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Research paper

A hepatitis C elimination model in healthcare for the homeless organization: A novel reflexive laboratory algorithm and equity assessment

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ABSTRACT

Background: Reaching World Health Organization hepatitis C (HCV) elimination targets requires diagnosis and treatment of people who use drugs (PWUD) with direct acting antivirals (DAAs). PWUD experience challenges engaging in HCV treatment, including needing multiple provider and laboratory appointments. Women, minoritized racial communities, and homeless individuals are less likely to complete treatment.

Methods: We implemented a streamlined opt-out HCV screening and linkage-to-care program in two healthcare for the homeless clinics and a medically supported withdrawal center. Front-line staff initiated a single-order reflex laboratory bundle combining screening, confirmation, and pre-treatment laboratory evaluation from a single blood draw. Multinomial logistic regression models identified characteristics influencing movement through each stage of the HCV treatment cascade. Multiple logistic regression models identified patient characteristics associated with HCV care cascade progression and Cox proportional hazards models assessed time to initiation of DAAs.

Results: Of 11,035 clients engaged in services between May 2017 and March 2020, 3,607 (32.7%) were screened. Of those screened, 1,020 (28.3%) were HCV PCR positive. Of those with detectable RNA, 712 (69.8%) initiated treatment and 670 (94.1%) completed treatment. Of those initiating treatment, 407 (57.2%) achieved SVR12. There were eight treatment failures and six reinfections. In the unadjusted model, the bundle intervention was associated with increased care cascade progression, and in the survival analysis, decreased time to initiation; these differences were attenuated in the adjusted model. Women were less likely to complete treatment and SVR12 labs than men. Homelessness increased likelihood of screening and diagnosis but was negatively associated with completing SVR12 labs. Presence of opioid and stimulant use disorder diagnoses predicted increased care cascade progression.

Conclusions: The laboratory bundle and referral pathways improved treatment initiation, time to initiation, and movement across the cascade. Despite overall population improvements, women and homeless individuals experienced important gaps across the HCV care cascade.

Introduction

Viral hepatitis C (HCV) is a worldwide public health concern, particularly for people who use drugs (PWUD) (Degenhardt et al., 2017; Grebely et al., 2019). The World Health Organization (WHO) targets eliminating HCV as a public health threat by 2030, defined as reducing new HCV infections by 80% and associated deaths by 65% (World Health Organization, 2017). Injection drug use is the primary mechanism of ongoing HCV transmission in higher income countries (World Health Organization, 2017). Accelerated treatment of HCV among people who inject drugs (PWID) is necessary to achieve WHO elimination targets (Grebely, Dore, Morin, Rockstroh, & Klein, 2017). However, treatment delivery and uptake among all PWUD—including those who use alcohol or do not inject—is crucial but challenging due to structural, social, and policy barriers. Many health systems, particularly in the United States, limit treatment in this high-risk popula-

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tion, citing inadequate outcomes data (Barua et al., 2015; Gowda et al., 2018; Reilley, Miller, Hudson, Haverkate, & Leston, 2019; Tumber, 2017).

A growing body of literature demonstrates comparable but slightly lower sustained viremic response at 12 weeks (SVR12), or cure, of HCV among PWUD compared to those who do not use drugs (Hajarizadeh et al., 2018). Hajarizadeh et al. demonstrated 97–98% treatment completion rates despite lower achieved SVR12, suggesting the possibility this difference reflects lower confirmatory lab completion, rather than lower rates of cure. modeling studies suggest that treating PWUD is essential to meet elimination targets (Grebely et al., 2017). Of equal public health importance, increased HCV treatment among PWUD would improve quality of life and lower liver disease-associated mortality (O'Sullivan et al., 2020; World Health Organization, 2017). Current strategies to efficiently screen for HCV and link individuals from vulnerable populations to expedited treatment are inadequate for achieving public health goals and equitable treatment outcomes among PWUD and other vulnerable populations (Bruggmann & Litwin, 2013; Lazarus, Sperle, Spina, & Rockstroh, 2016; Maaroufi et al., 2017).

Multiple studies have evaluated lowering barriers to screening vulnerable populations using street-outreach screening (Alimohammadi et al., 2018; Benitez, Fernando, Amini, & Saab, 2020; Broad et al., 2020; Conway, Hakobyan, Vafadary, Raycraft, & Sharma, 2015; O'Sullivan et al., 2020), dried blood spot testing (Barror et al., 2019; Harrison, Murray, Gore, & Penelope, 2019; Hickman et al., 2008), or point of care HCV ribonucleic acid (RNA) testing (Bajis et al., 2019; Saludes et al., 2020; Williams et al., 2019). However, less is known about lowering the barriers to pre-treatment evaluation, a major hurdle to treatment initiation. Many studies trying to streamline pre-treatment evaluation rely on elastography (Foucher et al., 2009; Marshall et al., 2015; Thurnheer, Schulz, Nguyen, MacLachlan, & Sasadeusz, 2016), which can be expensive and difficult to access in some settings (Borgia, 2015). While pangenotypic direct acting antiviral (DAA) regimens have simplified treatment safety, there are important clinical indications for pre-treatment evaluation such as screening for cirrhosis or hepatic decompensation using non-invasive fibrosis surrogates Fibrosis-4 (FIB-4) or Aspartate aminotransferase to Platelet Ratio Index (Burrage et al., 2020; Chou R, 2013; Fraser et al., 2019; Snyder & Gajula, 2006). Many payers also require an extensive laboratory evaluation prior to treatment initiation, an addional barrier to initiating treatment (Al-Khazraji et al., 2020; Do et al., 2015; Edlin, 2016; Javanbakht, Archer, & Klausner, 2020). Simplified pre-treatment evaluation protocols that remove unnecessary steps in the HCV care cascade are urgently needed (Kapadia & Marks, 2018).

Inequities exist related to screening and access to treatment of HCV across gender and racial/ethnic categories, and among people living with substance use disorders or experiencing homelessness (Corcorran, Tsui, Scott, Dombrowski, & Glick, 2021; Haley et al., 2020; Kim, Yang, El-Serag, & Kanwal, 2019; . Using National Behavioral Surveillance Survey data from Seattle, United States, Corcorran et al. demonstrated a substantially lower rate of DAA initiation among PWID identifying as female or homeless, compared to those identifying as male or housed (2021). Disparities in treatment initiation were also reported by racial categories, with Black (Haley et al., 2020; Kanwal et al., 2016) and Latinx (Wong et al., 2018) individuals less likely to initiate DAAs than White individuals. These equities may exist, in part, due to interpersonal and structural racism (Bailey et al., 2017). Assessing patient characteristics associated with disparities in care is crucial for understanding equitable uptake of HCV care cascade interventions.

There were two aims of this study. The first was to evaluate the impact of a novel, bundled reflexive screening to treatment-ready laboratory algorithm on progression along the HCV care cascade in our healthcare for the homeless HCV elimination program. Second, we evaluated the impact of patient characteristics on progression across all stages of the HCV care cascade to assess potential disparities in care.

Methods

Study design, participants, and setting

This was a prospective non-randomized interventional cohort study with a historical comparison cohort of low-income individuals with high rates of homelessness and drug use. Eligible patients were at least 18 years old, had not received HCV treatment, and had engaged in care at least once between May 12, 2017 through March 13, 2020. Three groups were compared: 1) Patients in the prospective "post-bundle" cohort receiving the lab bundle; 2) Patients in the "post-bundle" cohort who did not receive the lab bundle; and 3) A historical comparison "pre-bundle" cohort. The laboratory bundle intervention prospective cohort was defined as those engaged in care from November 2019 – March 2020. The prospective screening cohort period was intended to run until November 2020 but was shortened due to Coronavirus Disease 2019 (COVID-19) pandemic impacting services starting March 13, 2020. The follow-up period ended November 23, 2020, allowing those in the prospective screening cohort 60 days for DAA initiation, 6 months for treatment, and 30 days for collection of sustained virologic response (SVR12) RNA levels. The historical control cohort was defined as those engaged in care between May 12, 2017 and November 2019.

Patients underwent HCV screening and engagement during usual medical care at three sites in Portland, Oregon. These sites included two healthcare for the homeless clinics and a medically-supported withdrawal center, all run by the community organization Central City Concern (CCC). CCC is an organization dedicated to ending homelessness and caring for individuals affected by homelessness, substance use disorders, and severe and persistent mental illness. Old Town Clinic and Blackburn Clinic are inner-city, interdisciplinary federally qualified health centres caring for over 11,000 individuals living with homelessness, substance use disorders, or severe and persistent mental illness. These centres offer primary care medical services, low barrier medications for opioid use disorder (Maaroufi et al.), linkage to housing services, and integrated mental health treatment. Hooper Detoxification and Stabilization center is an inpatient medically-supported withdrawal center, which manages withdrawal from opioids, alcohol, benzodiazepines, and methamphetamines, and links individuals to substance use disorder treatment and housing upon discharge.

Patients were screened at all three sites and treated at one of the two integrated health clinics. General practitioners and HCV pharmacists were responsible for diagnosis, treatment, and management of HCV. Patients diagnosed with HCV could be treated regardless of degree of fibrosis or hepatic compensation. Patients were either uninsured or receiving government-sponsored health insurance (Medicaid or Medicare), with incomes below the United States federal poverty level. The Oregon Health and Science University's institutional review board determined that the proposed activity (STUDY 22,590) was not research involving human subjects, and hence IRB review and approval was not required.

Hepatitis C elimination program

The Central City Concern Hepatitis C elimination program provides low barrier access to HCV screening and linkage-to-care through a harm reduction and equity framework for treatment access. This program is supported by a multidisciplinary team of clinicians, pharmacists, care coordinators, and housing and employment specialists. Integrated substance use disorder treatment with medications for opioid use disorder (OUD) and counselling support is provided alongside health services. All patients with positive HCV RNA levels are offered treatment. Patients are supported through treatment with active case management from coordinators and are reminded to complete SVR12 laboratory confirmation. Medications are dispensed through an onsite pharmacy with the flexibility to tailor treatment plans according to patient efficacy and social vulnerability.

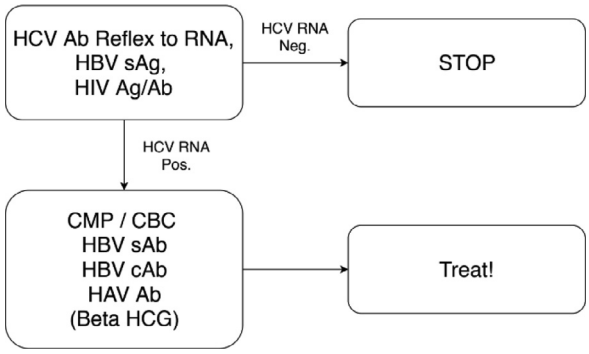

Fig. 1. Screening to treatment lab algorithm.

HCV elimination program procedures, laboratory bundle intervention

Pre-bundle implementation historical control

Between May 2017 and November 2019, general practitioners offered routine screening for HCV using serum HCV antibody with reflex to RNA testing. Pre-treatment laboratory evaluation was initiated after return of positive HCV RNA.

Laboratory bundle intervention

Beginning in November 2019, all patients presenting for intake to health services were offered routine opt-out HCV, HBV, and HIV screening with all pre-treatment labs reflexed through our novel single-order lab algorithm bundle (Fig. 1). All providers were recommended to use the lab bundle, though its uptake varied between ordering providers during the prospective cohort period. The lab bundle was designed by the authors and made commercially available in the Northwestern United States through the diagnostics laboratory Labcorp, using test code 245,069 for individuals with a uterus of reproductive age which includes serum beta human chorionic gonadotropin (Beta-HCG), and test code 245,047 for all others. The authors have no financial relationship with Labcorp and the bundle itself is not patented. A general practitioner with expertise in HCV treatment reviewed labs from HCV RNA positive individuals and prescribed a DAA regimen approved by insurance prior to the first clinical encounter. DAA regimen determination was based on treatment duration, evidence of hepatic decompensation, or in a minority of cases, insurance preference. Patients were linked to treatment initiation by dedicated HCV coordinators. Degree of fibrosis was assessed using clinical judgement based on a combination of fibrosis risk factors (e.g., metabolic syndrome, HIV co-infection, alcohol use) and FIB-4 score; those with concern for advanced fibrosis were referred for elastography. Hepatic decompensation was assessed with the Child-Turcotte-Pugh score (Pugh, M.-L., Dawson, Pietroni, & Williams, 1973). Individuals with no evidence of hepatic decompensation were treated by pharmacists with HCV treatment expertise. Those with concerns for decompensation or with a CTP score of 6 or greater were evaluated by a general practitioner with HCV treatment expertise prior to the HCV pharmacist initiation visit. The HCV pharmacist established an individualized treatment plan including follow-up frequency and amount of DAA dispensed (range daily to monthly) based on medical complexity and psychosocial determinants including housing status, active substance use, and mental illness severity. When possible, DAA dispensation and SUD treatment visits were coordinated.

Study assessments and data collection

We collected the following demographic and clinical variables from the electronic health record (EHR) for patients in the prospective cohort and historical comparison cohort: gender (male/female), race (White/Black or African American/Multiracial/American Indian or Alaska Native/ Other Person of Colour/Unknown or declined), site (Old Town Clinic, Blackburn Clinic, Hooper Detox), receipt of HCV lab bundle (engaged pre-bundle/engaged-post bundle, did not receive/engaged post-bundle, received/engaged post-bundle), alcohol use disorder (yes/no), opioid use disorder (yes/no), benzodiazepine use disorder (yes/no), stimulant use disorder (yes/no), and housing status (Housed/Homeless/Transitional Housing/Unknown or Other). Use disorder diagnoses were based on ICD-10 codes documented in the EHR.

The HCV care cascade was defined as: 1) Eligible for screening—defined as all patients accessing care within 1 year of cohort period; 2) Screened—defined as HCV antibody results in the EHR after May 2017; 3) HCV positive—defined as HCV RNA > 15 IU/mL results in EHR after May 2017; 4) Initiated treatment—defined as attending first HCV pharmacist appt and dispensed DAA; 5) Completed treatment—defined as receipt of last fill of DAA; and 6) Achieved Intention To Treat (ITT) SVR12—defined as confirmation of undetectable HCV RNA at least 12 weeks after end of treatment among patients who initiated DAA therapy. This ITT SVR12 definition was based on previous literature in this population (Dore et al., 2016; Grebely et al., 2018). A modified per protocol SVR12 was defined as those with undetectable HCV RNA 12 weeks after end of treatment, among those initiating treatment who completed SVR12 confirmation labs. HCV antibody and PCR results prior to May 2017 were not included in the analysis.

HCV RNA values for evaluation of treatment candidacy and SVR12 were measured on plasma samples tested on the Cobas TacMan RT-PCR platform by Labcorp, lower limit of detection 15IU/mL. Hepatitis B surface antigen performed on Immunochemiluminometric assay, HCV antibody and HIV antigen/antibody performed on enzyme immunoassay. Substance use disorder diagnoses were collected using ICD10 diagnosis codes entered by medical providers in the EHR problem list during routine care; patients without an ICD10 diagnosis were considered not to have an SUD diagnosis. For gender data, we assessed gender on intake surveys, and deferred to patient-defined gender by default. If gender information was missing from the intake survey, we used the gender listed in the EHR.

A combination of manual and digital validation efforts was used to confirm the accuracy and completeness of the dataset. HCV care cascade, site, and laboratory EHR observation terms were defined prior to prospective cohort initiation. Prospective cohort data definitions and collection methods were applied to the historical cohort and validated by two separate study team members according to a pre-determined protocol. All data were deidentified prior to analysis. We used Stata 16 for all data management and analyses (StataCorp, 2019).

Statistical methods

Assessing the impact of the HCV lab bundle intervention

We first report rates of progression through the HCV care cascade and SVR12. To assess the impact of receipt of the HCV lab bundle on progression through the HCV care cascade, we used a multinomial logistic regression to model the HCV care cascade during the prospective cohort period. We classified patients based on the furthest step in the cascade that they reached. Because all patients who received the bundle were screened, for this analysis, we eliminated the first screening step and evaluated the cascade from steps two through six, as defined above. We evaluated if the bundle was significantly associated with care cascade progression at each step of the multinomial model. We calculated predicted probabilities of progression through stages by whether patients had received the lab bundle intervention in unadjusted and adjusted analyses, where the model was adjusted for all covariates described above. Predicted probabilities estimate the proportion of patients who end at each stage and are easier to interpret than relative risk ratios (exponentiated beta values from multinomial logistic regression models). To display as a continuum, we totalled all patients who made it to each stage; thus, the overall number of patients decreases as the cascade stage increases.

Table 1
Demographics of patients eligible, screened and Hepatitis C positive at Central City Concern in Portland, Oregon, May 2017 – March 2020.

	Eligible (n = 11,035)	Screened (n = 3607)	HCV Positive (n = 1020)	
Gender	Male	6983 (63.3%)	2360 (65.4%)	700 (68.6%)
	Female	4052 (36.7%)	1247 (34.6%)	320 (31.4%)
Race	White	7475 (67.7%)	2529 (70.1%)	782 (76.7%)
	Black/African American	1229 (11.1%)	374 (10.4%)	88 (8.6%)
	Multiracial	730 (6.6%)	244 (6.8%)	61 (6.0%)
	American Indian/Alaska Native	353 (3.2%)	118 (3.3%)	31 (3.0%)
	Other Person of Color	559 (5.1%)	153 (4.2%)	24 (2.4%)
	Unknown/Declined	689 (6.2%)	189 (5.2%)	34 (3.3%)
Site	Old Town Clinic/Other	8394 (76.1%)	2786 (77.2%)	782 (76.7%)
	Blackburn Clinic	1823 (16.5%)	606 (16.8%)	191 (18.7%)
	Medically Supported Withdrawal center	818 (7.4%)	215 (6.0%)	47 (4.6%)
Bundle	Pre-bundle period	4990 (45.2%)	1947 (54.0%)	595 (58.3%)
	Bundle period	6045 (54.8%)	1660 (46.0%)	425 (41.7%)
Alcohol Use Disorder	No	7539 (68.3%)	2238 (62.0%)	663 (65.0%)
	Yes	3496 (31.7%)	1369 (38.0%)	357 (35.0%)
Opioid Use Disorder	No	7881 (71.4%)	2277 (63.1%)	411 (40.3%)
	Yes	3154 (28.6%)	1330 (36.9%)	609 (59.7%)
Benzodiazepine Use Disorder	No	10,551 (95.6%)	3388 (93.9%)	917 (89.9%)
	Yes	484 (4.4%)	219 (6.1%)	103 (10.1%)
Stimulant Use Disorder	No	7458 (67.6%)	2042 (56.6%)	490 (48.0%)
	Yes	3577 (32.4%)	1565 (43.4%)	530 (52.0%)
Housing Status	Housed	4118 (37.3%)	1263 (35.0%)	347 (34.0%)
	Homeless	3728 (33.8%)	1320 (36.6%)	363 (35.6%)
	Transitional Housing	1548 (14.0%)	514 (14.3%)	153 (15.0%)
	Unknown or Other	1641 (14.9%)	510 (14.1%)	157 (15.4%)

Second, we used Kaplan-Meier survival curves and Cox proportional hazards models to assess the impact of receipt of the lab bundle on time to DAA initiation. In model testing, some covariates did not meet proportional hazards assumptions for the Cox model. To address this, we stratified Cox models by covariates that violated the assumption (UCLA, 2021).

Third, we evaluated covariates that predicted receipt of the bundle in the post-bundle period. We report odds ratios and 95% confidence intervals of predictors associated with receipt of the bundle.

Assessing patient characteristics with HCV care cascade progression

To assess the impact of patient and clinic-level covariates on progression through the HCV care cascade, we used multinomial logistic regression to model the HCV care cascade in both the pre- and post-bundle periods. We classified patients according to the furthest step in the cascade they reached. We evaluated if each covariate was significantly associated with progression through the care cascade at each step of the multinomial model. We calculated predicted probabilities of progression through stages by each covariate, adjusting for all covariates described above, other than receipt of the bundle. Predicted probabilities estimate the proportion of patients who end at each stage. To display as a continuum, we totalled all patients who made it to at least each stage; thus, the overall number of patients decreases as the cascade stage increases.

Results

Participants

During the study period, 11,035 patients were engaged in care within the health system. Patients were predominately male (63.3%), White (67.7%) (Table 1). Nearly half of all patients were experiencing homelessness (33.8%) or in transitional housing (14.0%). Approximately one third had alcohol use disorder (31.7%), opioid use disorder (28.6%), and/or stimulant use disorder (32.4%). Of 11,035 clients engaged in services between May 2017 and March 2020, 3607 (32.7%) were screened. Of those screened, 1020 (28.3%) were HCV PCR positive. Of those with detectable RNA, 712 (69.8%) initiated treatment and of those 670 (94.1%) completed treatment. Of those initiated, 407 (57.2%) of those initiated achieved intention to treat (ITT) SVR12 (Fig. 2). Of those who initiated DAAs, overall ITT SVR12 and modified per protocol SVR12 were 57% and 97%, respectively. Of the 12 detectable RNA levels at SVR12, four were clinically determined to be reinfection and eight true treatment failures; six of these were subsequently reinitiated on treatment. The majority were treated with glecaprevir/pibrentasvir for eight weeks (610/85.9%). The remaining were treated with sofosbuvir/velpatasvir monotherapy for 12 weeks (66/9.3%), elbasvir/grazoprevir for 12 weeks (20/2.8%), sofosbuvir/velpatasvir/ribavirin for 12 weeks (7/0.8%), ledipasvir/sofosbuvir for 12 weeks (5/0.7%), and sofosbuvir/velpatasvir/voxilaprevir for 12 weeks (4/0.5%).

Assessing the impact of the HCV lab bundle

In unadjusted analyses, patients in the prospective cohort who received the bundled lab algorithm were 2.6% more likely to test HCV positive and 3.6% more likely to complete treatment than patients who did not receive the bundle ($p<0.05$). In adjusted analyses, there were no statistically significant differences in HCV cascade progression by receipt of the bundle (Fig. 3). Fewer than half of patients in the pre-bundle historical comparison cohort initiated DAA treatment. In the post-bundle cohort, median time to initiation of DAA was 95 days among those who did not receive the bundle versus 65 days among those who did receive the Fig. 4bundle. In unadjusted analysis, patients were more likely to initiate treatment in the post-bundle period in both those who did and did not receive the bundle, than in the pre-bundle period (log-rank $p<0.0001$, Fig. 3). In adjusted Cox regression analyses, patients in the post-bundle period were nearly twice as likely to initiate treatment as those in the pre-bundle period ($p<0.05$, Fig. 3). Less patients in the post-bundle period than pre-bundle period completed SVR12 labs, 46% vs 64%. Exploratory logistic regression analysis of factors predicting initiating DAAs and achieving SVR12, Beta coefficients, standard errors, and 95% confidence intervals are included in the appendix.

Patient characteristics associated with receipt of HCV lab bundle

In logistic regression models (Appendix 1, Table 2), among patients in the post-bundle period, patients who were American Indian/Alaska

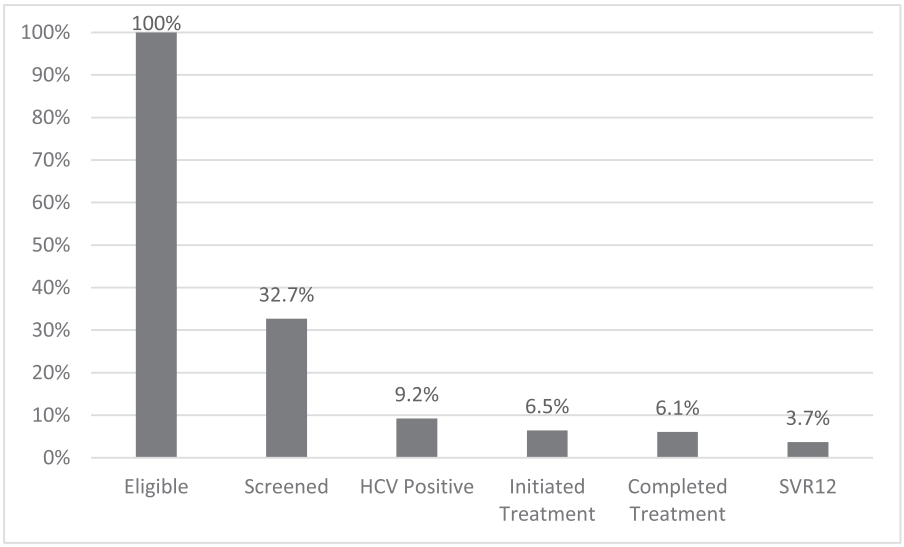

Fig. 2. HCV Treatment Cascade, Portland, Screening Eligibility to SVR12.

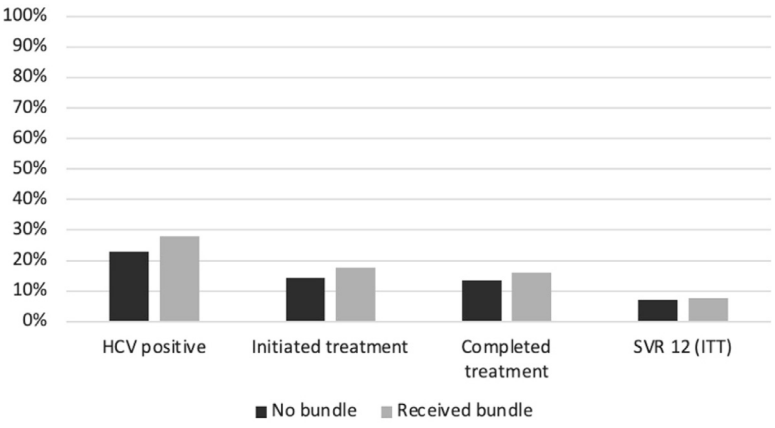

Fig. 3. Adjusted predicted probabilities of progression through the Hepatitis C care cascade post-bundle implementation.

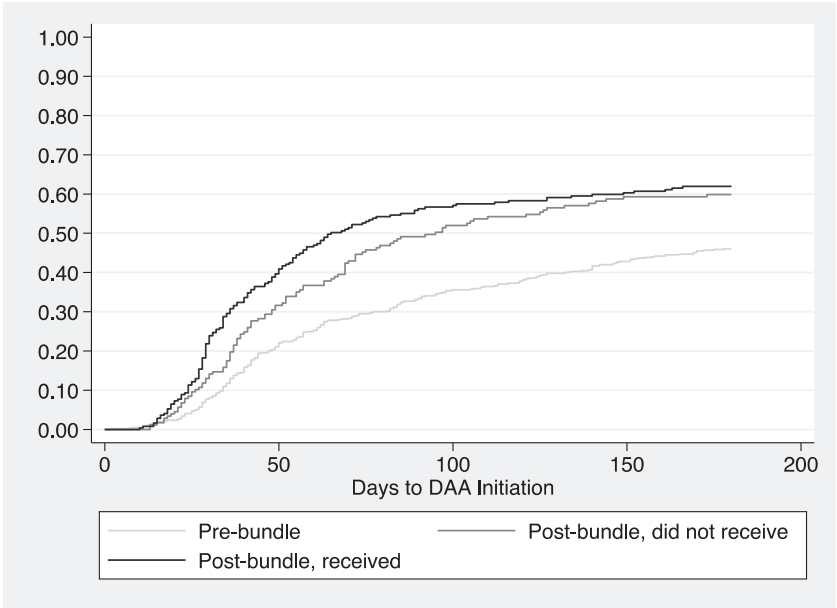

Fig. 4. Kaplan-Meier survival curves for time to DAA initiation.

Table 2
Predicted probabilities of Hepatitis C care cascade progression among patients seen at Central City Concern in Portland Oregon, May 2017 – March 2020.

		Screened	HCV Positive	Initiated Treatment	Completed treatment	SVR12 (ITT)
Gender	Male	33.6%	10.3%	7.4%	7.0%	4.2%
	Female	31.2%	7.6%	5.0%	4.7% *	2.8% *
Race	White	33.3%	9.8%	6.8%	6.5%	3.9%
	Black/African American	30.6%	8.3% *	6.3%	5.8%	3.7%
	Multiracial	33.0%	8.4%	6.5%	6.2%	3.9%
	American Indian/Alaska Native	33.2%	9.6%	5.6%	5.1%	3.6%
	Other Person of Color	29.8%	6.1% *	5.8%	5.3%	2.6%
	Unknown/Declined	30.3%	6.1%	2.3%	2.1% *	0.9% *
Alcohol Use Disorder	No	29.9%	8.8%	6.2%	5.8%	3.3%
	Yes	38.7% *	10.1% *	7.0%	6.6%	4.5% *
Opioid Use Disorder/Stimulant Use Disorder	No	25.0%	3.8%	2.5%	2.3%	1.4%
	Stimulant Use	40.0% *	9.6% *	6.2%	5.9% *	4.2% *
	Opioid Use	36.9%	17.0% *	11.8% *	11.2% *	6.7% *
	Both	47.9% *	21.6% *	17.0% *	15.9% *	9.2% *
Benzodiazepine Use Disorder	No	32.4%	9.0%	6.3%	6.0%	3.6%
	Yes	36.7%	12.1% *	7.8%	7.5%	4.7%
Housing Status	Housed	31.8%	9.1%	7.1%	6.9%	4.4%
	Homeless	35.0% *	9.4% *	5.4%	4.9%	2.6% *
	Transitional Housing	30.8%	8.6% *	5.6%	5.2%	3.1% *
	Unknown/Other	31.5%	9.8%	8.1%	7.9%	5.0%

* p-value less than 0.05.

Native (OR = 1.62, 95% CI = 1.12, 2.34), seen at Blackburn Clinic (OR=3.27, 95% CI=2.75, 3.88), or Hooper Detox site (OR=2.41, 95% CI = 1.93, 3.01), had an alcohol use disorder (OR=1.37, 95% CI = 1.17, 1.61), stimulant use disorder (OR=1.40, 95% CI = 1.13, 1.72), opioid use disorder (OR=1.31, 95% CI=1.04, 1.65), or both (OR=1.93, 95% CI = 1.57, 2.38), and who experienced homelessness (OR=1.75, 95% CI = 1.46, 2.11) or in transitional housing (OR=1.55, 95% CI = 1.20, 1.99) were more likely to receive the bundle (Appendix 1).

Assessing patient associations with HCV care cascade progression

Gender, race and housing status

In adjusted analyses (Table 2), women were 0.9% less likely to complete treatment and 1.4% less likely to successfully complete SVR12 labs than men. Black/African American patients and Other People of Colour were 1.0% and 2.8% less likely, respectively, to be HCV positive than White patients. People of unknown race or who declined to provide race information were 1.3% less likely to complete treatment and 3.0% less likely to successfully complete SVR12 labs than White patients. Patients experiencing homelessness were 3.0% more likely to be screened, 2.0% more likely to be HCV positive, and 1.8% less likely to successfully complete SVR12 labs than patients who were housed. Patients who were in transitional housing were 1.0% more likely to be HCV positive and 1.3% less likely to successfully complete SVR12 labs than patients who were housed Fig. 5.

Substance use

Patients with alcohol use disorder were 7.6% more likely to be screened, 0.4% more likely to be HCV positive, and 1.2% more likely to successfully complete SVR12 labs than patients without alcohol use disorder (Table 2). Patients with stimulant use disorder were 9.1% more likely to be screened, 2.0% more likely to be HCV positive, 0.8% more likely to complete treatment, and 2.8% more likely to successfully complete SVR12 labs than patients without stimulant or opioid use disorders. Patients with opioid use disorder were 3.9% more likely to be HCV positive, 0.4% more likely to initiate treatment, 3.6% more likely to complete treatment, and 5.3% more likely to successfully complete SVR12 labs than patients without stimulant or opioid use disorders. Patients with both opioid use disorder and stimulant use disorder were 5.0% more likely to be screened, 3.3% more likely to be HCV positive, 1.0% more likely to initiate treatment, 5.8% more likely to complete treatment, and 7.8% more likely to successfully complete SVR12 labs than patients without opioid use disorder or stimulant use disorder. Patients with benzodiazepine use disorder were 1.6% more likely to be HCV positive than patients without benzodiazepine use disorder.

Discussion

This combined prospective non-randomized interventional cohort study with historical controls demonstrates that a) a streamlined approach to HCV evaluation improved progression along the HCV treatment cascade, and b) women and patients experiencing homelessness had important gaps in the HCV care cascade.

This study, to our knowledge, is the only study evaluating the effectiveness of a novel single order reflexive laboratory bundle for initiating a streamlined evaluation for HCV treatment for patients with positive antibodies. Our findings add nuance to our understanding of disparities in progression along the HCV care cascade across categories of race/ethnicity, gender, and housing status.

Impact of the lab bundle

When used with an opt-out universal screening strategy, our data suggests those screened with the reflex lab bundle were more likely to complete DAA treatment but not SVR12 labs in the unadjusted multinomial analysis. However, Kaplan-Meier survival curves and Cox proportional hazards models suggest increased treatment initiation with the lab bundle. There are several factors that could be contributing to diminished apparent effect size of the laboratory bundle. First, given the recency of lab bundle implementation and shorter follow up time than the average time to initiation in our population, there may have been inadequate follow up period to see the full effect of the intervention (Haut, 2011). This follow-up time bias would have likely had the greatest effect on the rates of SVR12 lab completion, which we found to be lower in the bundle period than pre-implementation (46% vs 64%). Additionally, while screening in the cohort occurred prior to local effects of the COVID-19 pandemic, treatment initiation and SVR12 completion were likely negatively impacted in the post-bundle implementation follow up period (Blach et al., 2021). These factors suggest bias may have limited our ability to find a larger effect of the bundle intervention.

Overall, our elimination program treatment initiation rate compared favourably with experience in similar settings (Assoumou et al., 2020) and other real-world elimination models (Barror et al., 2019; Chouwdhury, Winston, Zeina, Shim, & T., 2020). One model demonstrated a comparable initiation rate in a similar population (Morris et al., 2020), though their rate of homelessness was substantially lower. Home-

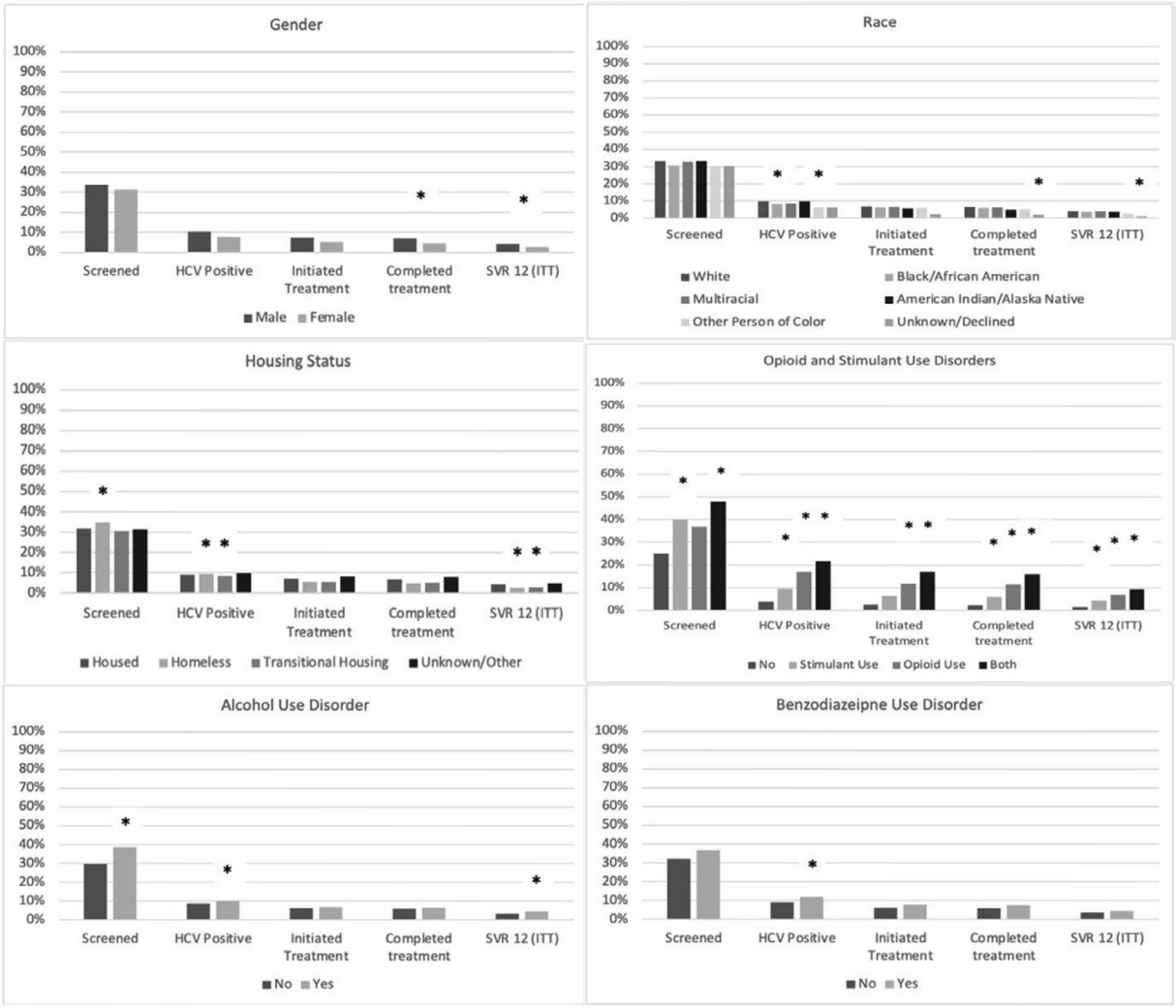

Fig. 5. Adjusted predicted probabilities of progression through the Hepatitis C care cascade, by covariate.

lessness has been shown in our data and elsewhere to be one of the strongest inhibitors of achieving various stages along the care cascade (Beiser, Smith, Ingemi, Mulligan, & Baggett, 2019; Harney et al., 2019; Morris et al., 2020). According to a report by the Centers for Disease Analysis Foundation, commissioned by the Oregon Health Authority, our elimination program's current yearly treatment initiation rates put us on track to treat approximately 20% of PWID in Multnomah County per year (Blach, 2019). Mathematical modeling in Australia (Razavi, 2015), and the U.S. (Fraser et al., 2019), suggests that treatment of at least 10% of PWID per year may be sufficient to reach WHO elimination targets (Grebely, Hajarizadeh, & Dore, 2017). If baseline HCV prevalence and injection drug use data in our region is accurate, this would place us among the few US urban areas on target for elimination.

SVR12 completion

As previously demonstrated (Coyle et al., 2019; Koustenis et al., 2020; Read et al., 2019), engaging patients to complete labs confirming SVR12 was a significant challenge in our setting. This reflects multiple factors. Intrinsic motivation may be less to complete confirmatory SVR12 labs than to take medications, as overall adherence was high, and patients are told their chance of cure is >95% upon treatment initiation. Those living with homelessness were substantially less likely than their housed counterparts to complete SVR12 labs, possibly reflecting lower perceived urgency as compared to other actions necessary to survival in this group (Read et al., 2019). Lack of reliable telephone and mailing address for lab outreach likely also factored into lower lab completion rates.

It should be noted that SVR12 lab completion rate was lower than seen in other studies with a similar population (Beiser et al., 2019; Hodges, Reyes, Campbell, Klein, & Wurcel, 2019; Read et al., 2017), though there are key differences between our data and these previous studies. None of these presented the full screening and HCV PCR rates from the baseline pool of patients and relied on some referral mechanism prior to initiating data collection. Hodges et al. and Read et al. did not report on process for determining candidacy for treatment initiation. Beiser et al. required a "treatment readiness" assessment and multiple pre-treatment initiation visits prior to receipt of DAA and only 60% of those referred initiated therapy, some of whom were excluded due to "social instability." These factors may be associated with a selection bias favouring patients more likely to engage in care through SVR12 completion. In contrast, our data represent all HCV PCR positive individuals with less visits required for pre-treatment evaluation, possibly leading to a more socially complex population initiating therapy who may be less likely to complete confirmation lab work. While more resources should be employed to improve SVR12 lab completion

moving forward, we must continue to treat more socially complex patients without pre-treatment conditions, though they may require more assistance completing the care cascade. Future feasibility and effectiveness interventions such as financial incentivization of SVR12 labs and medical cellular phones may help improve our ability to confirm HCV cure.

True treatment failure – or viremia after the SVR12 timepoint – was rare. The SVR12 endpoint is likely more reflective of return for lab results than true treatment failure. Previous prospective studies among PWUDs suggest treatment completion correlates highly with cure (Dore et al., 2016; Grebely et al., 2017), and retrospective analyses have shown cure rates to be similar among those who do and do not complete SVR12 confirmation labs (Boyle, M., Peters, & Barclay, 2018). This latter example from the Scottish health system may not hold true for our population, given that non-completion of treatment was also associated with laboratory non-completion.

Patient level associations with HCV care cascade progression

These data also demonstrate differences in progression along the care cascade by gender, race/ethnicity, and housing status, which is important for equity and public health reasons (Grebely, Hajarizadeh, Lazarus, Bruneau, & Treloar, 2019). Our findings are consistent with many other studies showing lower screening and treatment among these groups (Corcorran et al., 2021; Kanwal et al., 2016; , with some key differences. Most prominently, there is a pattern of similar screening and initiation rates across most baseline variables, with the exception of increased screening and initiation in people with opioid and stimulant use disorders. This is discordant with existing literature suggesting screening and initiation disparities to be substantial contributors to overall inequity. This holding consistent across risk factors and patient characteristics may imply that our routine opt-out screening and automated linkage-to-care systems—with or without the lab bundle—may be a protective factor from an equity standpoint early in the cascade. In addition, our analysis model adds nuance to the literature on inequity in HCV outcomes. Our model provides insight into important differences in movement across each stage of the care cascade, compared to showing disparities by individual stage or the SVR12 outcome. We think increased use of similar analytic models may allow health systems to employ targeted interventions to improve equity in HCV elimination programs by allocating resources more effectively to address the gaps in the care cascade most affecting unique populations.

The underlying reasons for gender disparities in HCV treatment initiation and completion rates remains unclear. Others hypothesize that lower treatment initiation rates are related to a higher burden of family care (Kanwal et al., 2016); greater mental and physical health comorbidities, the impact of pregnancy, accentuated stigma related to substance use, and lower education (Corcorran et al., 2021; Rojas Rojas et al., 2019). These factors may reasonably affect late-cascade disparities, as well. It is important to note that our data did not demonstrate lower screening or initiation rates among women. This may reflect the harm reduction-oriented staff and linkage-to-care systems, which manually tracked treatment evaluation labs—including pregnancy testing—from the onset. We also found the lab bundle's inclusion of pregnancy testing to be useful for navigating DAA insurance authorization for women of reproductive age, possibly preventing treatment delay in this group.

The existing data around HCV screening and treatment initiation disparities is less consistent based on racial and ethnic categories, making it more challenging to contextualize our results. In some studies, Black (Haley et al., 2020; Kanwal et al., 2016) and Latinx (Wong et al., 2018) individuals were less likely to initiate treatment. In contrast, one large retrospective review of safety net clinics in the United States showed Latinx, Asian, and "other/unknown" individuals to have higher likelihood of screening and treatment initiation, while Black individuals had increased screening without increased treatment initiation (Assoumou et al., 2020). In our study, adjusted screening and treatment initiation rates were similar across race and ethnicity categories, though treatment completion and SVR12 lab completion were lower in the Unknown/Declined group, which comprised 12% of the overall population. Without further categorization within this group these data are difficult to interpret. Thus, it is possible that our bundle and linkage-to-care programming could mitigate racial inequities in the HCV care cascade, although the mechanisms for mitigation are unknown.

The presence of a substance use disorder—most notably opioid use disorder and combined opioid and methamphetamine use disorder—strongly predicted forward progression through most steps of the HCV care cascade in the multinomial logistic regression model. Alcohol use disorder predicted only screening and SVR12 completion. Prior research suggests that current and past substance use is associated with lower treatment initiation (Bartlett et al., 2019; Haley et al., 2020; Kanwal et al., 2016; van Dijk et al., 2020) than those not using substances. Screening rates are often higher in people with substance use disorders (Assoumou et al., 2021; Corcorran et al., 2021; van Dijk et al., 2020), possibly due to both provider-driven risk factor-based screening and self-assessed risk by PWUD. On the other hand, presence of opioid use disorder slightly decreased likelihood of achieving SVR12 (Beiser et al., 2019). Our data diverges here, for several possible reasons. First, our data is based on EHR ICD-10 diagnoses, not active use. EHR ICD-10 diagnoses for substance use disorders are notoriously inaccurate (Howell et al., 2020), and active use data often suggests a trend toward lower ITT SVR12 outcomes (Bartlett et al., 2019; Hajarizadeh et al., 2018). Second, our program is fully integrated with addiction care including buprenorphine for opioid use disorder treatment, which has been shown to enhance adherence and engagement among people with HCV and opioid use disorder (Hajarizadeh et al., 2018; Norton, Akiyama, Zamor, & Litwin, 2018). Furthermore, there has been consistent messaging within our clinical setting about the potential transformative effects of HCV treatment beyond health outcomes for people with use disorders (Williams et al., 2019), which may have led to increased motivation for engagement. Conversely, this may represent selection bias, in that people with more severe use disorders may not be engaged in care. ICD-10 diagnoses codes may not reflect real time vulnerability and future efforts in our clinical setting will rely on prospective active use data.

Limitations

Our study has several important limitations. First, our novel reflexive laboratory bundle was implemented in a non-randomized fashion and factors not controlled for in our analyses may have biased our results. Second, the study design presented challenges interpreting differences between the prospective and historical comparison cohorts. The presence of payer prior authorization fibrosis requirements of METAVIR fibrosis score of F2 or greater prior to January 2019 may have falsely increased the apparent effect of universal opt-out screening with the reflexive lab bundle, while a substantially shorter window for care cascade movement in the bundle period likely falsely decreased the effect measured. This is further complicated by the COVID-19 pandemic. While we defined our cohort endpoint to mitigate the effect on screening, we suspect that treatment initiation, treatment completion, and especially SVR12 lab completion were adversely affected by the pandemic. Third, the use of receipt of full DAA regimen to define treatment completion is a suboptimal surrogate endpoint and likely overreports true treatment completion. Fourth, our race/ethnicity data lacked specificity in the unknown/declined group, a population was less likely to progress through the cascade than Whites, and thus may have left an important equity gap undescribed. Finally, the overall screening rate appears low due in part to our study design and inability to include screening data prior to May 2017, which likely substantially underrepresented screening rates for patients continuously engaged in care during the analysis period who were previously screened.

Conclusions

We describe a promising new streamlined screening and linkage-to-care tool, implemented in a community-based setting, with the potential to remove steps in the care cascade and improve individual and societal outcomes associated with the HCV epidemic. This model of care demonstrates equitable screening and treatment initiation, addressing disparities in treatment outcomes experienced between racial, gender, and housing status groups.

Declarations of Interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.drugpo.2021.103359.

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