

Time To Complete hepatitis C Cascade of Care Among Patients Identified During Mass Screening Campaigns in Rural Rwanda: A Retrospective Cohort Study

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Abstract

Background

Since the discovery of direct-acting antivirals, treatment for hepatitis C virus (HCV) is increasingly accessible in low-resource settings, but quality of care in these settings is not known. We described progression through the cascade of care among individuals who screened positive for HCV antibodies during a mass screening campaign in Kirehe and Kayonza, two rural Rwandan districts, in September 2019.

Methods

This retrospective cohort study used routine clinical data to assess proportions of participants completing each stage of the cascade of care, including: a) screening positive on rapid diagnostic test; b) return of initial viral load results; c) detectable viral load; d) treatment assessment; e) treatment initiation; f) return of sustained virological response (SVR12) results; and g) achieving SVR12. We proposed three indicators to assess timely care provision and used medians and interquartile ranges (IQR) to describe the time to complete the cascade of care.

Results

Overall, 666 participants screened HCV positive, among them, 452 (68.1%) were female and median age was 61 years (IQR: 47, 70). Viral load results were returned for 537 (80.6%) participants of whom 448 (83.4%) had detectable viral loads. Of these, 398 (88.8%) were assessed for treatment, 394 (99%) were initiated, but only 222 (56.3%) had results returned for SVR12. Among those with SVR12 results, 208 (93.7%) achieved SVR12. When assessing timely care provision, we found 65.9% (95% CI: 62.0, 69.7) of initial viral load results were returned \leq 30 days of screening; 45% (95% CI: 40.1, 49.8) of people with detectable viral load completed treatment assessment \leq 90 days of initial viral load results; and 12.5% (95% CI: 9.2,16.3) of SVR12 results were returned \leq 210 days of treatment initiation among those who initiated treatment. The overall median time from screening to SVR12 assessment was 437 days.

Conclusion

Despite high rates of SVR12 among those who completed all stages of the cascade of care, we identified gaps and delays in the treatment cascade. Improving communication between viral load testing hubs and health facilities could reduce the turn-around time for viral load testing, and actively monitor timeliness of care provision could improve quality of HCV care.

Introduction

Globally, hepatitis C virus (HCV) affects 58 million people(1). HCV increases the risk of developing liver cirrhosis and liver cancer and kills approximately 399,000 people annually(2). According to recent estimates, 15% of the global burden of HCV infection is in Africa, where it affects more than 11 million people, 140,000 of whom live in Rwanda(3, 4). Until the discovery of direct-acting antivirals (DAAs), treatment for HCV with interferon-based drugs was expensive, had poor efficacy, and often resulted in severe side-effects, making it practically impossible to treat the majority of people with HCV (4). Through DAA treatment, over 95% of HCV patients may be able to achieve a Sustained Virologic Response (SVR12), also known as virologic cure, which occurs when there is no detectable HCV ribonucleic acid (RNA) twelve weeks after treatment completion(5). DAAs have proved to be efficient and safe with high cure rates in the management of the disease in both high and low-income countries (6, 7).The recent reduction in the price of DAAs in low and middle income countries LMICs has made it possible to plan for a widespread treatment in those settings (8).

In Rwanda, the viral hepatitis program was established in 2011, and in 2018 the national hepatitis elimination plan announced an ambitious target to treat 90% of those infected by 2024 (9). Subsequently, the Rwandan Ministry of Health introduced rapid diagnosis testing for HCV in all health facilities, capability to assess HCV RNA viral loads in 15 laboratory hubs, and free DAA treatment in all district hospitals and health centres. Since 2017, the Ministry of Health has organized national viral hepatitis mass screening campaigns for people aged 15 years and above as a strategy to identify patients who are HCV positive and link them to care. Since the launch of Rwanda's hepatitis elimination plan, as of March 2017, over 700,000 people have been screened and 9,000 have been initiated to treatment, with a 92% treatment success (i.e achieving SVR12). (7).

Despite this rapid scale-up of testing and treating for hepatitis C in Rwanda, there is limited information about the time it takes for patients who screen positive for hepatitis C in mass screening campaigns to be enrolled, initiated to DAA treatment, and assessed for a cure. To be effective, HCV screening campaigns should be coupled with timely initiation treatment of those chronically infected. Long delays in treatment initiation may result in loss-to-follow-up, which could undermine the efforts of the elimination campaign. Similarly, delays in assessing the outcome of

treatment may prevent further management for those in need. A previous modeling study concluded that the imperfect follow-up during the HCV cascade of care can reduce the real-world effectiveness of HCV therapy by as much as 75% (10). In this study, we aim to understand the cascade of care for HCV among patients in rural Rwanda, with an emphasis on understanding the time from screening to SRV12 ascertainment among HCV patients identified through mass screening campaigns. By identifying gaps and delays in care provision, we hope to identify strategies for HCV management programs in Rwanda.

Methods

Study setting

Our study was conducted in two rural Rwandan districts, Kirehe and Southern Kayonza, supported by Partners in Health/Inshuti Mu Buzima (PIH/IMB). PIH/IMB is a non-governmental organization which has been supporting the Rwandan Ministry of Health in health systems strengthening since 2005. In September 2019, the national government implemented a mass screening campaign for hepatitis B and C. PIH/IMB supported the screening and linkage to care activities in Kirehe and Southern Kayonza. SD Bioline RDTs manufactured by Abbott Diagnostics Korea Inc. were used to detect HCV antibodies(11). In Rwanda, the standard of care for people who were screened positive during a mass campaign is same-day collection of venous blood samples, which are transported to a testing hub for viral load testing. If the viral load is detectable (≥ 15 IU/mL), the patients are assessed for eligibility for treatment initiation on DAAs, following the national guidelines(12). Most of patients are prescribed a 12-week course of DAAs; however, patients with decompensated cirrhosis are prescribed a 24-week course of the treatment. Twelve weeks after the completion of DAA treatment, a second viral load test is performed to assess SVR12 and to identify whether patients are cured or will need further management. At the time of the September 2019 screening campaign, HCV infection management was not yet decentralized at the primary level health centres. To facilitate patients' access to care during the period of the screening and linkage to care activities described in this study, PIH/IMB organized a mobile clinic where clinicians and lab technicians from district hospitals met with patients at their nearest health facilities. This approach allowed patients to attend their local primary-level health centres for same-day clinical consultations, lab exams and treatment initiation, as has been described in detail elsewhere (13).

Study design and population

We conducted a retrospective cohort study among participants aged 15 years and above who screened positive for HCV antibodies during the September 2019 mass hepatitis screening campaign in Kirehe and Kayonza districts. We excluded those with negative or indeterminate HCV screening results or who were not screened at a PIH-supported site.

Data source

Routine clinical data were collected during the mass screening campaign by trained clinicians and included self-reported demographic data and clinical characteristics. Additional data on viral load testing, linkage to care, treatment initiation, and treatment outcomes were extracted from HCV patient files. For programmatic purposes, all data were digitalized and entered into a dedicated Research Electronic Data Capture (REDCap) database to support clinical management (14).

Data was extracted from REDCap and de-identified for analysis. Data was extracted on March 24th, 2021, 18 months after the completion of the screening campaign.

Data analysis

We analyzed the socio-demographic characteristics of participants who screened positive for HCV antibodies, including district of residence, gender, age, and marital status categorized as single, married or cohabitating and widow or divorced. In addition, we described Ubudehe category, which reflects the socio-economic status of households. There are four Ubudehe categories, where category one reflects the poorest and category four reflects the wealthiest(15). We also reported health insurance status, which was categorized as, community based health insurance (CBHI), locally known as Mutuelle; other public and private health insurances; or uninsured. We also described patients' self-reported comorbidities at the time of screening, including heart disease, HIV, hypertension, diabetes and chronic renal failure and self-reported risk factors for known for HCV infection, including history of traditional surgical practice, surgery, multiple sex partners, viral hepatitis in the family, blood transfusion, and unhygienic medical or household practices and genocide survivor status. Those who reported a previous diagnosis of hepatitis B, hepatitis C, liver disease, or having previously been screened for hepatitis were grouped into a single category reflecting prior history of hepatitis or liver disease. We described categorical data using frequencies and percentages and continuous data using medians and interquartile ranges (IQR). We also reported the numbers and percentages of participants completing each stage of the cascade of care for HCV infection. Stages in the cascade of care included: a) screening positive on a rapid diagnostic test; b) return of initial viral load results; c) having a detectable viral load; d) being assessed for treatment; e) initiating treatment; f) return of results for a post-treatment viral load test (SVR12 results); and g) achieving SVR12.

We defined three key indicators to assess timely provision of HCV care. These indicators included: a) percentage of people who screened RDT positive for HCV who had their initial viral load test results returned within 30 days of screening; b) percentage of people with detectable HCV RNA who completed their treatment assessment within 90 days of receiving their viral load results; and c) the percentage of patients who initiated treatment who had their SVR12 results returned within 210 days of treatment initiation. For each indicator, patients who had not completed the stage of interest at the time of data analysis were included in the denominator, but not the numerator. Patients who were documented as having completed a stage but were missing data on dates such that it was not possible to classify them as having completed the stage of interest within the desired window were excluded from the complete case analysis. However, we considered two sensitivity analyses: a best-case scenario where all those who were missing relevant dates were considered to have experienced the event of interest within the desired time window and a worst-case scenario where all those who were missing relevant dates were considered to have experienced the event of interest after the desired time window. For each indicator, we reported proportions with 95% confidence interval (CI). Finally, we calculated median and IQRs to estimate the days required to complete key stages of the HCV infection cascade of care, including: a) days between screening and return of initial viral load results; b) days between return of initial viral load results and treatment initiation; c) days between treatment initiation and return of SVR12 results and; d) the overall days from screening to return of SVR12 results. People who were eligible to have completed a stage but had not yet completed it at the time of data analysis were considered to be right censored at the extreme end of the distribution and were included in the calculation of the median and IQR. All analyses were conducted using Stata v.15.1 (Stata Corp, College Station, TX, USA).

Results

Of the 9,240 people included in the REDCap database at the time of data extraction, 8,776 (94.5%) were from PIH/IMB supported sites, and 1,725 (19.6%) had been screened during the September 2019 campaign. Of the 1,725, we excluded 1,057 (61.2%) people with HCV-RDT negative results and 2 people without HCV-RDT results for a final sample size of 666 participants. Because district officials often refer only RDT + cases to PIH/IMB, the proportion of HCV-RDT individuals in our database, does not reflect the prevalence of HCV in these districts. The majority of patients were from Kirehe district (n = 459, 68.9%) and most were female (n = 452, 68.1%) (Table 1). The median age was 61 years (IQR: 47,70). Almost half of study participants were married or cohabitating (n = 357, 54.2%). Ubudehe category 3 was the most common (n = 310, 48.6%), and nearly all study participants used Mutuelle as their health insurance (n = 641, 96.4%). The most common self-reported comorbidities were heart disease (n = 33, 5.0%) and HIV (n = 20, 3.0%) respectively. The most common self-reported risk factor was history of traditional surgical practice (n = 215, 32.3%).

Table 1
Socio-demographic and clinical characteristics (N = 666)

Variable	N	%
District (N = 666)		
Kayonza	207	31.1
Kirehe	459	68.9
Sex(N = 664)		
Female	452	68.1
Male	212	31.9
Age, years (Median (IQR), N = 661)		
	61 (47,70)	
Marital status(N = 659)		
Single	74	11.2
Married or cohabitating	357	54.2
Widowed/Divorced	228	34.6
Ubudehe category (N = 638)		
Category 1	104	16.3
Category 2	224	35.1
Category 3	310	48.6
Insurance status (N = 665)		
Mutuelle	641	96.4
RSSB/RAMA, MMI, Others	22	3.3
No Insurance	2	0.3
Co-morbidities (N = 666)¹		
Heart Disease	33	5.0
HIV	20	3.0
Hypertension	14	2.1
Diabetes	12	1.8
Chronic renal failure	11	1.7
HCV Risk factors (N = 666)²		
Traditional operation	215	32.3
Ever had surgery	55	8.3
Ever experienced physical trauma	51	7.7
Multiple sexual partners	44	6.6
Viral Hepatitis in the family	46	6.9
Blood transfusion or needle stick	32	4.8
Unhygienic medical or household practices	30	4.5
History of hepatitis diagnosis, liver disease, or screening (N = 666)		
	9	1.4
¹ Patients could report more than one comorbidity		
² Patients could report more than one risk factor		

Of the 666 people who screened HCV RDT positive, initial viral load results were returned for 537 (80.6%) people (Fig. 1) Of those, 448 (83.4%) had a detectable viral load and 398 (88.8%) of patients with detectable viral loads were assessed for treatment. Almost all patients who were assessed for treatment, were initiated on treatment (n = 394, 99%), but only 222 (56.3%) of patients who initiated treatment had results returned for their post-treatment SRV12 test. Among those 222 patients assessed, 208 (93.7%) achieved SRV12.

When assessing the key indicators for timely provision of HCV care, we found that 65.9% (95% CI: 62.0, 69.7) of people who screened positive had their initial HCV viral load results returned within 30 days of screening (Table 2). Among patients with a detectable viral load, 45.0% (95% CI: 40.1, 49.8) were assessed for treatment initiation within 90 days of receipt of viral load results. Only 12.5% (95% CI: 9.2, 16.3) of the participants who initiated treatment had their SVR12 results returned within 210 days of treatment initiation. Our findings were not sensitive to assumptions about the timing of events among individuals who were missing data on dates. Overall, among individuals who initiated treatment, the median number of days from screening to return of SRV12 results was 437 days The median time between screening and return of initial viral load results was 15 days the median time between return of initial viral load results and treatment assessment was over three months (104 days); and the median time between treatment initiation and return of SVR12 results was almost 12 months (334 days).

Table 2
Proportion of patients receiving timely provision of care for hepatitis C

Indicator	N	%	95% CI
Proportion of initial HCV viral load results returned \leq 30 days of screening among people who screened RDT+			
Complete case analysis ¹ (N = 594)	392	65.9	(62.0, 69.8)
Worst case scenario ² (N = 666)	392	58.9	(55.0, 62.6)
Best case scenario ³ (N = 666)	464	69.7	(66.0, 73.1)
Proportion of patients who were assessed for treatment eligibility \leq 90 days after receiving a viral load results among those with a detectable viral load			
Complete case analysis ¹ (N = 420)	189	45.0	(40.2, 49.9)
Worst case scenario ² (N = 448)	189	42.2	(37.7, 46.9)
Best case scenario ³ (N = 448)	217	48.4	(43.7, 53.2)
Proportion of SVR12 results returned \leq 210 days of treatment initiation among patients who initiated treatment			
Complete case analysis ¹ (N = 368)	46	12.5	(9.3, 16.3)
Worst case scenario ² (N = 394)	46	11.7	(8.7, 15.23)
Best case scenario ³ (N = 394)	72	18.3	(14.6, 22.5)

¹ Complete case analyses excluded individuals who completed the stage of interest, but were missing data on the relevant start or end dates necessary to assess timing of the event. ²The worst-case scenario assumed that all individuals who were missing relevant dates had experienced the event of interest after the cut off. ³The best-case scenario assumed that all individuals missing relevant dates experienced the event of interest before the cut-off.

Table 3

Median time to complete key stage of the hepatitis C cascade of care. All durations are defined in days

Variable	N	Median	(IQR)	
Time between screening and return of initial viral load results	594	15	13	61
Time between return of initial viral load results and assessment for treatment eligibility	420	104	66	123
Time between treatment initiation and return of SVR12 results	368	334	287	— ¹
Time between screening and SVR12 and return of SVR12 results among those who initiated treatment	368	437	406	— ¹

¹Less than 75% of the eligible population reached this milestone; so, the 75th percentile is not defined.

Discussion

In accordance with the WHO goal of eliminating HCV as a public health threat by 2030, countries worldwide are expanding access to HCV diagnosis and treatment services (8). However, to ensure HCV elimination, these programs must complete the full cascade of care for HCV in a timely fashion. Among the 666 patients who were identified as anti-HCV positive during the September 2019 screening campaign, only 222 had their SVR12 results returned by March 2021. The two biggest gaps in the cascade of care were return of initial viral load results and the return of SVR12 results. During the September 2019 screening campaign, viral load samples were collected on the same day as RDT administration. Consequently, we believe that missing or delayed initial viral load results could be explained by poor communication between the health facilities and the testing hub. The proportion of patients whose SRV12 test results were returned was even lower (56.3%), which likely reflects both poor communication between health facilities and viral load hubs and challenges in following up with patients for sample collection. This aligns with the findings from Nsanzimana et al., where 34% of patients who completed HCV treatment were found to either be lost to follow-up for SVR12 assessment or to not having HCV RNA results returned (7). These gaps point to a need to improve the overall laboratory communication and turnaround time, which has previously been reported to be an important element impacting provider performance and patient care(16, 17).

Although viral load testing was a barrier to provision of care, our treatment initiation and treatment assessment rates were quite high. These outcomes were achieved in the context of a mobile clinical campaign, which has previously been reported as a low-cost strategy to support linkage to care, and may be a scalable model for improving patients' access to care (13).

Similarly, among patients whose SVR12 results were returned, we found that HCV cure rate was very high (93.5%). This level slightly exceeds levels previously reported in Rwanda among treatment naïve patients with non-cirrhotic or with compensated cirrhosis treated with ledipasvir 90mg/sofosbuvir 40mg (87%) (18) and among a combination of treatment naïve and experienced patients treated through the national program (92%) (7). Our results reinforce previous findings that treatment for HCV can be successfully implemented in low-income countries and among individuals living in limited resources settings (19).

Among patients who completed treatment, it took over 14 months to complete the full HCV cascade of care. In general, the time to complete individual stages of the cascade of care compares favorably to what has been reported in other similar settings. For example, while in our study the median time to receive initial viral load results was 15 days, in Malawi's HIV program, the median turn-around time is almost three months (20). Our median time between return of initial viral test results and treatment assessment (104 days) is very similar to what has been reported in an HCV program at a tertiary hospital in the USA (107 days) (21) and better than what was found in another HCV program at a tertiary care centre in the USA (300 days) (22). However, these studies were conducted in routine care settings, while our data reflects treatment initiation following a mass screening campaign and targeted mobile clinic outreach program to support decentralized care. In Rwandan settings where HCV infected patients do not have access to this targeted, decentralized outreach program, gaps in the cascade of care are likely even larger and delays in service provision are likely even longer than reported here. Addressing these delays will be critical for Rwanda to achieve its national target of treating 90% of those infected with HCV by 2024.

We proposed three indicators for assessing timely provision of hepatitis C care: a) proportion of initial HCV viral load results returned \leq 30 days of screening among people who screened RDT+; b) proportion of patients who were assessed for treatment eligibility \leq 90 days after receiving a viral load results among those with a detectable viral load; and c) proportion of SVR12 results returned \leq 210 days of treatment initiation among patients who initiated treatment. In a health system where each of these indicators are met, a patient could expect to complete treatment for HCV in less than 11 months from screening. A second strategy that could reduce turn-around time for lab results and eliminate the risk of poor communication between testing hubs and health facilities is the introduction of point of care tests to assess hepatitis C viraemia. There are currently two major approaches to providing point of care testing. The first replaces viral RNA test with core antigen tests, which can

provide results in 60 minutes (23–25). Core antigen tests have been approved by the WHO as an alternative for confirmatory viral load testing (26, 27), and may also provide an alternative approach for assessing SRV12 (28).

The second uses GeneXpert to provide point-of-care viral load testing. Similar applications of GeneXpert have achieved success in HIV programs in limited-resource settings, as they allow patients to receive viral load results on the same day as sample collection (19), and have been successfully used in HCV pilot programs in Egypt (29), Indonesia (30), and Tanzania (31). Given that HCV GeneXpert is WHO pre-qualified for HCV viral load testing, it provides an opportunity for improving HCV patients monitoring and would also allow for integrated multi-disease testing platforms (32).

Our study has some limitations. First, our results are not fully generalizable as they focused on catchment areas for two district hospitals that receive substantial support from PIH/IMB. As noted, these catchment areas were serviced by a targeted mobile clinic to support HCV treatment initiation during the study period. As discussed above, we anticipate that this limitation means that the observed gaps or delays in care provision in our setting would be lower than elsewhere in Rwanda. Second, the cascade of care for the patients in our study was interrupted by the COVID-19 pandemic. However, most patients were initiated through the mobile clinic program, which was active between November 2019 and January 2020 and preceded the COVID-19-related national lockdown in Rwanda, which occurred between 14th March 2020 and 3rd May 2020. Furthermore, SRV12 follow-up for most patients should have occurred between January and March 2021, during which time no lockdowns or restrictions on intra-district travel were in place and patients should have had uninterrupted access to their local health facilities. Third, our study used routine clinical records, which are subject to missing data, particularly on dates for steps of cascade of care. However, we assessed the sensitivity of our results to missing data and did not find that it meaningfully changed our results. Fourth, our recommended quality of care indicators, “Proportion of SVR12 results returned \leq 210 days of treatment initiation among patients who initiated treatment” does not account for the fact that some patients could have been prescribed a 24 week course of treatment and would not be eligible to receive SRV12 testing until at least 270 days after treatment initiation. Treatment duration was not readily available from our clinical database, however, based on previous estimates of higher APRI (Aspartate Aminotransferase to Platelet Ratio Index) score among people initiating HCV treatment elsewhere in Rwanda (15), we believe that fewer than ten percent of patients were prescribed a 24 week-course treatment. In the interest of proposing a single indicator that would be easy to implement for the monitoring of future programs, we do not recommend disaggregating this indicator by treatment duration.

Conclusion

Although HCV treatment was successful in rural Rwanda, we identified some gaps and delays among patients' progress through the cascade of care. The major gaps and delays were related to viral load testing, suggesting that shortening the turnaround time for viral load results and improving communication between testing hubs and health facilities could improve patient outcomes and strengthen the national HCV elimination program. Our proposed indicators for timely provision of HCV care could be used by future screening programs to monitor their quality of care.

List Of Abbreviations

CBHI Community Health Insurance;

CI Confidence Interval;

DAAs Direct Acting Antivirals;

HCV Hepatitis C Virus

IHDPC Institute of HIV Disease Prevention and Control;

IMBRC Inshuti Mu Buzima Research Committee;

IQR Interquartile range; PIH/IMB: Partners In Health/Inshuti Mu Buzima;

LMIC Low and Middle Income Countries

MoH Ministry of Health;

SVR12 Sustained Virologic Response after 12 weeks

RNEC Rwanda National Ethics Committee

RDT Rapid Diagnostic Test;

RBC Rwanda Biomedical Centre; REDCap: Research Electronic Data Capture;

RNA Ribonucleic Acid; RNEC: Rwanda National Ethics Committee;

WHO World Health Organization

Declarations

Ethics approval and consent to participate

The approval of this study was obtained from Inshuti Mu Buzima Research Committee (IMBRC) and Rwanda National Ethics Committee (RNEC) 015/ RNEC/2020). This study used retrospective data, which was collected as part of routine clinical practice; therefore, informed consent was not required by the Rwanda National Ethics Committee.

Consent for publication

Not Applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

IK, FS led the study design, literature search, data cleaning and analysis, results interpretation and manuscript writing. DAB and JDA conceptualized the study and DAB provided mentorship for paper development. FN, JPG, WD, EN, JDM, GNB, PH, JS, JDA and DAB participated in the study design and provided input in literature search, data analysis and interpretation of the results. All authors critically reviewed and approved the manuscript for publication. IK and FS hold joint first authorship.

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Figures

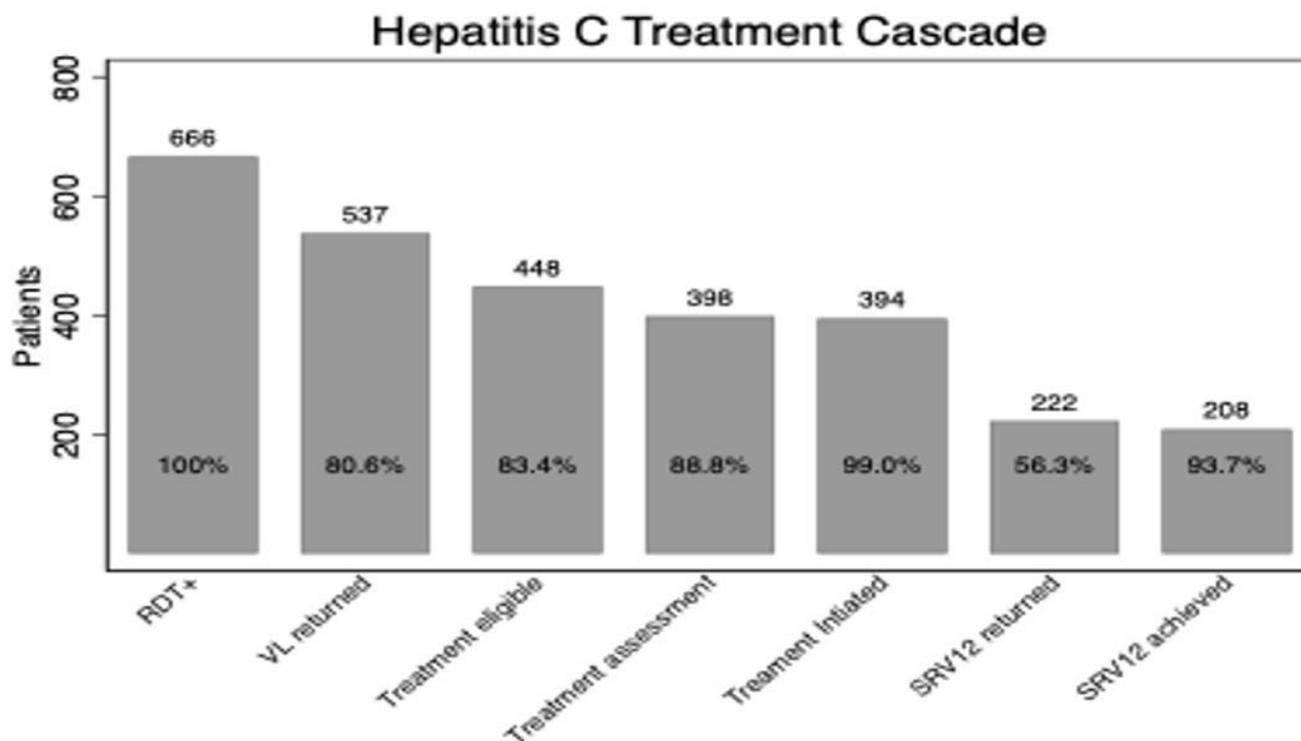


Figure 1

Cascade of care for management of hepatitis C among patients identified in the mass screening campaign. *RDT+: Rapid Diagnostic Test positive *VL: Viral load *SVR 12: Sustained Virologic Response after treatment completion