Open Forum Infectious Diseases

MAJOR ARTICLE

GRAND PLAN: Safety and Efficacy of Glecaprevir/Pibrentasvir for the Treatment of Hepatitis C Virus Infection Among People Initially Disengaged From Health Care Who Use Drugs—A Systematic Multidisciplinary Approach

Brian Conway,[1,2,©] Shana Yi,[1] Rossitta Yung,[1] and Shawn Sharma[1]

[1]Vancouver Infectious Diseases Center, Vancouver, British Columbia, Canada, and [2]Faculty of Health Sciences, Simon Fraser University, Burnaby, British Columbia, Canada

Background. GRAND PLAN is a prospective, open-label, phase 4 study. Based at a single center and with a single arm, GRAND PLAN evaluated the safety and efficacy of an 8-week course of glecaprevir/pibrentasvir (G/P) among active drug users with hepatitis C virus (HCV) infection in a population enriched for factors that may reduce treatment uptake and success, such as disengagement from health care and unstable housing.

Methods. Participants were ≥19 years old and actively using drugs and were confirmed viremic, noncirrhotic, and HCV treatment naive. All participants provided informed consent before any study procedures. They received G/P for 8 weeks within a multidisciplinary model of care, with daily, weekly, or monthly dispensing of medications to optimize adherence.

Results. We identified 117 eligible patients with a median age of 46 years (range, 22–75): 27% were female, 21.4% were Indigenous, 48.7% were unstably housed, and 95.7% were active drug users (94.9% fentanyl). One patient did not start treatment, and 4 underwent <1 week of treatment, leaving 112 completed treatments with 94.6% picking up medications weekly. HCV RNA was undetectable at the end of treatment in all 112 patients. One died of unknown causes shortly after treatment. A cure was demonstrated in 108 of 111 (97.3%) cases at the SVR12 time point (sustained virologic response at ≥12 weeks); the other 3 experienced virologic relapse. Considering the entire cohort, the intent-to-treat success rate was 92.3% (108/117). HCV reinfection was documented at SVR24 in 5 cases, 2 of which were successfully retreated.

Conclusions. GRAND PLAN demonstrates that administration of an 8-week course of G/P to inner-city residents with HCV infection leads to a cure >95%. With a short course of treatment, G/P is an attractive option for this population in helping us achieve the World Health Organization's HCV objectives by 2030.

Keywords. active drug users; community pop up clinic; hepatitis c; inner city; multidisciplinary.

Hepatitis C virus (HCV) is a global pandemic affecting >70 million people and is associated with significant morbidity and mortality [1]. The World Health Organization has set an ambitious goal to eliminate viral hepatitis (including HCV infection) as a public health concern by the end of this decade. To do so will require concerted efforts aimed at all target populations, including people who use or inject drugs. An estimated >15.6 million people inject drugs in the world, with 6.1 million living with HCV infection [2]. Of 1.5 million new infections per year, 40% occur in drug users. In the United States, of those who have ever used drugs in their lifetime, 50% are infected [3, 4]. In general, active drug users were excluded from registrational trials of agents currently used for the treatment of HCV infection in clinical practice. Postlicensure studies have shown impressive results even among people with recent injection drug use. In the SIMPLIFY study of sofosbuvir and velpatasvir, 97 of 103 participants achieved a cure, with no documented cases of virologic failure [5].

However, if we are to apply the findings of the SIMPLIFY study to more heterogeneous groups of drug users living with HCV infection, we must consider the development of systems of care that will deliver antiviral treatment in the context of multidisciplinary programs to address their more urgent needs. This will favor meaningful engagement in care and increase the likelihood of initiation of antiviral therapy and its completion. It is worth acknowledging that a substantial portion of the

Received 02 November 2023; editorial decision 07 December 2023; published online 5 March 2024

Correspondence: Brian Conway, MD, Vancouver Infectious Diseases Centre, 201-1200 Burrard St, Vancouver, BC V6Z 2C7, Canada; Faculty of Health Sciences, Simon Fraser University, 8888 University Dr W, Burnaby, BC V5A 1S6, Canada (brian.conway@vidc.ca)

Open Forum Infectious Diseases®

https://doi.org/10.1093/ofid/ofad638

many patients who are easier to treat, who are securely housed, and whose street drug use is less hectic may have already received HCV treatment. It is important to address less stable individuals—poorly housed, disengaged from addiction therapy, and using more dangerous street drugs with fentanyl and xylazine—and determine if structures can be designed and evaluated to increase access to successful HCV therapy.

Glecaprevir and pibrentasvir (G/P; administered as 3 tablets once daily) are direct-acting antiviral agents with pangenotypic activity against HCV. This regimen is administered for 8 weeks to treatment-naive noncirrhotic and compensated cirrhotic cases, with success rates exceeding 95% among those who complete treatment across multiple clinical trials. It has not been formally evaluated among drug users who are HCV infected, in particular those who would present challenges to engagement in care and treatment. In certain settings, the availability of a shorter course of treatment (8 vs 12 weeks) may be an important variable to consider in deciding to initiate HCV therapy among more vulnerable and disengaged individuals.

With this in mind, we have undertaken the phase 4 GRAND PLAN study—a prospective, open-label, single-arm trial based at a single center—to evaluate the safety and efficacy of an 8-week course of G/P among active/recent drug users with HCV infection in a population enriched for factors that may reduce treatment uptake and success, such as disengagement from health care and unstable housing.

METHODS

Study Design and Participants

The GRAND PLAN trial was conducted at the Vancouver Infectious Diseases Centre (VIDC), Vancouver, Canada. This academic center is low threshold and community based, offering multidisciplinary referral services in infectious diseases, with an emphasis on inner-city residents living with HCV and/or HIV infection. All referred patients would have access to antiviral therapy free of cost as needed. They would also have access to support services to address other medical, social service, and addiction-related needs (including opiate agonist therapy prescribed by center staff), as well as expedited access to mental health services.

Participants were ≥19 years old, documented to be viremic with any HCV genotype at the time of enrollment, previously untreated for their infection, and actively using or injecting drugs or doing so in the previous 3 months. Individuals were excluded for any of the following reasons: cirrhosis (as documented by a FibroScan measure >12.5 kPa) or decompensated liver disease, pregnant or breastfeeding, positive test result for hepatitis B surface antigen at the time of presentation, judged to be too unstable to engage in care, unable to provide informed consent, or medical contraindication to the prescription of G/P. Women of childbearing potential were eligible to participate if sexually abstinent or using 2 effective methods of birth control. Potential participants found to be cirrhotic were offered immediate access to alternative HCV therapy, most often the combination of sofosbuvir and velpatasvir.

Potential drug interactions with G/P were evaluated prior to the initiation of HCV treatment via the University of Liverpool HEP Drug Interactions website (https://www.hep-druginteractions.org/checker). In all cases, G/P therapy was able to be prescribed without any adjustment in concomitant medications.

All participants provided informed consent before any study procedures were performed. The study protocol was approved by Advarra and done according to the Declaration of Helsinki and International Conference on Harmonization good clinical practice guidelines.

Procedures

Participants were identified from March 2019 to April 2022 through weekly events known as community pop-up clinics (CPCs) held in the inner city of Vancouver, Canada, as well as targeted follow-up events to engage inner-city residents previously identified as having chronic HCV infection. CPCs are held at a variety of inner-city sites, including shelters, community service centers, modular housing facilities, and single-room occupancy dwellings, all located in the Downtown Eastside of Vancouver. CPCs are designed to evaluate as many as 30 adults over a 3-hour period. Eligible participants are required to provide informed consent, sign a release of medical information, and complete a demographic questionnaire.

Participants are tested with the OraQuick HCV Rapid Antibody Test (OraSure Technologies Inc; sensitivity and specificity >97%) [6]. This is a single-use fingerstick kit to measure the presence of HCV antibodies in a qualitative manner. All participants receive a CAD $10 gift card for completing the test and receiving the results, regardless of whether they choose to consult the on-site physician to discuss their results or not. Some participants directly referred to our center for evaluation (quite apart from the CPC program) were considered for participation in GRAND PLAN, if all eligibility criteria were met. Recruitment was suspended between March and June 2020 due to COVID-19 pandemic–related restrictions in the provision of health care. Other than during this brief period, recruitment proceeded in a satisfactory and steady manner, and our program was able to function without restrictions.

If they elect to proceed, participants are given the results of their tests in a confidential setting. Before the consultation, provincial laboratory databases are reviewed with the participants' consent to establish whether there is a prior diagnosis of HCV infection and a history of therapy for this condition in the province of British Columbia. During the consultation, the outline of a comprehensive individual plan of care is developed, and participants are given the option to make an appointment with a physician at VIDC within the next week. Those who schedule

an appointment are given a meal voucher (CAD $10 value) that they can redeem during their first VIDC clinic visit.

At their VIDC appointment, patients are offered a multidisciplinary suite of services, such as assistance with paperwork for housing, government disability funding, and nutritional support. A full medical history is recorded. A list of medical, psychological/psychiatric, and addiction-related needs is then established. All medical and addiction-related needs can be addressed by VIDC staff, including applications to drug treatment programs. Mental health referrals to appropriate agencies can be expedited. Any required nonprescription medications are provided free of charge, along with small snacks and beverages, including protein drinks.

Patients are then offered the opportunity to participate in the GRAND PLAN study for the treatment of their HCV infection. Once informed consent is obtained, baseline evaluations include confirmation of HCV RNA and genotype, standard laboratory testing (including confirmation of hepatitis B surface antigen status), FibroScan transient elastography, and any other evaluations that are clinically indicated.

G/P is obtained through fully funded government programs, supplemented by patient support programs as required. In this way, G/P is provided free of charge to all study participants. G/P is administered as 3 pills once daily with food for a treatment duration of 8 weeks. Treatment is provided in partnership with a central pharmacy (Specialty Rx) with a long history of partnership with VIDC on many outreach initiatives, as well as great experience and knowledge in the field of antiviral therapy, evaluation of drug interactions and side effects, and support for the monitoring of treatment adherence. Initially, a 1-week supply of G/P is provided to the participant, and adherence is evaluated at the end of that week. The program allows for daily, weekly, or monthly dispensing of the medications, as is required over 8 weeks to optimize adherence. This is evaluated on a dynamic basis over the 8 weeks of G/P therapy and adapted as appropriate.

During the course of treatment, a participant may be evaluated at VIDC as needed for acute medical conditions, to discuss issues of G/P side effects or adherence, or to assess any other concerns. Additional clinical and laboratory evaluations may be completed as indicated, as part of routine medical care. After G/P treatment is completed, individuals remain within the multidisciplinary care program as much as possible to ensure that the outcome of HCV therapy can be ascertained. The primary outcome of the study is measurement of HCV RNA ≥12 weeks after treatment completion (ie, sustained virologic response at ≥12 weeks [SVR12]). If an individual is not available for evaluation at the prescribed time point, additional outreach efforts are undertaken to obtain the required blood sample at the earliest possible time, whether in-person attendance at VIDC is possible or not.

Outcomes

The primary efficacy endpoint of the study was the proportion of participants achieving SVR12, defined as HCV RNA below the limit of quantitation ≥12 weeks after completing G/P therapy. This analysis was performed excluding participants who did not achieve SVR12 for reasons unrelated to their HCV infection or its treatment (modified intent-to-treat analysis). Secondary endpoints of interest included the rate of premature treatment discontinuation, loss to follow-up during the course of the study, mortality, and early HCV reinfection following demonstration of cure.

Statistical Analysis

In this single-arm prospective study, descriptive statistics were used to report on the primary outcome and all secondary outcomes. A priori there was the intention to enroll 100 participants as a proof of concept of the feasibility of this novel program of patient identification and engagement in care to be implemented on a broader scale, should this initial study produce favorable results. As appropriate, correlates of unfavorable outcomes were evaluated. With an expected SVR12 rate of ≥90%, this sample size will allow us to establish statistical noninferiority to the historical control rate of >95% achieved in clinical trials conducted in similar populations.

RESULTS

A total of 119 people were screened for participation, and 2 were excluded for cirrhosis. No one else was excluded from participation, not even for concerns about the likelihood of remaining engaged in care. As seen in Table 1, we identified 117 eligible participants with a median age of 46 years (range, 22–75), among whom 27% were female and 21.4% were Indigenous. The majority of participants were genotype 1 (56.4%) or 3 (32.5%). Very few had advanced liver fibrosis (F3-F4, 8.5%) by study design. Problematic/regular alcohol use was documented in >30% of participants, and the majority were smokers. Almost half (48.7%) were not in stable housing, living in shelters that needed to be vacated during the day or short-term rooms needing to be vacated in the coming weeks or few months. Active drug use, defined as using or injecting >2 days in the previous week, was confirmed in >95% of cases. As evaluated by baseline urine drug screening, fentanyl was the most commonly used substance (94.9%), followed by amphetamines (48.7%) and cocaine (26.5%), with the majority (96.6%) consuming multiple illicit substances. Benzodiazepines were not typically isolated, and only 41.9% were undergoing opiate agonist therapy with methadone. Hydromorphone, often prescribed as a harm reduction intervention in this population, was not evaluated by the urine drug assay used at our center (Table 1).

The inception cohort for study purposes comprised 117 participants. Of these, 5 either did not start treatment [1] or underwent

Table 1. Study Population (N = 117)

Characteristic	No. (%)
Age, y, median (range)	46 (22–75)
Sex	
Female	32 (27.4)
Male	85 (72.6)
Ethnicity	
Caucasian	87 (74.4)
Indigenous	25 (21.4)
Other	3 (2.6)
Genotype	
1	66 (56.4)
2	13 (11.1)
3	38 (32.5)
Fibrosis stage	
F0-F2	107 (91.5)
F3-F4	10 (8.5)
Alcohol use	
Yes	36 (30.8)
No	81 (69.2)
Smoking status	
Yes	99 (84.6)
No	18 (15.4)
Active drug user	112 (95.7)
Drug use profile	
Amphetamines	57 (48.7)
Cocaine	31 (26.5)
Fentanyl	111 (94.9)
Methadone	49 (41.9)
Benzodiazepine	15 (12.8)
Morphine	41 (35)
Unstable housing [a]	57 (48.7)

Baseline characteristics of participants who filled out the questionnaire during the community pop-up clinic.

[a]Unstable housing is defined by living in single-room occupancies, shelters, or homelessness.

<1 week of treatment [4]. These 5 patients were 30 to 70 years old, 2 were female, 5 had unstable housing, and all were active fentanyl users. All 112 remaining participants completed treatment. No side effects requiring intervention or treatment discontinuation were documented. Pickup of all G/P medications could be confirmed, with the majority (94.6%) receiving medications on a weekly basis or less frequently. HCV RNA was undetectable at the end of treatment in 112 of 112 participants. One died of unknown causes shortly after end of treatment. Of the 111 patients in whom HCV RNA at the SVR12 time point was available, a cure (ie, undetectable HCV RNA) was demonstrated in 108 (97.3%; Figure 1). In the other 3 cases, HCV RNA was detected within 12 weeks of the end of treatment. This was conservatively interpreted as a virologic relapse rather than initial success of therapy followed by early reinfection (Table 2). Considering the entire inception cohort, the intent-to-treat success rate of HCV treatment with G/P was 108 of 117 (92.3%).

Cases of virologic relapse are summarized in Table 2. For those in whom a virologic relapse was documented, second-line HCV treatment with the combination of sofosbuvir, velpatasvir, and voxilaprevir was available free of charge and provided to them. Patient 1 was treated during incarceration and was lost to follow-up after release. Patients 2 and 3 were still engaged and in the process of initiating a retreatment program.

HCV RNA was measured again in all cases 24 weeks after end of treatment, and virologic reinfection was documented in 5 cases (Table 3). These 5 patients were aged 31 to 67 years, 5 were male, 5 had unstable housing, and all were active fentanyl users. In these cases, first-line HCV treatment would be made available through government programs, free of charge, as soon as requested. To date, 2 individuals received a 12-week course of sofosbuvir and velpatasvir, with a cure being documented in both cases. The other 3 remain in care, and there is a plan to provide them with HCV treatment in the short term.

DISCUSSION

The World Health Organization's (WHO's) global hepatitis strategy, endorsed by all WHO member states, aims to reduce new hepatitis infections by 90% and deaths by 65% between 2016 and 2030 [7]. With respect to HCV infection, the advent of highly potent, safe, and easily administered oral agents for its treatment has been essential to the development of strategies to achieve these important goals. Before the pandemic, significant progress was being made, but momentum was lost over the past several years. As we build back better, we must be mindful of the need for targeted programs to address the needs of priority populations, such as vulnerable inner-city residents who face many challenges beyond HCV infection and who often continue to use and inject drugs.

The 2 most commonly used regimens for initial antiviral therapy are G/P and sofosbuvir/velpatasvir. Both combinations have been extensively studied in a range of populations in clinical trials [5, 8–13]. Although never compared head-to-head, they have produced equivalent cure rates (>95%) in all genotypes and in all stages of disease up to compensated cirrhosis [14]. Drug users were generally excluded from clinical trials. For sofosbuvir/velpatasvir, a phase 4 study (SIMPLIFY) was conducted and showed comparable results to those achieved in clinical trials [5]. To date, there has not been a similar study conducted with G/P, and the GRAND PLAN protocol is meant to fill this void. There has been some concern regarding the potential interaction of G/P with agents such as fentanyl (the drug of choice in the majority of participants in the GRAND PLAN study), leading to an increased risk of opioid overdoses among people who use drugs who may receive G/P as HCV therapy. This has been discussed on https://www.hep-druginteractions.org/checker. However, recent data suggest that this interaction is minimal at worst and not likely to be of any clinical significance [15]. Building on an established program for engagement of inner-city residents in care, we identified 117 persons with

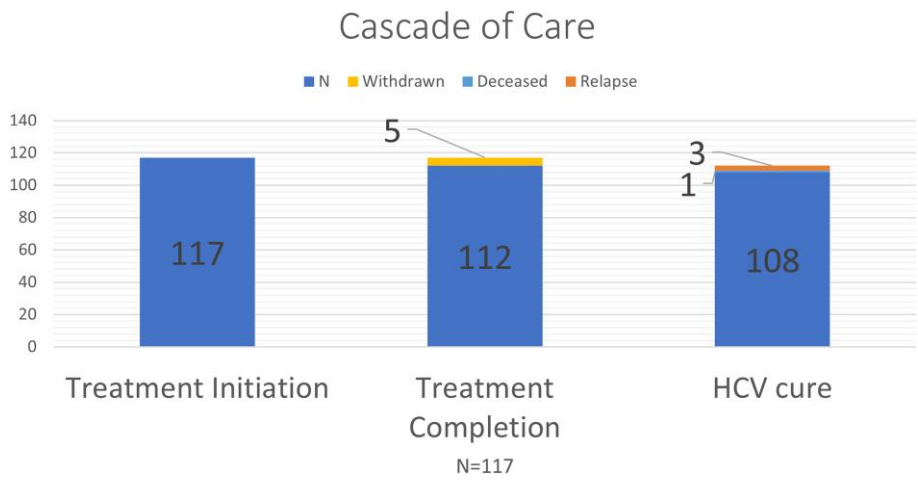

Figure 1. Cascade of HCV treatment care of the study cohort shows the progression from initiation to treatment completion to achieving cure at SVR12 (sustained virologic response at ≥12 weeks). HCV, hepatitis C virus.

HCV infection who were eligible to receive government-funded antiviral therapy. When they were offered such therapy within the context of a broader program designed to meet their more urgent self-identified needs, they agreed to engage in care under those terms. Treatment was provided in a structured way to maximize adherence and minimize loss to follow-up. This structure was maintained after treatment was completed to ensure that the results of therapy could be ascertained. A financial incentive was provided on a number of occasions throughout the course of the study. This has been an integral part of our program for several years, quite apart from the GRAND PLAN study. It was specifically reviewed and approved by the research ethics board (Advarra). It is difficult to speculate on the role the incentive played in maintaining individuals on HCV therapy, as many other aspects of our program are meant to serve this purpose. In particular, the participation of the Specialty Rx pharmacy team in our program is key. This allows for daily dispensing of the medications at the pharmacy or the participant's place of residence if needed, direct communication with the study team about missed doses, and linkage with the clinic for study visits. Going forward, this partnership will be scaled up as we develop elimination programs for the entire inner city of Vancouver.

Of 117 patients who initiated therapy, 108 were cured, as determined by a negative HCV RNA measure obtained ≥12 weeks after treatment completion, for an intention-to-treat SVR12 rate of 92.3%. Five did not complete treatment, with one never stratng and 4 receiving less than 1 week of treatment [1, 4]. One patient died after completing treatment due to unknown causes. This analysis yields a cure rate of 97.3% (108/111) by modified intent-to-treat analysis.

Our results closely mirror those of the SIMPLIFY study. Arguably, a more vulnerable population was enrolled according to patterns of drug use, including high rates of fentanyl use in the context of an opioid crisis claiming 6 or 7 lives per day in British Columbia and instability of housing [16]. We were, with established structures, able to maintain almost all participants in follow-up and measure an outcome, as was the case in SIMPLIFY.

The HERO study explored innovative and simplified models of care for HCV treatment among participants enrolled in opioid treatment programs [17], including nurse-led care and telemedicine approaches. It is encouraging to note that, by modified intent-to-treat analysis, 462 of 623 (74%) participants achieved an SVR12. It is quite possible that with enhanced supports, such as those that were made available to participants in the GRAND PLAN study, the success rate could have been even higher, increasing the benefits of offering multiple pathways to care via nonphysician-led initiatives. The American Association for the Study of Liver Diseases and the Infectious Diseases Society of America have developed simplified guidelines for HCV management [18]. Various studies have supported the concept of minimal monitoring in HCV care [19–21]. There is a need to carefully evaluate these simplified approaches among vulnerable inner-city residents to ensure that engagement in treatment is well maintained throughout the entire course of therapy and that achievement of HCV cure is not jeopardized.

Reinfection following successful HCV therapy among drug users is a well-documented outcome, with meta-analyses showing rates of 2 to 5 cases per 100 person-years; however, some real-world data sets report rates as high as ≥20 cases per 100 person-years [22–24], although rates of 5 cases per 100 person-years are increasingly being reported among PWID populations. In SIMPLIFY, a single case of short-term reinfection was identified. In GRAND PLAN, with longer follow-up, we noted 5 reinfection cases, of which 2 were already retreated, achieved SVR12, and were cured.

Table 2. Patients With Documented Virologic Relapse

No.	Age, y	Sex	Genotype	Fibrosis Stage	Type of Drug [a]	Viral Load, IU/mL	
						Baseline	Confirmation at Point of Relapse
1	48	Male	1A	F0	F, M	3 038 030	61 826
2	54	Male	3A	F0	F, A	10 969 093	14 858 439
3	41	Female	2	F2	F, C	2 942 871	8 479 148

Baseline characteristics of patients with documented virologic relapse and their baseline and confirmation viral loads at point of relapse. All 3 patients were active drug users and had unstable housing.

[a]A, amphetamines; C, cocaine; F, fentanyl; M, methadone.

Table 3. Patients With Documented Reinfection

No.	Age, y	Genotype	Fibrosis Stage	Type of Drug[a]	Time Point: Viral Load, IU/mL (Undetectable)[b]	Genotype (Reinfection)
4	67	3A	F1	F, MOR	SVR24: 2591 (SVR12)	3 (unable to subtype)
5	33	1A	F0	F, A, MOR	SVR24: 79 090 (SVR4)	3A
6[c]	33	3A	F0	F, A, M	SVR24: 552 987 (SVR12)	Not available
7[c]	42	2B	F0	F, A, M, MOR	SVR24: 7688 (SVR4)	1A
8	31	1A	F1	F, A, M	SVR19: 94 890 (SVR4)	3A

Baseline characteristics of patients with documented reinfection and their corresponding viral loads and genotype of reinfection. All patients were male active drug users with unstable housing.

[a]A, amphetamines; C, cocaine; F, fentanyl; M, methadone; MOR, morphine.

[b]SVR, sustained virologic response. The number indicates weeks (eg, SVR24 = sustained virologic response at ≥24 weeks).

[c]Patients 6 and 7 were retreated with sofosbuvir/velpatasvir and cured.

Our study has many strengths. We were able to enroll >100 highly vulnerable individuals with HCV infection and active drug use (before and during HCV therapy) and provide them with HCV therapy, with a successful outcome in almost all cases. We are quite heartened by the fact that in the context of an opioid overdose crisis in place in Vancouver since 2016, we observed a single overdose death over the period of observation in the GRAND PLAN study, suggesting that engagement in care may play a role in reducing opioid-related mortality. This demonstrates quite clearly that G/P is a credible option alongside sofosbuvir/velpatasvir for initial therapy of HCV infection among drug users—the latter of which consists of taking 1 pill per day for 12 weeks, for a duration of treatment 4 weeks longer than the former. In some cases, the availability of an 8-week option for duration of treatment (albeit taking 3 pills per day instead of 1) may present a significant advantage in some settings, such as time-limited incarceration or drug treatment. It is important that it be available.

Another strength of the study is its demonstration that disengaged persons may be able to receive HCV therapy if it is offered to them in the right context. HCV infection is rarely a high priority for active drug users who are poorly housed and face other medical and social challenges. We have clearly demonstrated that if the priority is on engagement and multidisciplinarity in the interactions with these individuals, HCV therapy can be started and successfully completed in the majority of cases. Furthermore, it is worth noting that >20% of the study population identified as Indigenous. In British Columbia and all of Canada, men and women of Indigenous descent are overrepresented in our inner cities and more likely to be disengaged from care [25, 26]. It is a strength of our overall approach that we were able to identify, treat, and cure these patients. Increasing their participation in our program and having them access the health care services that they request and deserve is a high priority for us. Our study also has weaknesses. Cirrhotic cases were excluded. This was by necessity, as G/P had been approved but not yet reimbursed for the treatment of HCV infection in the setting of cirrhosis within government programs at the time when the study was designed. It was also conducted at a single site. One could argue that unique site- or city-specific considerations contributed to its success. We would respond that the programmatic approach that we have put into place is well described and could be easily reproduced in several similar settings. One could also argue that the resources dedicated to the HCV treatment program are excessive and would not be able to be reproduced due to financial and human resource limitations. We would point out that the basic clinical infrastructure that we provide should be the standard for health care delivery to inner-city populations. The only part of our program that goes beyond this is the CPC, a weekly 3-hour event that draws on existing personnel and whose cost of operation is modest when compared with other more ambitious outreach programs that, based on their published results, have been less productive. Furthermore, the potential interaction of G/P and fentanyl is yet to be studied in the field, and this study has not encountered clinical issues or documented any increase in overdose due to this interaction [15].

In conclusion, the GRAND PLAN study demonstrates that the administration of an 8-week course of G/P as 3 tablets once a day with food to vulnerable inner-city residents with HCV infection (most of whom are actively using drugs and/or unstably housed) leads to a cure of HCV infection in >95% cases. As such, G/P may be an attractive option in this population and play an important role in helping us achieve WHO objectives for HCV elimination by the end of this decade.

Notes

Acknowledgments. We thank and recognize all study participants—most of whom are vulnerable inner-city residents—who contributed their time and efforts to the success of this study.

Author contributions. B. C.: conceptualization, operation, writing, reviewing, and editing. S. Y.: operation, writing, reviewing, and editing. R. Y.: operation, reviewing, and editing. S. S.: operation.

Data availability. Deidentified original data are available through the corresponding author.

Disclaimer. The funder had no role in the analysis or interpretation of the study results and did not have access to the raw data. No antiviral medications were provided. VIDC staff designed and implemented the study and evaluated its outcome under the supervision of B. C.

Financial support. This work was supported by a research grant from AbbVie Corporation, Canada to VIDC (grant numbers A19-331).

Potential conflicts of interest. B. C. received research grants, honoraria, and consultation fees from AbbVie, Astra Zeneca, Gilead Sciences, Indivior Canada, Merck, Moderna, Sanofi Pasteur, Seqirus, and ViiV Healthcare. S. S. received honoraria and consultation fees from AbbVie and Gilead Sciences. All other authors report no potential conflicts.

References

1. Messina JP, Humphreys I, Flaxman A, et al. Global distribution and prevalence of hepatitis C virus genotypes. Hepatology **2015**; 61:77–87.
2. Grebely J, Larney S, Peacock A, et al. Global, regional, and country-level estimates of hepatitis C infection among people who have recently injected drugs. Addiction **2019**; 114:150–66.
3. Thomas DL, Vlahov D, Solomon L, et al. Correlates of hepatitis C virus infections among injection drug users. Medicine (Baltimore) **1995**; 74:212–20.
4. Lorvick J, Kral AH, Seal K, Gee L, Edlin BR Prevalence and duration of hepatitis C among injection drug users in San Francisco, Calif. Am J Public Health **2001**; 91: 46–7.
5. Grebely J, Dore GJ, Zeuzem S, et al. Efficacy and safety of sofosbuvir/velpatasvir in patients with chronic hepatitis C virus infection receiving opioid substitution therapy: analysis of phase 3 ASTRAL trials. Clin Infect Dis **2016**; 63:1479–81.
6. Cha YJ, Park Q, Kang ES, et al. Performance evaluation of the OraQuick hepatitis C virus rapid antibody test. Ann Lab Med **2013**; 33:184–9.
7. World Health Organization. Hepatitis. Available at: https://www.who.int/healthtopics/hepatitis/elimination-of-hepatitis-by-2030tab=tab_1. Accessed 2023.
8. Lampertico P, Carrión JA, Curry M, et al. Real-world effectiveness and safety of glecaprevir/pibrentasvir for the treatment of patients with chronic HCV infection: a meta-analysis. J Hepatol **2020**; 72:1112–21.
9. Feld JJ, Jacobson IM, Hézode C, et al. Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. N Engl J Med **2015**; 373:2599–607.
10. Zeuzem S, Foster GR, Wang S, et al. Glecaprevir-pibrentasvir for 8 or 12 weeks in HCV genotype 1 or 3 infection. N Engl J Med **2018**; 378:354–69.
11. Kwo PY, Poordad F, Asatryan A, et al. Glecaprevir and pibrentasvir yield high response rates in patients with HCV genotype 1–6 without cirrhosis. J Hepatol **2017**; 67:263–71.
12. Asselah T, Kowdley KV, Zadeikis N, et al. Efficacy of glecaprevir/pibrentasvir for 8 or 12 weeks in patients with hepatitis C virus genotype 2, 4, 5, or 6 infection without cirrhosis. Clin Gastroenterol Hepatol **2018**; 16:417–26.
13. Foster GR, Gane E, Asatryan A, et al. ENDURANCE-3: safety and efficacy of glecaprevir/pibrentasvir compared to sofosbuvir plus daclatasvir in treatment-naïve HCV genotype 3-infected patients without cirrhosis. J Hepatol **2017**; 66:S33.
14. Liu C, Liu C, Su T, Tseng T, Chen P, Kao J. Sofosbuvir/velpatasvir or glecaprevir/pibrentasvir for treating patients with hepatitis C virus reinfection following direct-acting antiviral-induced sustained virologic response. Adv Dig Med **2023**; 10:34–42.
15. Mukherjee D, Collins M, Dylla DE, et al. Assessment of drug-drug interaction risk between intravenous fentanyl and the glecaprevir/pibrentasvir combination regimen in hepatitis C patients using physiologically based pharmacokinetic modeling and simulations. Infect Dis Ther **2023**; 12:2057–70.
16. Ministry of Public Health British Columbia. BCCS illicit drug type data. Available at: https://www2.gov.bc.ca/assets/gov/birth-adoption-death-marriage-and-divorce/deaths/coroners-service/statistical/illicit-drug-type.pdf. Accessed 31 January 2023.
17. Litwin AH, Lum PJ, Taylor LE, et al. Patient-centred models of hepatitis C treatment for people who inject drugs: a multicentre, pragmatic randomised trial. Lancet Gastroenterol Hepatol **2022**; 7:1112–27.
18. . AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology **2015**; 62:932–54.
19. Solomon SS, Sulkowski MS, Amrose P, et al. Directly observed therapy of sofosbuvir/ribavirin +/− peginterferon with minimal monitoring for the treatment of chronic hepatitis C in people with a history of drug use in Chennai, India (C-DOT). J Viral Hepat **2018**; 25:37–46.
20. Solomon SS, Wagner-Cardoso S, Smeaton L, et al. A minimal monitoring approach for the treatment of hepatitis C virus infection (ACTG A5360 [MINMON]): a phase 4, open-label, single-arm trial. Lancet Gastroenterol Hepatol **2022**; 7:307–17.
21. Davis JS, Young M, Marshall C, et al. Minimal compared with standard monitoring during sofosbuvir-based hepatitis C treatment: a randomized controlled trial. Open Forum Infect Dis **2020**; 7:ofaa022.
22. Hajarizadeh B, Cunningham EB, Valerio H, et al. Hepatitis C reinfection after successful antiviral treatment among people who inject drugs: a meta-analysis. J Hepatol **2020**; 72:643–57.
23. Muller A, Vlahov D, Akiyama MJ, Kurth A. Hepatitis C reinfection in people who inject drugs in resource-limited countries: a systematic review and analysis. Int J Environ Res Public Health **2020**; 17:4951.
24. Simmons B, Saleem J, Hill A, Riley RD, Cooke GS. Risk of late relapse or reinfection with hepatitis C virus after achieving a sustained virological response: a systematic review and meta-analysis. Clin Infect Dis **2016**; 62:683–94.
25. Nguyen NH, Subhan FB, Williams K, Chan CB. Barriers and mitigating strategies to healthcare access in indigenous communities of Canada: a narrative review. Healthcare **2020**; 8:112.
26. Hayashi K, Ti L, Dong H, et al. Moving into an urban drug scene among people who use drugs in Vancouver, Canada: latent class growth analysis. PLoS One **2019**; 14:e0224993.