Preferences of Persons With or at Risk for Hepatitis C for Long-Acting Treatments

Citation: thel D Weld, Jacqueline Astemborski, Gregory D Kirk, Mark S Sulkowski, Stephanie Katz, Richard Rothman, Sunil S Solomon, Gail V Matthews, Yu Hsiang Hsieh, Malvika Verma, Giovanni Traverso, Susan Swindells, Andrew Owen, Jordan Feld, Charles Flexner, Shruti H Mehta, David L Thomas, Preferences of Persons With or at Risk for Hepatitis C for Long-Acting Treatments, Clinical Infectious Diseases, Volume 75, Issue 1, 1 July 2022, Pages 3–10.

As Published: 10.1093/cid/ciab913

Publisher: Oxford University Press

Persistent URL: https://hdl.handle.net/1721.1/155049

Version: Final published version: final published article, as it appeared in a journal, conference proceedings, or other formally published context

Clinical Infectious Diseases

MAJOR ARTICLE

Preferences of Persons With or at Risk for Hepatitis C for Long-Acting Treatments

Ethel D. Weld,[1,2] Jacqueline Astemborski,[2] Gregory D. Kirk,[2,3] Mark S. Sulkowski,[2] Stephanie Katz,[2] Richard Rothman,[4] Sunil S. Solomon,[2] Gail V. Matthews,[5] Yu-Hsiang Hsieh,[4] Malvika Verma,[6] Giovanni Traverso,[7,8] Susan Swindells,[9] Andrew Owen,[10] Jordan Feld,[11] Charles Flexner,[1,2] Shruti H. Mehta,[3] and David L. Thomas[2]

[1]Department of Medicine, Division of Clinical Pharmacology, The Johns Hopkins University School of Medicine, Baltimore, MD, USA; [2]Department of Medicine, Division of Infectious Diseases, The Johns Hopkins University School of Medicine, Baltimore, MD, USA; [3]Department of Epidemiology, Division of Infectious Disease Epidemiology, The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; [4]Department of Emergency Medicine, The Johns Hopkins University School of Medicine, Baltimore, MD, USA; [5]The University of New South Wales, Sydney, Australia; [6]Department of Biological Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA; [7]Department of Mechanical Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA; [8]Division of Gastroenterology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; [9]Department of Internal Medicine, Section of Infectious Diseases, The University of Nebraska Medical Center, Omaha, Nebraska, USA; [10]Department of Pharmacology and Therapeutics, Centre of Excellence in Long acting Therapeutics (CELT), University of Liverpool, Liverpool, United Kingdom; and [11]The Toronto Centre for Liver Disease, University Health Network, University of Toronto, Toronto, Ontario, Canada

Background. Whereas safe, curative treatments for hepatitis C virus (HCV) have been available since 2015, there are still 58 million infected persons worldwide, and global elimination may require new paradigms. We sought to understand the acceptability of approaches to long-acting HCV treatment.

Methods. A cross-sectional, 43-question survey was administered to 1457 individuals with or at risk of HCV at 28 sites in 9 countries to assess comparative interest in a variety of long-acting strategies in comparison with oral pills.

Results. Among HCV-positive participants, 37.7% most preferred an injection, 5.6% an implant, and 6% a gastric residence device, as compared with 50.8% who stated they would most prefer taking 1–3 pills per day. When compared directly to taking pills, differences were observed in the relative preference for an injection based on age ($P < .001$), location ($P < .001$), and prior receipt of HCV treatment ($P = .005$) but not sex. When an implant was compared with pills, greater preference was represented by women ($P = .01$) and adults of younger ages ($P = .01$ per 5 years). Among participants without HCV, 49.5% believed that injections are stronger than pills and 34.7% preferred taking injections to pills. Among those at-risk participants who had received injectable medications in the past, 123 of 137 (89.8%) expressed willingness to receive one in the future.

Conclusions. These data point to high acceptability of long-acting treatments, which for a substantial minority might even be preferred to pills for the treatment of HCV infection. Long-acting treatments for HCV infection might contribute to global efforts to eliminate hepatitis C.

Keywords. Hepatitis C Long-Acting Treatments Patient Preferences Medication Acceptability Novel Drug Delivery Methods.

With the advent of oral pangenotypic therapies, nearly all infections caused by hepatitis C virus (HCV) can be cured with 8–12 weeks of pills [1, 2]. Accordingly, in 2016 the World Health Organization called for elimination of viral hepatitis as a public health threat by 2030 [3, 4]. Nonetheless, since 2016, the estimated number of persons with chronic hepatitis C worldwide has only dropped from 71 million to 58 million persons, and HCV remains a leading cause of deaths associated with infectious diseases globally [5–8]. The net global burden of HCV infection remains high because the number of persons who receive curative treatments remains only slightly higher than the number of new infections occurring each year [6, 9]. That dynamic is especially unfavorable in many low- and middle-income countries, where treatment initiation remains low, despite the availability of lower-cost generic formulations.

Multiple factors contribute to low HCV treatment initiation in low- and middle-income countries and in populations such as inmates in high-income countries. Foremost among them, insufficient or nonexistent medical infrastructure critically constrains HCV diagnosis and treatment and global elimination efforts. New treatment paradigms are needed. One strategy that is not dependent on building traditional medical infrastructure is a "test and cure" public health approach in which testing and cure occur in a single encounter. Since point-of-care testing for HCV already exists, this strategy would be advanced considerably by development of long-acting treatments that allow the entire 8–12-week oral curative treatment course to be provided immediately. Moreover, given differences among persons, the choice of alternative treatment formulations might increase net effectiveness.

Long-acting approaches already have been advanced for multiple indications—including prevention of pregnancy and human immunodeficiency virus (HIV) and treatment of

Received 28 July 2021; editorial decision 20 October 2021; published online 26 October 2021.
Correspondence: David L. Thomas, Suite 437 1830 Monument St, Baltimore, MD 21205 (dthomas@jhmi.edu).

Clinical Infectious Diseases® 2022;75(1):3–10

https://doi.org/10.1093/cid/ciab913

schizophrenia, HIV, and hormonally driven cancers—and they have gained regulatory approval [10–14]. In fact, long-acting treatments for HIV can be given monthly or bimonthly and have been shown to be noninferior or superior to pills for treatment or prevention of infection [15–17]. Populations likely to benefit from long-acting HIV therapeutics include those who prefer the practicality of a long-acting solution, as well as those in settings where the infrastructure for traditional medical care is insufficient. The example of the superiority of long-acting cabotegravir for prevention of HIV is especially relevant, since failure to understand the preferences of persons living with HIV may partially explain the relative failure of other preventive strategies that depend on fastidious adherence to a regimen of daily pills [18–20]. Differences in preferences within populations have also been shown with contraception and underscore the importance of understanding preferences and, when indicated, developing alternatives [21].

Accordingly, to seek the critical perspective of patients on the acceptability of long-acting approaches for HCV treatment, we conducted a survey among persons with or at risk of HCV infection at 28 international sites. The survey solicited preferences around 3 approaches that have been approved by regulatory agencies or are in early-stage human clinical trials and recognized as long-acting formulations, including injection, implant, and a star-shaped gastric-resident drug delivery system (GRS), which is swallowed once in capsule form and expands in the stomach to slowly release drug while escaping passage through the pylorus [22, 23]. These preferences were compared with the current standard of care for HCV treatment: 1–3 pills taken daily for 8–12 weeks.

METHODS

People with diagnosed HCV or who were at risk of HCV because of injection drug use were recruited at 28 sites in 9 countries. The sites included 2 within the Johns Hopkins Hospital in Baltimore Maryland: the Bartlett Specialty Practice (an infectious diseases clinic) and the Johns Hopkins Hospital Emergency Department [24–26] . In addition, participants were recruited at venues for persons who previously or currently injected drugs, including the AIDS Linked to the IntraVenous Experience (ALIVE) cohort, Baltimore, Maryland [27]; the Spatial Network Study in New Delhi, India, and participants from a substudy of the larger REACT study (Randomised Study of Interferon-free Treatment for Recently Acquired Hepatitis C in PWID and People with HIV Coinfection), with sites in Germany, the United Kingdom, Canada, the United States, Switzerland, Australia, New Zealand, and the Netherlands [28]. Institutional review boards at all the sites approved the study.

A 43-question survey instrument (Supplementary Materials), modified from one previously used to measure interest in long-acting antiretroviral therapy [29], was used to assess interest in various long-acting HCV treatment strategies and beliefs about their relative potency, as well as clinical and demographic characteristics of the respondents. The survey relied on self-report of the participants and was administered verbally at clinical sites by trained study staff. To prevent misleading participants, most questions were asked separately, depending on whether HCV infection had been diagnosed and/or already treated.

For those with HCV, the questions specifically asked about treatment of HCV and compared 8–12 weeks of 1–3 pills per day to alternative treatments. Participants who had previously been treated were instructed to respond as if they were being treated again and to consider the various methods compared with taking pills, and their results were compiled together with results from those who had never been treated. For those who responded that they had never been told they had HCV infection, similar questions were worded to measure prior experiences and acceptability of long-acting treatments in general. However, as the language of those questions differed, the data are stratified by self-reported HCV status. A provisional questionnaire was pilot tested in the ALIVE cohort, revised to improve the precision and flow, and then used at all sites; only data from the final questionnaire are presented. Photographs of the therapeutic modalities were used to guide respondents (see Supplementary Materials).

Descriptive statistics were used to summarize the respondents' demographic and clinical characteristics . For comparisons, the variable of race was analyzed in 4 categories (white, black, South Asian/Indian, or other), and age was analyzed both in quartiles and as a continuous variable. We used χ^2 analysis to compare characteristics between respondents who preferred the long-acting strategies and those who preferred pills. The impact of past exposure to injectable medications on likelihood of using injectable strategies was assessed, as was the impact of past injection of illicit substances. To determine potential regional differences in treatment preferences, outcomes were analyzed by site. Multinomial logistic regression was used to assess differences in the most preferred route of administration (with oral use as the reference standard) by study site, age, sex, and prior HCV treatment experience.

RESULTS

Overall Survey Population

The demographic and clinical characteristics of 1457 enrolled participants are presented in Table 1. Overall, the majority of respondents were African American (64.7%) and non-Hispanic (88.9%); their median age (interquartile range) was 55 (46–61) years; 28.4% were female, 71.1% male, and 0.6% male-to-female transgender or other. The majority of respondents (73.7%) were taking pills for conditions other than HCV, and a third of those were taking ≥6 pills daily. Almost half of participants taking

Table 1. Demographic and Clinical Characteristics of 1457 Study Participants by Hepatitis C Virus Status

Characteristic	Study Participants, No. (%)[a]			*P* Value (χ^2 Value)
	Overall	HCV Negative (n = 309)	HCV Positive (n = 1140)	
Site[b]				
India	149 (10.2)	56 (18.1)	93 (8.2)	<.001 (125.7)
REACT study	128 (8.8)	0 (0)	128 (11.2)	
Baltimore				
ED	194 (13.3)	11 (3.6)	181 (15.9)	
Clinic	248 (17.0)	29 (9.4)	218 (19.1)	
ALIVE cohort	738 (50.7)	213 (68.9)	520 (45.6)	
Age, median (IQR), y	55 (46–61)	52 (42–58)	56 (46–61)	<.001
Sex				
Male	1028 (71.1)	216 (69.9)	812 (71.4)	.81 (.98)
Female	410 (28.4)	92 (29.8)	318 (28.0)	
Male-to-female transgender	6 (0.004)	1 (0.3)	5 (0.4)	
Ethnicity[c]				
Latinx	42 (2.9)	7 (2.3)	35 (3.1)	<.001 (36.3)
Not Latinx	1294 (88.9)	302 (97.7)	984 (86.5)	
Unsure	116 (8.0)	0 (0)	116 (10.2)	
Race[c]				
White	306 (21.0)	30 (9.7)	274 (24)	<.001 (47.1)
African ancestry	941 (64.7)	212 (68.6)	724 (63.6)	
Asian/Pacific Islander	5 (0.3)	0 (0)	5 (0.4)	
Native American	14 (1.0)	5 (0.8)	9 (0.8)	
Asian (India)	150 (10.3)	54 (17.5)	96 (8.4)	
Other	39 (2.7)	8 (2.6)	30 (2.6)	
Taking any pills/medicine?				
Yes	1069 (73.72)	256 (70.7)	858 (80.8	<.001 (21.8)
No	362 (24.97)	106 (29.3)	203 (19.1)	
Special instructions for pills?				
Yes	635 (58.3)	129 (64.5)	501 (58.6)	.001 (17.8)
No	357 (32.8)	71 (35.5)	283 (33.1)	
Unsure or don't know	96 (8.7)	0 (0)	71 (8.3)	
No. of pills per day				
1–2	310 (29)	68 (33.5)	240 (28)	.44 (2.7)
3–5	401 (37.5)	74 (36.4)	325 (37.8)	
6–9	240 (22.5)	40 (19.7)	196 (22.8)	
>9	118 (11)	21 (10.3)	97 (11.3)	
Last time missed any medications?				
<1 wk ago	255 (23.4)	44 (21.7)	207 (23.6)	.45 (4.7)
1–2 wk ago	93 (8.6)	20 (9.9)	72 (8.2)	
3–4 wk ago	28 (2.6)	3 (1.5)	25 (2.9)	
1–3 mo ago	79 (7.3)	10 (4.9)	69 (7.9)	
>3 mo ago	56 (5.2)	10 (4.9)	46 (5.3)	
Never	577 (53)	116 (57.1)	458 (79.8)	
How many days in the past 4 did you miss any doses?				
0	146 (43.5)	4 (11.4)	141 (47.5)	<.001 (27.5)
1	138 (41.1)	17 (48.6)	120 (40.4)	
2	31 (9.2)	8 (22.9)	21 (7.1)	
3	10 (3)	2 (5.7)	8 (2.7)	
4	11 (3.3)	4 (11.4)	7 (2.4)	
Ever injected recreational drugs?				
Yes	1185 (82.2)	260 (84.1)	925 (81.6)	<.001 (28.5)
No	172 (12)	49 (15.9)	123 (10.9)	
Unsure	84 (5.8)	0 (0)	84 (7.4)	

Abbreviations: ALIVE, AIDS Linked to the IntraVenous Experience; ED, emergency department; HCV, hepatitis C virus; IQR interquartile range; REACT, Randomised Study of Interferon-free Treatment for Recently Acquired Hepatitis C in PWID and People with HIV Coinfection.

[a]Data represent no. (%) of study participants unless otherwise specified. HCV status was self-reported without regard to whether treatment was already received; 8 persons (0.6%) reported not knowing their HCV status. Differences in the sum of the individual elements and the 1147 total correspond to missing data, except when a question specifically characterizes a subset. For example, the question about how many days in the past 4 a dose was missed was answered by those taking medications and who admitted missing a dose.

[b]The REACT study includes 21 sites across 7 countries. ED refers to the Johns Hopkins School of Medicine ED. Clinic refers to a Johns Hopkins Hospital–based clinic specializing in treatment of infectious diseases. ALIVE is a community-based cohort of current and former persons who inject drugs (see Methods).

[c]Asked as Hispanic/non-Hispanic or African American.

pills (47.0%) had skipped pills from time to time, and within the past 4 days, most (56.5%) of the participants had missed ≥1 day. Most of the respondents (82.1%) had a history of injection drug use. In the REACT substudy, the majority (68%) had HIV coinfection.

Practices and Preferences of Persons With Prior or Current HCV Infection

The majority of survey respondents (1140 of 1457 [78.2%]) had prior or ongoing HCV infection; 754 (66.3%) had been previously treated for HCV, including 73 (9.6%) treated with injectable interferon. The proportion of participants with current or prior HCV infection ranged from 62.4% at the India site to 70.5% in the ALIVE cohort, 87.9% in the Bartlett Clinic, 93.3% in the Hopkins emergency department (ED), and 100% at the sites involved in the international REACT trial.

When HCV-positive participants were asked which treatment option they would most prefer, 37.7% selected an injection, 5.6% an implant, and 6% a gastric residence device, compared with 50.8% who stated they would most prefer taking 1–3 pills per day (Figure 1). When the converse was asked (which option they would *least* prefer), 9.7% stated that they would least prefer an injection, 37.3% an implant, and 48.4% a gastric residence device, compared with 4.6% who thought that pills were the worst method. There was a preference for injections in the buttocks (31.6%), followed by the arm (24.4%), and then the thigh (14.0%); 30.0% said that the injection site did not matter to them. The top concern for using injectable treatments for HCV was greater occurrence and longer duration of adverse effects, followed by concerns about getting 2 injections at once and having local swelling (Table 2). For implantable treatments, the top concerns were similar but also included the need for removal, scarring, and visibility of the implant. Finally, for the expandable gastric residence device, the top concerns were bad taste, the need for removal, and longer-lasting adverse effects.

Analysis of Most Preferred Method by Age, Sex, Site, and Prior HCV Treatment

The most preferred method of receiving HCV treatment differed by sex ($P < .001$). Compared with men, women were less likely to prefer pills (45.4% vs 53.0%, respectively) but more likely to prefer injections (40.1% vs 36.7%) and implants (8.5% vs 4.4%). There were also differences in preferences by age ($P \leq .01$). Among those who preferred pills, the median (interquartile range) age was 56 (47–62) years, compared with 57 (51–64) years for injectables, 56 (47.5–61) years for implants, and 55 (43–61) years for the expandable GRS. Overall differences in method preference also existed by site ($P < .001$). Respondents at the India site expressed the highest preference for daily pills (76.3% vs 20.4% preferring injections). In contrast, participants in the REACT substudy preferred injections over pills (43.7% vs 38.1%, respectively), and some expressed that the implant or expandable methods were best (9.5% and 8.7%). At the Baltimore sites, there were similar preferences between the Bartlett Clinic and the ALIVE cohort, with 52.2% and 54.2% preferring pills, respectively and 35.8% and 34.2% preferring injections. However, among the 181 study participants in the Hopkins ED, the reverse preference order was seen: 54.7% preferred injections, compared with 34.8% who preferred pills. Notably, in the 2 sites with the highest prevalence of HCV-positive respondents (Hopkins ED and Australian sites), there was a preference for injectable methods over pills.

Multivariable analysis was used to explore the independence of the apparent differences in selecting injection or implant as

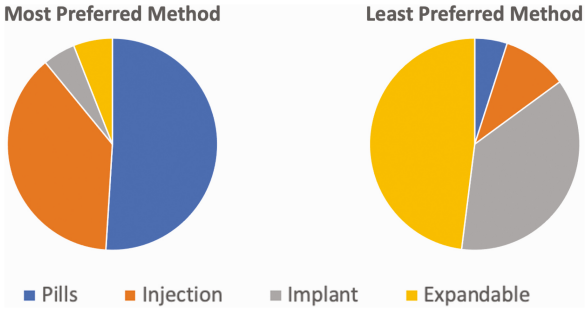

Figure 1. Preferences of hepatitis C virus (HCV)–positive participants for most and least preferred method of HCV treatment.

Table 2. Principal Concerns About Long-Acting Treatments Among 1140 Hepatitis C Virus–Positive Study Participants

Adverse Events	Degree of Concern, No. (%)[a]			
	Not at All Concerned	A Little Concerned	Somewhat Concerned	Very Concerned
Injection				
Skin swelling or pain	404 (35.6)	331 (29.2)	162 (14.3)	237 (20.9)
2 Injections at once	455 (40.1)	248 (21.9)	163 (14.4)	268 (23.6)
Adverse effects	237 (20.9)	305 (26.9)	223 (19.7)	369 (32.5)
Longer-lasting adverse effects	265 (23.4)	278 (24.5)	208 (18.4)	382 (33.7)
Implant				
Scar	374 (32.9)	275 (24.3)	159 (14)	326 (28.8)
Has to be removed	234 (20.7)	231 (20.4)	218 (19.2)	450 (39.7)
Visibility	393 (34.7)	229 (20.2)	206 (18.2)	306 (27)
Adverse effects	149 (13.1)	278 (24.5)	257 (22.7)	450 (39.7)
Longer-lasting adverse effects	192 (16.9)	253 (22.3)	230 (20.3)	459 (40.5)
Expandable gastric-resident drug delivery system				
Bad taste	471 (41.5)	263 (23.2)	158 (13.9)	243 (21.4)
Has to be removed	196 (17.3)	210 (18.5)	227 (20)	502 (44.2)
Blocks food	150 (13.2)	139 (12.3)	193 (17)	653 (57.5)
Adverse effects	149 (13.1)	237 (20.9)	250 (22)	499 (44)
Longer-lasting adverse effects	180 (15.9)	212 (18.7)	240 (21.2)	503 (44.3)

[a]Differences between the sums of the rows and the 1140 total represent missing data. Hepatitis C virus status was based on self-report.

the most preferred method of administration instead of taking 1–3 pills daily for 8–12 weeks. Although no sex preference was detected after adjustment for other factors, we continued to detect differences in preference for an injection by age, site, and prior HCV treatment status (Table 3). In contrast, the associations of female sex and younger age with preference for an implant were independent of other factors, and fewer differences were detected between the sites.

Practices and Preferences of HCV-Negative Persons

A total of 309 persons did not have HCV infection. HCV-negative participants were mostly (69.9%) male and mostly (68.9%) from the Baltimore ALIVE cohort; none came from the REACT study. When asked to compare injections with pills in general, 154 (49.5%) of respondents thought that injections are a stronger form of medication, compared with 88 (28.3%) who thought pills were stronger, 28 (9%) who thought they were the same strength, and 41 (13.2%) who did not know. When asked which method they preferred, 110 (34.7%) preferred taking injections, 168 (53%) preferred taking pills, 15 (4.7%) expressed no preference, and 24 (7.6%) did not know. A total of 138 (43.5%) reported having already received medication via an injectable route—most frequently antibiotics, painkillers, and depot medroxyprogesterone acetate (Depo-Provera). Of those who had received injections, 91% were willing to receive an injectable treatment again (94.1% or men and 87.5% of women) (Table 4).

When 309 HCV-negative participants were asked to compare implants with pills, 86 (27.1%) responded that implants were a stronger form of medication, 142 (44.8%) believed that pills were the stronger method, 19 (6.0%) thought they were the same, and 70 (22.1%) did not know. When asked which method they preferred, only 49 (15.5%) preferred implants; however, 123 (38.8%) indicated that they were willing to try an implant. Only 23 (7.4%) of the HCV-negative respondents reported having received medication from an implant in the past, 64.3% of whom were willing to try an implant again. When 309 HCV-negative participants were asked to compare pills to an expandable GRS device, 202 (63.7%) said they preferred pills over the GRS device, and only 91 (28.7%) said that the GRS was a stronger or more effective method of treatment.

Table 3. Factors Independently Associated With Selection of Injection or Implant as Most Preferred Method of Curative Hepatitis C Virus Treatment

Characteristic	RRR (95% CI)[a]	*P* Value
Injection		
Female sex	1.03 (.76–1.40)	>.1
Age (per 5 y)	0.86 (.80–.93)	<.001
Prior HCV treatment	0.64 (.47–.87)	.005
ALIVE cohort	Reference[b]	…
JHH HCV clinic	1.11 (.79–1.60)	>.1
JHH ED	2.34 (1.61—3.42)	<.001
India cohort	0.16 (.08–.32)	<.001
REACT cohort	1.54 (.94–2.51)	.09
Implant		
Female sex	2.16 (1.20–3.87)	.01
Age (per 5 y)	0.84 (.73–.96)	.01
Prior HCV treatment	1.00 (.49–2.02)	>.1
ALIVE cohort	Reference[b]	…
JHH HCV clinic	0.67 (.30–1.50)	>.1
JHH ED	1.32 (.61–2.88)	>.1
India cohort	0.07 (.01–.59)	.02
REACT cohort	1.96 (.78–4.91)	>.1

Abbreviations: ALIVE, AIDS Linked to the IntraVenous Experience; CI, confidence interval; ED, emergency department; HCV, hepatitis C virus; JHH, Johns Hopkins Hospital; REACT, Randomised Study of Interferon-free Treatment for Recently Acquired Hepatitis C in PWID and People with HIV Coinfection; RRR, relative risk ratio.

[a]Multinomial logistic regression was used to adjust the associations of shown factors with selection of an injection or an implant as the most preferred way to receive HCV treatment, compared with selection of 1–3 pills daily for 8–12 weeks. Higher RRRs reflect a positive association.

[b]Reference population used to establish RRR.

DISCUSSION

These data reveal a high level of acceptability for long-acting treatments among persons who have or are at risk for HCV infection; for a substantial minority, long-acting treatments are even preferred over pills. This finding reinforces the potential for long-acting treatments to contribute to global efforts to eliminate HCV. Equally, sex-, age-, and location-based differences in preferences underscore the importance of understanding local knowledge and attitudes in each setting and of providing education that aligns with public health services. Overall, the results of this survey should inform the development of long-acting HCV treatments.

We are aware of no other studies of the acceptability of long-acting HCV treatments to compare with our results. However, the field of HIV prevention has underscored the importance of comparative acceptability studies as a key precursor to drug development [30–33]. The overriding lesson from studies of HIV and contraception is that comparative acceptability should be assessed in the population to whom the drug will be given.

Of particular interest in our survey results were regional differences in acceptability of injections. Prior studies have demonstrated that widespread belief in the greater potency of injections compared with pills has contributed to the spread of HCV and other blood-borne infections in low- and middle-income regions of the world [34, 35]. Our team in India previously found high acceptance of injection treatments for HCV (using interferon) compared with pills. However, in this survey, 76.3% of respondents at the India site reported pills as their most preferred method, compared with 20.4% who preferred injections and 1% and 2% who preferred implants and expandables, respectively. In contrast, in the REACT and Hopkins ED cohorts, respondents reported a preference for injectable methods over the other listed methods (most REACT

Table 4. Experience and Preferences of Hepatitis C Virus–Uninfected Persons for Long-Acting Treatments

	Preference for Treatment, No. (%)[a]		
Experience	Injection	Implant	Expandable Pill
Prior experience	138/316 (43.7)	23/310 (7.4)	NA
Willingness to get in future			
Had past experience	123/134 (91.8)	18/28 (64.3)	NA
Regardless of past experience	110/317 (34.7)	123/281 (41.1)	NA
Stronger than a pill	154/270 (57)	86/247 (34.8)	91/247 (36.8)
Prefer long-acting, in general[b]	110/293 (37.5)	49/279 (17.6)	75/282 (26.6)

Abbreviation: NA, not applicable.

[a]Responses for preference compared with taking of 1–3 pills per day for 8–12 weeks. Percentages represent the total number of participants with potential responses, including 309 who were hepatitis C virus (HCV) negative and 8 with HCV status unknown or the reference subset (eg, those with past experience). Differences between the sum of the shown numbers and 317 (or the reference subset total) reflect either missing data or "do not know" responses.

[b]Respondents were advised to consider that the strategies had equivalent efficacy.

participants had HIV and may have been exposed to or experienced long-acting HIV treatment/prevention strategies). A few possible explanations for a stronger preference for pills in India could be explored in future studies. For example, there may be differences in preferences according to whether someone is currently actively injecting. Some preferences may also change over time with growing familiarity or understanding of a relatively new approach.

Perhaps not surprisingly, we found that patterns of prior use of methods informed future acceptability. For example, of HCV-negative participants who reported prior use of implants, 64.3% were willing to try an implant again, higher than the 12.5% of those who had never had implants and stated that they preferred taking implants to pills. Similarly, of those who had previously received injectable medicines, 89.8% reported willingness to use injectable medicines in future, much higher than the 26.4% of HCV-negative respondents who had never taken injectable medicines in the past and preferred taking injectables to pills. These data indicate that past experience with a technology may heighten its acceptability (aspects such as fear of needles may be important and were not explored).

Although these data are an important beginning, more work is needed. Young people with recently acquired HCV (a key population in the current US HCV epidemic) were not well represented. Likewise, respondents were mostly from the 3 sites in Baltimore (1180 of 1457 [81%]), with the second highest percentage (10.2%) from India and 8.8% from the REACT substudy. Thus, the ability to assess interest at international sites was somewhat limited owing to smaller sample size. Our survey in India was abbreviated because of coronavirus disease 2019 and certainly needs to be expanded. We also need to understand the acceptability of long-acting approaches in other settings and in more countries, including China, Pakistan, Egypt, and Russia, where (together with India) collectively 47.3% of the world's 71 million HCV infections are found [7]. Although respondents were directed to consider that all treatments might work equally, responder bias may also have influenced the estimates, especially in settings where HCV pills are understood to be highly efficacious and safe. An example might be the greater preference for pills among those already treated for HCV infection.

As important as it is to understand persons with HCV infection, it is also essential to understand the perspective of other stakeholders, including providers, health ministries, regulatory agencies, and global health funders. Preferences matter only when there are choices, and considerable effort is still needed even to bring existing HCV treatments to most parts of the world. Initial assessments of compatibility for existing HCV medications have indicated that glecaprevir and pibrentasvir may be compatible with certain long-acting technologies. Accordingly, at least one program has begun work on these agents as part of the LONGEVITY project funded by Unitaid [36]. Finally, we need to innovate, develop, scalably manufacture, and widely distribute safe, effective, and tolerable long-acting products for the treatment of HCV, which can be especially challenging, given the chemistry and doses required of some anti-HCV compounds, though early work has demonstrated the capacity to support depot-based delivery of these compounds [37].

A key pillar of the feasibility of global eradication efforts for helminth/parasitic infections has been the ability to deploy single-dose interventions, as they do not require existing infrastructure but can still abrogate community infection with a single visit [38–41]. Although there are notable differences in transmission patterns, populations most affected, and pharmacological properties of the agents used to treat parasites, compared with HCV, similar benefits toward elimination can be expected if testing and cure can be provided in a single encounter.

In summary, this study demonstrates that most persons with or at risk of HCV would be willing to be cured by a long-acting treatment, and some even prefer that approach to pills. Clearly, the next steps are to produce safe, affordable, and effective approaches to provide these options to the 58 million persons who remain HCV infected.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Disclaimer. The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding agencies.

Financial support. This work was supported by the Johns Hopkins University Center for AIDS Research, a National Institutes of Health (NIH)–funded program (developmental grant 1P30AI094189) supported by the following NIH cofunding and participating institutes and Centers: National Institute of Allergy and Infectious Diseases (NIAID), National Cancer Institute, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Heart, Lung, and Blood Institute, National Institute on Drug Abuse, National Institute on Aging, National Institute of General Medical Sciences, National Institute of Diabetes and Digestive and Kidney Diseases, and National Institute on Minority Health and Health Disparities. The work is also supported by the National Institute of Allergy and Infectious Diseases (grant R24AI118397), Unitaid (https://unitaid.org/project/long-acting-medicines-for-malaria-tuberculosis-and-hepatitis-c/#), and the NIH (grants R01DA041736 to the India cohort [Spatial Network Study]), 4R01DA040506-05 to the REACT [Randomised Study of Interferon-free Treatment for Recently Acquired Hepatitis C in PWID and People with HIV Coinfection] cohort, and R01DA048063 to the Baltimore AIDS Linked to the IntraVenous Experience [ALIVE] cohort).

Potential conflicts of interest. E. D. W. reports serving on an Study Monitoring Committee (SMC) for the HPTN 091 study and producing CME materials for medical education companies, including DKBMed and Clinical Care Options (organizations supported by unrestricted educational grants from Gilead, ViiV, and other pharmaceutical companies, which have no editorial oversight over the peer-reviewed materials E. D. W. produces and edits). G. D. K. reports grants from the NIAID (grant K24AI118591) and the National Institute on Drug Abuse (grant 2U01DA036297), NIH, during the submitted work. M. S. S. reports partial salary support during the conduct of the study from the NIH (grant K24DA034621), personal consulting fees from Gilead Sciences and AbbVie, personal support for participation on a data and safety monitoring board (DSMB) or advisory board related to coronavirus disease 2019 for Gilead Sciences and AbbVie, serving as unpaid chair of a hepatitis C virus special interest group for American Association for the Study of Liver Diseases,, and personal fees received as the editor of the *Journal of Viral Hepatitis*. R. R. reports grants or contracts, outside the submitted work, from the Gilead Focus Program and the Baltimore City Health Department and support for attending the Gilead Focus Program meeting. S. S. S. reports grants and study product to their institution from Gilead Sciences and Abbott Laboratories, outside the conduct of the study; an honorarium for a presentation from Gilead Sciences; and airfare and accommodations to attend Asian Pacific Association for the Study of the Liver and deliver a presentation from Gilead Sciences. G. V. M. reports grants or contracts made to the institution, outside the submitted work, from Gilead and AbbVie, payment or honoraria from Janssen for serving on a speakers bureau, and service as a board member for ASHM. M. V. reports receiving consulting fees for serving as project leader at Boston Consulting Group in the San Francisco office for Boston Consulting Group (no consulting in areas related to the current study). G. T. reports receiving grant funding from the Bill & Melinda Gates Foundation to develop long-acting dosage forms, during and outside the conduct of the study; royalties from licensing on long-acting technologies from Lyndra; and consulting fees as cofounder and board member of Lyndra. G. T. is also coinventor on multiple patent applications and has patents issued in the area of long-term gastric residency, serves on Lyndra's board of directors, and is cofounder and holder of stock options for Lyndra; other relationships can be found at https://www.dropbox.com/sh/szi7vnr4a2ajb56/AABs5N5i0q9AfT1IqIJAE-T5a?dl=0. S. S. reports research grants to their institution from ViiV Healthcare, outside the submitted work, and participation on a DSMB or advisory board for the Division of AIDS and a coronavirus DSMB for the NIH. A. O. reports payments to their institution from Gilead, ViiV Healthcare, Merck, Janssen, and Tandem Nano, outside the submitted work; consulting fees from ViiV Healthcare, Merck, and Gilead; numerous drug delivery patents, published and pending; and serving as director of Tandem Nano. J. F. reports grants or contracts from AbbVie and Gilead, outside the submitted work, and consulting fees from AbbVie and Gilead. C. F. reports payments for consulting from Gilead Sciences, Merck, and ViiV Healthcare; being named as coinventor on 2 issued patents for methods to create long-acting antiretroviral formulations (no income generated); and payment from Algernon Pharmaceuticals for participation on a DSMB or advisory board. S. H. M. reports grants or contracts from the NIH, outside the submitted work, and payment or honoraria for lectures, presentations, speakers bureau participation, manuscript writing or educational events from Gilead Sciences. D. L. T. reports funds to their institution from Unitaid (longevity grant), during the conduct of the study; various NIH grants, outside the submitted work; royalties or licenses from UpToDate; consulting fees for service on scientific advisory boards for Merck and Excision Bio; various payments for expert testimony; serving on an SMC for Merck molupinavir trials; holding stock or stock options from Excision Bio as scientific advisor; and various CME activities, approved by their university. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Feld JJ, Jacobson IM, Hezode C, et al. Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. N Engl J Med **2015**; 373:2599–607.
2. Puoti M, Foster GR, Wang S, et al. High SVR12 with 8-week and 12-week glecaprevir/pibrentasvir therapy: an integrated analysis of HCV genotype 1-6 patients without cirrhosis. J Hepatol **2018**; 69:293–300.
3. Organization WH. Global health sector strategy on viral hepatitis, 2016-2021: towards ending viral hepatitis. Geneva, Switzerland: World Health Organization, **2016**.
4. United Nations. Resolution 70/1. Adopted by the United Nations General Assembly on 25 September 2015: transforming our world—the 2030 agenda for sustainable development. New York, NY: United Nations General Assembly, **2015**.
5. Foreman KJ, Marquez N, Dolgert A, et al. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016-40 for 195 countries and territories. Lancet **2018**; 392:2052–90.
6. Hill AM, Nath S, Simmons B. The road to elimination of hepatitis C: analysis of cures versus new infections in 91 countries. J Virus Erad **2017**; 3:117–23.
7. Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol Hepatol **2017**; 2:161–76.
8. World Health Organization. Global progress report on HIV, viral hepatitis, and sexually transmitted infections, 2021. Accountability for the global health sector strategies 2016–2021: actions for impact. Available at: https://www.who.int/publications/i/item/9789240027077. Accessed 10 November 2021.
9. Heffernan A, Cooke GS, Nayagam S, Thursz M, Hallett TB. Scaling up prevention and treatment towards the elimination of hepatitis C: a global mathematical model. Lancet **2019**; 393:1319–29.
10. Cobb DA, Smith NA, Edagwa BJ, McMillan JM. Long-acting approaches for delivery of antiretroviral drugs for prevention and treatment of HIV: a review of recent research. Expert Opin Drug Deliv **2020**; 17:1227–38.
11. Winner B, Peipert JF, Zhao Q, et al. Effectiveness of long-acting reversible contraception. N Engl J Med **2012**; 366:1998–2007.
12. Citrome L. Long-acting injectable antipsychotics: what, when, and how. CNS Spectr **2021**; 26:1–12.
13. Shore ND, Guerrero S, Sanahuja RM, Gambús G, Parente A. A new sustained-release, 3-month leuprolide acetate formulation achieves and maintains castrate concentrations of testosterone in patients with prostate cancer. Clin Ther **2019**; 41:412–25.
14. Swindells S, Andrade-Villanueva JF, Richmond GJ, et al. Long-acting cabotegravir and rilpivirine for maintenance of HIV-1 suppression. N Engl J Med **2020**; 382:1112–23.
15. Marzinke MA, Grinsztejn B, Fogel JM, et al. Characterization of HIV infection in cisgender men and transgender women who have sex with men receiving injectable cabotegravir for HIV prevention: HPTN 083. J Infect Dis **2021**; 224:1581–92.
16. Landovitz RJ, Donnell D, Clement M, et al. HPTN 083 final results: Cabotegravir for HIV prevention in cisgender men and transgender women. NEJM **2021**; 385:595–608.

17. Delany-Moretlwe S, Hughes J, Bock P, et al. Long acting injectable cabotegravir is safe and effective in preventing HIV infection in cisgender women: interim results from HPTN 084. HIV R4P (HIV Research for Prevention). **2021**. Late-Breaker Oral Abstract # HY01.02LB.
18. Mensch BS, van der Straten A, Katzen LL. Acceptability in microbicide and PrEP trials: current status and a reconceptualization. Curr Opin HIV AIDS **2012**; 7:534–41.
19. Simoni JM, Beima-Sofie K, Wanje G, et al. "Lighten this burden of ours": acceptability and preferences regarding injectable antiretroviral treatment among adults and youth living with HIV in coastal Kenya. J Int Assoc Provide AIDS Care **2021**; 20:23259582211000517.
20. Scarsi KK, Swindells S. The promise of improved adherence with long-acting antiretroviral therapy: what are the data? J Int Assoc Provid AIDS Care **2021**; 20:23259582211009011.
21. United Nations. Contraceptive use by method. Available at: https://digitallibrary.un.org/record/3849735?ln=en. Accessed 10 November 2021.
22. Kirtane AR, Abouzid O, Minahan D, et al. Development of an oral once-weekly drug delivery system for HIV antiretroviral therapy. Nat Commun **2018**; 9:2.
23. Kirtane AR, Hua T, Hayward A, et al. A once-a-month oral contraceptive. Sci Trans Med **2019**; 11:eaay2602.
24. Hsieh YH, Rothman RE, Laeyendecker OB, et al. Evaluation of the Centers for Disease Control and Prevention recommendations for hepatitis C virus testing in an urban emergency department. Clin Infect Dis **2016**; 62:1059–65.
25. Hsieh YH, Signer D, Patel AV, et al. Advanced liver fibrosis and care continuum in emergency department patients with chronic hepatitis C. Am J Emerg Med **2019**; 37:286–90.
26. Falade-Nwulia O, Sutcliffe C, Moon J, et al. High hepatitis C cure rates among black and nonblack human immunodeficiency virus-infected adults in an urban center. Hepatology **2017**; 66:1402–12.
27. Vlahov D, Anthony JC, Munoz A, et al. The ALIVE study, a longitudinal study of HIV-1 infection in intravenous drug users: description of methods and characteristics of participants. NIDA Res Monogr **1991**; 109:75–100.
28. Matthews GV, Bhagani S, Van der Valk M, et al; REACT study group; Protocol Steering Committee; Coordinating Centre; Site Principal Investigators. Sofosbuvir/velpatasvir for 12 vs. 6 weeks for the treatment of recently acquired hepatitis C infection. J Hepatol **2021**; 75:829–39.
29. Williams J, Sayles HR, Meza JL, et al. Long-acting parenteral nanoformulated antiretroviral therapy: interest and attitudes of HIV-infected patients. Nanomedicine (Lond) **2013**; 8:1807–13.
30. Baeten JM, Palanee-Phillips T, Brown ER, et al; MTN-020–ASPIRE Study Team. Use of a vaginal ring containing dapivirine for HIV-1 prevention in women. N Engl J Med **2016**; 375:2121–32.
31. Nel A, Bekker LG, Bukusi E, et al. Safety, acceptability and adherence of dapivirine vaginal ring in a microbicide clinical trial conducted in multiple countries in sub-Saharan Africa. PLoS One **2016**; 11:e0147743.
32. Weinrib R, Minnis A, Agot K, et al. End-users' product preference across three multipurpose prevention technology delivery forms: baseline results from young women in Kenya and South Africa. AIDS Behav **2018**; 22:133–45.
33. van der Straten A, Agot K, Ahmed K, et al; TRIO Study Team. The Tablets, Ring, Injections as Options (TRIO) study: what young African women chose and used for future HIV and pregnancy prevention. J Int AIDS Soc **2018**; 21:e25094.
34. Drucker E, Alcabes PG, Marx PA. The injection century: massive unsterile injections and the emergence of human pathogens. Lancet **2001**; 358:1989–92.
35. Hauri AM, Armstrong GL, Hutin YJ. The global burden of disease attributable to contaminated injections given in health care settings. Int J STD AIDS **2004**; 15:7–16.
36. Unitaid. Long-acting medicines for malaria, tuberculosis, and hepatitis. Available at: https://unitaid.org/project/long-acting-medicines-for-malaria-tuberculosis-and-hepatitis-c/#en. Accessed 10 November 2021.
37. Verma M, Chu JN, Salama JAF, et al. Development of a long-acting direct-acting antiviral system for hepatitis C virus treatment in swine. Proc Natl Acad Sci U S A **2020**; 117:11987–94.
38. Kirby T. WHO celebrates 40 years since eradication of smallpox. Lancet Infect Dis **2020**; 20:174.
39. Ramzy RMR, Rabiee A, Abd Elaziz KM, et al. Test, treat, track, test, and treat active surveillance toward elimination of schistosomiasis: a feasibility study. Am J Trop Med Hyg **2020**; 103:1572–7.
40. Bandyopadhyay AS, Macklin GR. Final frontiers of the polio eradication endgame. Curr Opin Infect Dis **2020**; 33:404–10.
41. Gebre T. Rethinking disease eradication: putting countries first. Int Health **2021**; 13:215–21.