice guidelines or elimination plans. We agree that these measures can be suitable and feasible to apply in Latin America.

This multinational study allows a better understanding of the complexities surrounding HCV treatment implementation in Latin America region in this new DAA era. However, this study has some limitations. First, medical records were retrospectively evaluated and cannot account for undocumented patients' characteristics, which were tried to be addressed by submitting queries to the participating institution on the missing values and inconsistencies. Also, we did not evaluate the rate of DAA initiation by patients who were contacted and re-linked to care. This will be assessed in a future study given that access to antiviral therapies is different among the participating countries.

In conclusion, this study showed that implementing re-linkage to care strategies for patients with chronic HCV who are not under routine care is feasible and potentially effective in achieving HCV micro-elimination. We believe our strategy provides a frame-work for other local or nationwide reengagement projects to achieve HCV micro-elimination. The implementation of artificial intelligence or digital innovations such as digital case-finding algorithm can help to identify untreated patients with HCV and further reduce the workload and costs.[18] Strong efforts to link patients LTFU back to HCV care, in combination with maintaining HCV screening strategies, and providing prompt access to HCV treatment are necessary to reach WHO elimination targets.

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## CONFLICT OF INTEREST

Dr. Mendizabal reports personal fees from Janssen, Gador and Gilead. Dra. Graciela Elia Castro Narro is a speaker for Gilead. Dr. Aldo Torre is a speaker for Viatrix, Grifols, Medix, Alfa Wasserman and Grunenthal. Dr. Marciano reports personal fees from Gador, Gielad and Abbvie. Dr. Marcelo Silva reports personal fees from Gilead. The rest of the authors have nothing to disclose.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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