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Elbasvir–Grazoprevir to Treat Hepatitis C Virus Infection in Persons Receiving Opioid Agonist Therapy

A Randomized Trial

Gregory J. Dore, MD; Frederick Altice, MD; Alain H. Litwin, MD; Olav Dalgard, MD; Edward J. Gane, MD; Oren Shibolet, MD; Anne Luetkemeyer, MD; Ronald Nahass, MD; Cheng-Yuan Peng, MD; Brian Conway, MD; Jason Grebely, PhD; Anita Y.M. Howe, PhD; Isaias N. Gendrano, MPH; Erluo Chen, MPH; Hsueh-Cheng Huang, PhD; Frank J. Dutko, PhD; David C. Nickle, PhD; Bach-Yen Nguyen, MD; Janice Wahl, MD; Eliav Barr, MD; Michael N. Robertson, MD; and Heather L. Platt, MD; on behalf of the C-EDGE CO-STAR Study Group*

Background: Hepatitis C virus (HCV) infection is common in persons who inject drugs (PWID).

Objective: To evaluate elbasvir–grazoprevir in treating HCV infection in PWID.

Design: Randomized, placebo-controlled, double-blind trial. (ClinicalTrials.gov: NCT02105688)

Setting: Australia, Canada, France, Germany, Israel, the Netherlands, New Zealand, Norway, Spain, Taiwan, the United Kingdom, and the United States.

Patients: 301 treatment-naive patients with chronic HCV genotype 1, 4, or 6 infection who were at least 80% adherent to visits for opioid-agonist therapy (OAT).

Intervention: The immediate-treatment group (ITG) received elbasvir–grazoprevir for 12 weeks; the deferred-treatment group (DTG) received placebo for 12 weeks, no treatment for 4 weeks, then open-label elbasvir–grazoprevir for 12 weeks.

Measurements: The primary outcome was sustained virologic response at 12 weeks (SVR12), evaluated separately in the ITG and DTG. Other outcomes included SVR24, viral recurrence or reinfection, and adverse events.

Results: The SVR12 was 91.5% (95% CI, 86.8 to 95.0) in the ITG and 89.5% (95% CI, 81.5 to 94.8) in the active phase of the DTG. Drug use at baseline and during treatment did not affect SVR12 or adherence to HCV therapy. Among 18 patients with posttreatment viral recurrence through 24-week follow-up, 6 had probable reinfection. If the probable reinfections were assumed to be responses, SVR12 was 94.0% (CI, 89.8 to 96.9) in the ITG. One patient in the ITG (1 of 201) and 1 in the placebo-phase DTG (1 of 100) discontinued treatment because of an adverse event.

Limitation: These findings may not be generalizable to PWID who are not receiving OAT, nor do they apply to persons with genotype 3 infection, a common strain in PWID.

Conclusion: Patients with HCV infection who were receiving OAT and treated with elbasvir–grazoprevir had high rates of SVR12, regardless of ongoing drug use. These results support the removal of drug use as a barrier to interferon-free HCV treatment for patients receiving OAT.

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For author affiliations, see end of text.

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* For members of the C-EDGE CO-STAR (A Phase III Randomized Clinical Trial to Study the Efficacy and Safety of the Combination Regimen of MK-5172/MK-8742 in Treatment-Naive Subjects With Chronic HCV GT1, GT4, and GT6 Infection Who Are on Opioid Substitution Therapy) Study Group, see the **Appendix** (available at www.annals.org).

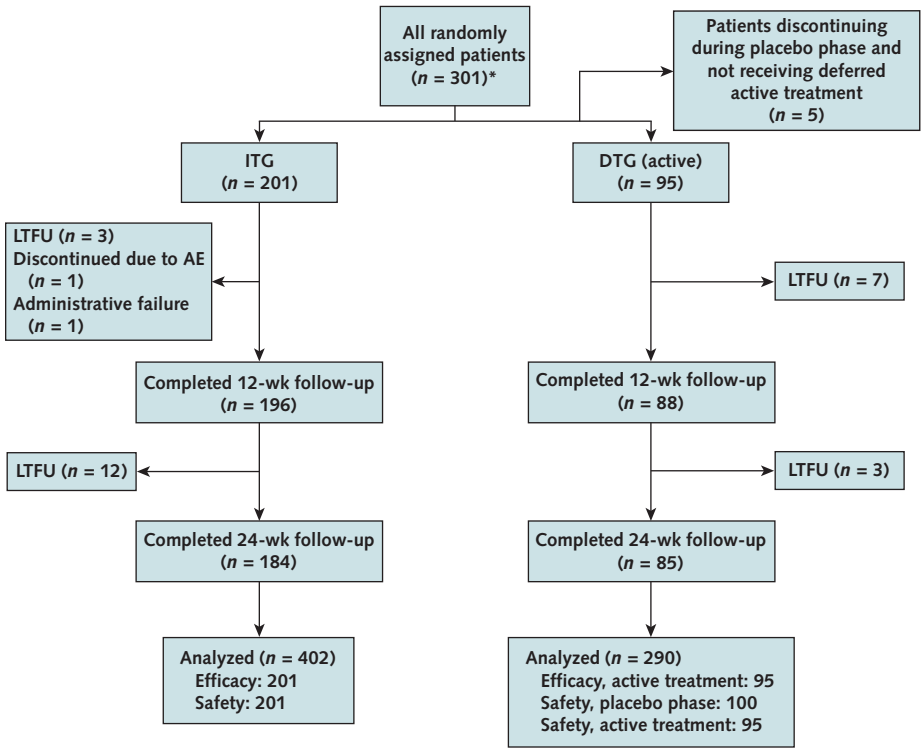
Globally, an estimated 130 million to 170 million persons have hepatitis C virus (HCV) infection (1). Morbidity and mortality from chronic HCV infection continue to increase, particularly among persons who inject drugs (PWID) (2). In most high-income countries, PWID are the major population affected by HCV, although injection drug use–related HCV epidemics are emerging in many other locales, with an estimated HCV prevalence of 60% to 80% (1, 3). Yet, most trials of direct-acting antiviral (DAA) therapies for HCV have excluded persons with recent injection drug use, although small studies suggest favorable outcomes among those receiving opioid-agonist therapy (OAT) (4). The once-daily dosing, low side-effect profile, and shortened treatment duration of interferon-free DAA regimens are particularly suited to HCV treatment in PWID.

Elbasvir–grazoprevir is a fixed-dose combination recently approved in the United States for treating HCV genotypes (GTs) 1 and 4 (5). Elbasvir (an NS5A inhibitor) and grazoprevir (an NS3/4A protease inhibitor) have demonstrated potent in vitro activity against most HCV GTs, including first-generation protease inhibitor resistance–associated variants (RAVs), as well as RAVs related to daclatasvir and ledipasvir treatment failures (6–8). Phase 1 studies found no clinically significant drug interactions between methadone or buprenorphine and elbasvir or grazoprevir (9–11). A once-daily, oral, 12-week regimen of elbasvir–grazoprevir demonstrated favorable safety and high efficacy in a phase 3 clinical development program among treatment-naive and -experienced patients with HCV monoinfection or HIV–HCV co-infection (12–15).

See also:

Web-Only
Supplement

Figure 1. Study flow chart.



This CONSORT (Consolidated Standards of Reporting Trials) diagram shows the disposition of patients randomly assigned to the ITG and DTG, the number of patients in each group who completed 12-wk and 24-wk follow-up after active treatment with elbasvir–grazoprevir, and the number of patients analyzed for efficacy and safety. AE = adverse event; DTG = deferred-treatment group; ITG = immediate-treatment group; LTFU = lost to follow-up.

* Who received at least 1 dose of the study drug. The number of randomly assigned patients from each country was as follows: Australia, 51; Canada, 14; France, 17; Germany, 12; Israel, 6; Netherlands, 4; New Zealand, 10; Norway, 9; Puerto Rico, 7; Romania, 15; Spain, 21; Taiwan, 15; United Kingdom, 27; and United States, 93.

The objective of this study of the CO-STAR (Hepatitis C Patients on Opioid Substitution Therapy Antiviral Response) trial was to evaluate the efficacy and safety of a 12-week regimen of elbasvir–grazoprevir for PWID with HCV infection receiving OAT.

METHODS

Patients

From 2 September 2014 through 9 December 2014, investigators screened 371 treatment-naive patients aged 18 years or older with chronic HCV GT1, GT4, or GT6 infection and a baseline HCV RNA level of 10 000 IU/mL or greater in 13 countries, and 301 patients were enrolled (see footnote to **Figure 1**). Eligible patients were receiving OAT with methadone, buprenorphine, or buprenorphine–naloxone for at least 3 months before enrollment and were at least 80% adherent to OAT appointments. Patients actively using drugs of potential abuse while receiving OAT were not excluded. Patients with HIV-1 infection either were naive to antiretroviral therapy or were receiving stable antiretroviral therapy with tenofovir or abacavir; emtricitabine or lamivudine; and dolutegravir, raltegravir, or rilpivirine before enrollment. Planned enrollment included up to 20% of patients with cirrhosis as demonstrated by aspartate aminotransferase (AST)–platelet ratio index combined with FibroTest (BioPredictive), hepatic elastography, or biopsy (**Supplement 1**, available at www.annals.org).

Study Design and Interventions

C-EDGE CO-STAR (protocol 5172-062) was a randomized, placebo-controlled, multisite, double-blind trial of the once-daily, fixed-dose combination of elbasvir (50 mg) and grazoprevir (100 mg) (**Figure 1** and **Figure 1** of **Supplement 1**). Randomization was done centrally through an interactive voice and integrated Web response system, and was stratified according to GT and presence or absence of cirrhosis. Patients were randomly assigned 2:1 to the immediate-treatment group (ITG) (blinded elbasvir–grazoprevir for 12 weeks) or the deferred-treatment group (DTG) (placebo for 12 weeks, followed by 4 weeks of follow-up, then 12 weeks of open-label treatment with elbasvir–grazoprevir). Patients remained blinded until the 16-week visit to allow all safety data through week 12 to be reviewed before unblinding. Patients were followed for 24 weeks after they completed active treatment. In addition, they were eligible to enroll in a 3-year observational study to as-

sess the durability of the sustained virologic response (SVR), incidence of HCV reinfection, and drug use behaviors. Three-year follow-up data were unavailable at the time of this report.

Study Assessments

Hepatitis C virus GT was assessed at enrollment with the Versant HCV Genotype 2.0 Assay (Line Probe Assay; Siemens Healthcare). Hepatitis C virus RNA was assessed at baseline; at day 7; every 2 weeks during treatment; and at follow-up weeks 4, 8, 12, and 24 for the ITG and DTG, during both the placebo and active treatment phases, by using COBAS AmpliPrep and COBAS TaqMan HCV 2.0 (Roche) (lower limit of quantitation, 15 IU/mL).

Safety was assessed by monitoring clinical adverse events (AEs) and laboratory values. At screening, assessments included physical examination, electrocardiography, and evaluation of hepatitis B and HIV status. At screening and each study visit, spontaneously reported AEs and laboratory measurements, including complete blood count and chemistry and coagulation panels, were evaluated. Urinalysis was done at baseline and treatment weeks 4, 8, and 12. Nonspecific hepatic laboratory "events of clinical interest" were defined to create a sensitive screen for the presence of potential liver abnormalities. These events were categorized as tier 1 AEs and included the following laboratory abnormalities, which were assessed from the start of study therapy through 14 days after treatment and were not associated with virologic failure: alanine aminotransferase (ALT) or AST levels greater than 500 IU/L, ALT or AST levels greater than 3 times the baseline value and greater than 100 IU/L, or alkaline phosphatase levels greater than 3 times the upper limit of normal. Urine drug screening (UDS) was conducted at each study visit for the following substances: amphetamines, barbiturates, benzodiazepines, buprenorphine, cannabinoids, cocaine, methadone, other opioids, phencyclidine, and propoxyphene.

Study End Points

The primary efficacy end point was the proportion of patients in the ITG achieving an SVR, defined as an HCV RNA level less than the lower limit of quantitation (<15 IU/mL) at 12 weeks after the end of treatment (SVR12). A secondary end point was SVR24 (HCV RNA <15 IU/mL 24 weeks after the end of active treatment). The incidence of clinical and laboratory AEs in ITG patients treated with elbasvir–grazoprevir was compared with that in DTG patients during the placebo phase. Hepatic events of clinical interest were designated as tier 1 AEs and included the first instance of an ALT or AST level greater than 3 times the upper limit of normal and greater than 100 IU/mL, or the first instance of an alkaline phosphatase level greater than 3 times the upper limit of normal. Tier 2 AEs included the proportion of patients with at least 1 AE, a drug-related AE, a serious AE, a serious and drug-related AE, and an AE leading to discontinuation.

Analysis of Viral Resistance and Recurrence

Hepatitis C virus genotyping of the patients who had a virologic recurrence was conducted to determine whether there was a change in GT from baseline. Viral resistance was assessed at baseline, at time of failure, and at all subsequent follow-up time points in patients who met the criteria for virologic failure (HCV RNA >15 IU/mL, measured from 2 separate blood draws within 2 weeks). Hepatitis C virus population sequencing (*NS3* and *NS5A* genes; sensitivity about 25%) was done to assess resistance and to distinguish viral relapse from probable reinfection in patients with viral recurrence (see **Supplement 2**, available at www.annals.org, for the HCV sequencing analysis method). To assess the possibility of a mixed infection at baseline, ultradeep sequencing was done on the baseline sample with GT-dependent primers of the GT found at recurrence.

Adherence

Study medication was dispensed every 2 weeks. An electronic study medication diary was provided to patients to assess adherence. Patients were asked to enter the time and dose taken daily; they also could program medication reminders.

Statistical Analysis

All patients were analyzed based on their randomized treatment assignment, and all randomly assigned patients were included in the main safety and efficacy analyses, except for 5 patients in the DTG who discontinued treatment during the placebo phase and could not be included in the efficacy evaluation of the DTG while receiving active treatment. Patients who stopped treatment and had not had a relapse before the time of discontinuation were considered as treatment failures. These analyses follow intention-to-treat principles. The protocol (**Supplement 2**) specified the primary efficacy end point as SVR12 in the ITG, defined as HCV RNA less than 15 IU/mL at 12 weeks after treatment in an analysis that considered patients with reinfection as responders. The more conservative analysis presented here assumed that reinfections were treatment failures, and we provide the other results (reinfections = responders) as ancillary. We calculated 95% CIs for SVR and differences in AE incidence by using the Clopper–Pearson and Miettinen–Nurminen methods, respectively (16, 17).

The study planned to randomly assign 300 patients in a 2:1 ratio to the ITG or DTG. Assuming a response rate of at least 85% in the ITG, the study had greater than 99% power to demonstrate the superiority of SVR12 to the reference rate of 67%, with a 1-sided α level of 2.5% (18). The reference SVR12 rate of 67% was derived at the time this protocol was initiated from the phase 2 trial of sofosbuvir plus peginterferon plus ribavirin in GT1-infected patients with HIV co-infection after adjustments for the expected higher proportion of patients with cirrhosis and improved safety profile in this trial.

Study Oversight

The trial was approved by the institutional review board or independent ethics committee at each participating site and conducted in adherence with the provisions of the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulatory requirements.

Role of the Funding Source

The sponsor (Merck) funded the study, collected the data, monitored study conduct, and performed the statistical analyses.

RESULTS

Baseline Characteristics

Of 371 patients screened for enrollment, 301 were randomly assigned: 201 to the ITG and 100 to the DTG. Baseline characteristics were similar between the 2 groups (**Table 1**).

Efficacy

The SVR12 rate was 91.5% (184 of 201 [95% CI, 86.8% to 95.0%]) in the ITG and 89.5% (CI, 81.5% to 94.8%) in the active-phase DTG (**Table 2**). Although SVR12 was similar in GT1a-, GT1b-, and GT4-infected patients, it was lower in the few patients with GT6 infection (**Table 2**). In the ITG overall, the SVR12 of 91.5% and the lower bound of the 95% CI both were greater than the historical reference rate of 67%. Of the 17 patients who did not achieve SVR12, 12 had viral recurrence and 5 had nonvirologic reasons for failure (discontinuation due to an AE [*n* = 1], an administrative reason [*n* = 1], or loss to follow-up [*n* = 3]). On the basis of GT assessment, sequencing, and phylogenetic analysis, 7 of the 12 patients with viral recurrence had findings consistent with relapse, and 5 had signs consistent with probable reinfection (**Figure 3** of **Supplement 1**). When patients with probable reinfection were assumed to have a response, SVR12 was 94.0% (189 of 201 [CI, 89.8% to 96.9%]). At 24 weeks, 2 additional relapses were identified and 12 more patients were lost to follow-up (**Table 2**). **Table 1** of **Supplement 1** shows the percentage of patients with an HCV RNA level less than 15 IU/mL in the ITG and in both the placebo and active phases of the DTG.

In the DTG, 100 patients received placebo for the first 12 weeks, and as expected, all patients had detectable HCV RNA at treatment week 16, or day 1 of active treatment. After the 4-week unblinding period, 95 patients started open-label study medication. Of these, 85 (89.5% [CI, 81.5% to 94.8%]) achieved SVR12 in the analysis that considered reinfections to be treatment failures (**Table 2**). This SVR12 is similar to that in the ITG, and the lower bound of the 95% CI is greater than the 67% reference rate. Of the 10 patients categorized as having failures, 3 had viral recurrence (breakthrough [*n* = 2] and relapse [*n* = 1]) and 7 were lost to follow-up. Through week 24, 1 additional patient had viral recurrence, with data consistent with probable reinfection, and another 3 patients were lost to follow-up (**Table 2**).

Subgroup analyses showed consistently high virologic response rates in several subgroups, including the important subgroups of patients with cirrhosis and those with positive UDS results (**Figure 2** of **Supplement 1**). In the few patients of Asian or other race/ethnicity, as well as those with GT6 infection (all of whom were Asian), SVR12 was lower, with wide CIs.

The proportion of patients with HCV RNA less than 15 IU/mL (intention-to-treat population) at various time points during and after treatment is shown in **Table 1** of **Supplement 1**. A per protocol analysis of SVR12 by GT is defined and provided in **Table 2** of **Supplement 1**.

Adherence

During the initial treatment period, adherence greater than 95% (>79 doses) was reported by 96.5% of patients (192 of 199) in the ITG and 100% of those in the placebo-phase DTG (97 of 97). In the active-phase DTG, adherence greater than 95% was reported in 95.8% of patients (91 of 95).

UDS

More than 50% of patients in each group had positive results on UDS for at least 1 potential drug of abuse, excluding methadone and buprenorphine, at each visit. There were no meaningful differences in drug use between the study groups: day 1 UDS results were positive in 62% of patients in the ITG and 53% in the DTG. Based on UDS results, drug use remained relatively stable throughout treatment (**Figure 2**). Seventy-eight percent of patients (59 of 76) in the ITG and DTG groups with a positive benzodiazepine UDS result at baseline also had a benzodiazepine listed as a concomitant medication, indicating that most probably were using prescription benzodiazepines. Positive UDS results at baseline or during treatment (2 or more positive UDS results) did not affect adherence or efficacy, regardless of which drug class was positive on UDS (**Tables 3** and **4** of **Supplement 1**).

Reinfections

Eighteen patients had recurrent viremia after active treatment through week 24: 14 in the ITG and 4 in the active-phase DTG. Recurrent viremia was determined to be probable reinfection in 5 of the 14 patients in the ITG (all with recurrent viremia at follow-up week 8) and 1 patient in the DTG (recurrent viremia at follow-up week 24). Probable reinfection was supported by population sequencing and phylogenetic analysis (**Figure 3** of **Supplement 1**). From the end of treatment through follow-up week 24 for all patients, the incidence of reinfection was 4.6 reinfections (CI, 1.7 to 10.0 reinfections) per 100 person-years (130.6 person-years of follow-up). In 4 of 6 cases of probable reinfection, the HCV GT at failure was determined to differ from that at baseline (**Table 4** of **Supplement 1**). In all 6 cases, phylogenetic analysis determined that the virus at baseline and the one present at recurrence were from distinct lineages (**Figure 3** of **Supplement 1**). Ultradeep sequencing of the baseline samples with the GT-dependent primers based on the viral recurrence sample failed to amplify, indicating that these patients acquired a new virus and did not have a mixed infection at baseline. Of note, in 3 of the 6 cases, recurrent

Table 1. Demographic Characteristics of Patients at Baseline*

Characteristic	ITG: Elbasvir and Grazoprevir for 12 wk	DTG: Placebo for 12 wk; Elbasvir and Grazoprevir for 12 wk	Total
Patients, n	201	100	301
Sex			
Male	153 (76.1)	77 (77.0)	230 (76.4)
Female	48 (23.9)	23 (23.0)	71 (23.6)
Age			
18–35 y	29 (14.4)	16 (16.0)	45 (15.0)
36–50 y	88 (43.8)	50 (50.0)	138 (45.8)
51–64 y	81 (40.3)	34 (34.0)	115 (38.2)
≥65 y	3 (1.5)	0 (0)	3 (1.0)
Race			
White	157 (78.1)	84 (84.0)	241 (80.1)
African American	31 (15.4)	7 (7.0)	38 (12.6)
Asian	9 (4.5)	7 (7.0)	16 (5.3)
Other	4 (2.0)	2 (2.0)	6 (2.0)
Interleukin-28b genotype			
CC	57 (28.4)	29 (29.0)	86 (28.6)
Non-CC	141 (70.1)	67 (67.0)	208 (69.1)
Missing	3 (1.5)	4 (4.0)	7 (2.3)
Baseline HCV RNA level			
≤800 000 IU/mL	50 (24.9)	29 (29.0)	79 (26.2)
>800 000 IU/mL	151 (75.1)	71 (71.0)	222 (73.8)
≤2 000 000 IU/mL	87 (43.3)	49 (49.0)	136 (45.2)
>2 000 000 IU/mL	114 (56.7)	51 (51.0)	165 (54.8)
HCV genotype			
1a	153 (76.1)	75 (75.0)	228 (75.7)
1b	30 (14.9)	15 (15.0)	45 (15.0)
4	12 (6.0)	6 (6.0)	18 (6.0)
6	5 (2.5)	4 (4.0)	9 (3.0)
Mixed†	1 (0.5)	0 (0)	1 (0.3)
Cirrhosis			
No‡	161 (80.1)	78 (78.0)	239 (79.4)
Yes§	40 (19.9)	22 (22.0)	62 (20.6)
HIV status			
HCV–HIV co-infected	16 (8.0)	5 (5.0)	21 (7.0)
HCV monoinfected	185 (92.0)	95 (95.0)	280 (93.0)
Opioid agonist therapy at day 1			
Methadone	162 (80.6)	77 (77.0)	239 (79.4)
Buprenorphine or buprenorphine plus naloxone‖	39 (19.4)	22 (22.0)	61 (20.3)
Positive results on urine drug screening on day 1			
Total, *n*	196	98	294
Amphetamines	10 (5.1)	6 (6.1)	16 (5.4)
Barbiturates	0 (0)	0 (0)	0 (0)
Benzodiazepines	49 (25.0)	24 (24.5)	73 (24.8)
Cannabinoids	58 (29.6)	27 (27.6)	85 (28.9)
Cocaine	20 (10.2)	10 (10.2)	30 (10.2)
Opioids	43 (21.9)	19 (19.4)	62 (21.1)
Phencyclidine	5 (2.6)	1 (1.0)	6 (2.0)
Propoxyphene	1 (0.5)	0 (0)	1 (0.3)
Any 1 positive result for 8 drugs¶	122 (62.2)	52 (53.1)	174 (59.2)
Any 1 positive result for 7 drugs**	92 (46.9)	44 (44.9)	136 (46.3)

DTG = deferred-treatment group; HCV = hepatitis C virus; ITG = immediate-treatment group.
* Values are numbers (percentages) unless otherwise indicated.
† Includes 1 patient with genotype 1a and 1b.
‡ METAVIR score of F0–F3.
§ METAVIR score of F4.
‖ Of the 39 ITG patients, 22 received buprenorphine and 17 received buprenorphine–naloxone. Of the 22 DTG patients, 9 received buprenorphine and 13 received buprenorphine–naloxone; 1 additional DTG patient received naltrexone.
¶ Excluding methadone and buprenorphine.
** Excluding methadone, buprenorphine, and cannabinoids.

Table 2. Efficacy in the ITG and Active-Phase DTG*

Variable	ITG				
	Total	GT1a	GT1b	GT4	GT6
SVR12					
Assuming reinfections are failures					
n/N	184/201	144/154	28/30	11/12	1/5
Percentage (95% CI)	91.5 (86.8–95.0)	93.5 (88.4–96.8)	93.3 (77.9–99.2)	91.7 (61.5–99.8)	20.0 (0.5–71.6)
Assuming reinfections are responses					
n/N	189/201	147/154	28/30	11/12	3/5
Percentage (95% CI)	94.0 (89.8–96.9)	95.5 (90.9–98.2)	93.3 (77.9–99.2)	91.7 (61.5–99.8)	60.0 (14.7–94.7)
Viral recurrence, *n*					
Relapse	7	4	1	0	2
Breakthrough	0	0	0	0	0
Probable reinfection, *n*	5	3	0	0	2
Lost to follow-up, *n*	3	1	1	1	0
Discontinuation, *n*					
Unconfirmed viral recurrence	1	1	0	0	0
Related to treatment	1	1	0	0	0
SVR24					
Assuming reinfections are failures					
n/N	170/201	131/154	27/30	11/12	1/5
Percentage (95% CI)	84.6 (78.8–89.3)	85.1 (78.4–90.3)	90.0 (73.5–97.9)	91.7 (61.5–99.8)	20.0 (0.5–71.6)
Assuming reinfections are responses					
n/N	175/201	134/154	27/30	11/12	3/5
Percentage (95% CI)	87.1 (81.6–91.4)	87.0 (80.7–91.9)	90.0 (73.5–97.9)	91.7 (61.5–99.8)	60.0 (14.7–94.7)
Viral recurrence, *n*					
Relapse	9	5	2	0	2
Breakthrough	0	0	0	0	0
Probable reinfection, *n*	5	3	0	0	2
Lost to follow-up, *n*	15	13	1	1	0
Discontinuation, *n*					
Unconfirmed viral recurrence	1	1	0	0	0
Related to treatment	1	1	0	0	0

DTG = deferred-treatment group; GT = genotype; ITG = immediate-treatment group; SVR12 = sustained virologic response at 12 wk after end of treatment; SVR24 = sustained virologic response at 24 wk after end of treatment.
* Efficacy was determined by SVR12 and SVR24. 95% CIs were determined by the Clopper–Pearson method.
† Excludes 5 randomly assigned patients who discontinued treatment during the placebo phase and did not receive deferred active treatment.

viremia was transient, with subsequent HCV RNA after recurrence undetectable. In 4 of 6 probable cases of reinfection, the patients tested positive for opioids other than OAT (**Table 5** of **Supplement 1**).

Viral Resistance

Baseline NS3 RAVs were detected via population sequencing in 43.0% of patients with GT1a infection (64 of 149) and 10.3% with GT1b infection (3 of 29). Of the NS3 RAVs known to confer a greater than 5-fold decrease in grazoprevir potency, D168A was detected in only 1 GT1a-infected patient, who subsequently achieved SVR12; none was detected in any GT1b-infected patient. Baseline NS5A RAVs were detected in only 2% of GT1a-infected patients (3 of 150) and in 10.3% of GT1b-infected patients (3 of 29). All 3 patients with GT1a infection harbored M28V (2 achieved SVR12), and all 3 with GT1b infection harbored Y93H (all achieved SVR12). Among patients with GT1 infection, SVR12 was achieved by 98.2% (109 of 111) of those without and 95.5% (64 of 67) of those with detectable NS3 RAVs. Regarding GT1-infected patients without and those with detectable baseline NS5A RAVs, SVR12 was achieved by 97.7% (169 of 173) and 83.3% (5 of 6), respectively. No GT4-infected patients had detectable NS3 RAVs at baseline, and 100% of GT4-infected patients with baseline NS5A RAVs (3 of 3) achieved SVR12. All 5 patients with GT6 infection had baseline NS3 RAVs, and 60% of them (3 of 5) achieved SVR12; 75% of those with baseline NS5A RAVs (3 of 4) achieved SVR12, and the 1 patient without a baseline RAV did not achieve SVR12. For specific NS3 and NS5A RAVs detected, see **Supplement 1**.

Safety

The safety profile of elbasvir–grazoprevir in the ITG was generally similar to that of placebo in the DTG (**Table 3**), with low frequencies of serious AEs (3.5% in the ITG and 4% in the DTG) and discontinuations due to AEs (<1% in the ITG and 1% in the DTG). Of the 201 ITG patients, 1 discontinued treatment because of a drug-related AE: moderate-intensity abdominal pain at day 13. Of the 100 DTG patients, 1 discontinued treatment during the placebo phase after being hospitalized with pneumonia and developing acute respiratory distress syndrome; the patient subsequently died. No ITG patient met criteria for any hepatic event of clinical interest, whereas 2 DTG patients receiving placebo met criteria for ALT or AST levels greater than 3 times the baseline value and greater than 100 IU/mL. Eleven patients had serious AEs during the treatment period and the first 14 days of follow-up: 7 in the ITG (7 of 201

Table 2–Continued

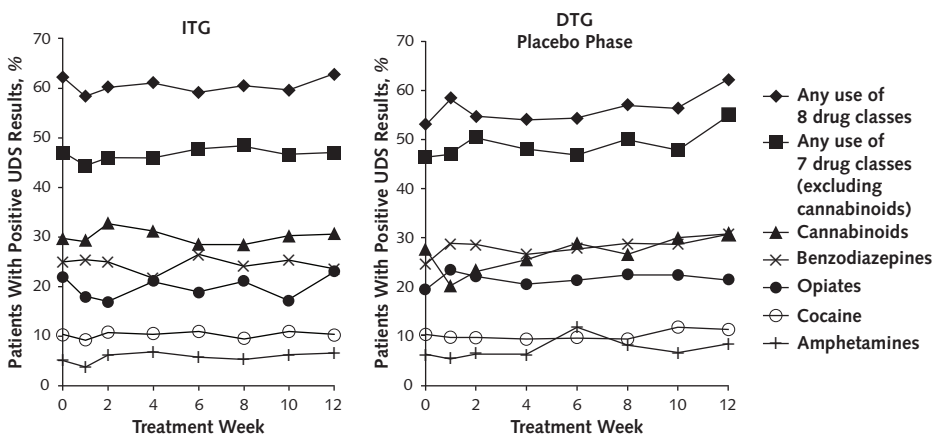
Active Phase of the DTG†				
Total	**GT1a**	**GT1b**	**GT4**	**GT6**
85/95	64/71	13/14	6/6	2/4
89.5 (81.5–94.8)	90.1 (80.7–95.9)	92.9 (66.1–99.8)	100.0 (54.1–100.0)	50.0 (6.8–93.2)
85/95	64/71	13/14	6/6	2/4
89.5 (81.5–94.8)	90.1 (80.7–95.9)	92.9 (66.1–99.8)	100.0 (54.1–100.0)	50.0 (6.8–93.2)
1	0	0	0	1
2	1	0	0	1
0	0	0	0	0
7	6	1	0	0
0	0	0	0	0
0	0	0	0	0
81/95	61/71	12/14	6/6	2/4
85.3 (76.5–91.7)	85.9 (75.6–93.0)	85.7 (57.2–98.2)	100.0 (54.1–100.0)	50.0 (6.8–93.2)
82/95	61/71	13/14	6/6	2/4
86.3 (77.7–92.5)	85.9 (75.6–93.0)	92.9 (66.1–99.8)	100.0 (54.1–100.0)	50.0 (6.8–93.2)
1	0	0	0	1
2	1	0	0	1
1	0	10	0	0
10	9	1	0	0
0	0	0	0	0
0	0	0	0	0

[3.5%]) and 4 in the DTG (4 of 100 [4.0%]). One serious AE in each treatment group was considered drug related. The most common AEs reported were fatigue, headache, nausea, and diarrhea (Table 3).

Discussion

This study demonstrated high efficacy and safety of 12 weeks of elbasvir–grazoprevir in PWID with HCV infection who were receiving OAT. To our knowledge,

Figure 2. UDS (day 1 to treatment week 12).



Shown is the percentage of patients in the ITG (*left*) and placebo-phase DTG (*right*) who tested positive on UDS for the indicated drugs from day 1 to treatment week 12. The category "Any use of 8 drug classes" includes patients with positive UDS results for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, phencyclidine, or propoxyphene at the indicated time point. The category "Any use of 7 drug classes (excluding cannabinoids)" includes patients with positive UDS results for amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, or propoxyphene at the indicated time point. DTG = deferred-treatment group; ITG = immediate-treatment group; UDS = urine drug screening.

Table 3. Safety in the ITG and DTG

Variable	ITG (*n* = 201), *n* (%)	DTG, *n* (%)		Estimated Difference Between the ITG and Placebo-Phase DTG (95% CI), *percentage points**
		Placebo Phase (*n* = 100)	Active Phase (*n* = 95)	
Tier 1 AEs				
First instance of ALT or AST levels >500 IU/L	0 (0)	0 (0)	0 (0)	0 (−3.7 to 1.9)
First instance of ALT or AST levels >3 times baseline levels and >100 IU/L	0 (0)	2 (2.0)	0 (0)	−2.0 (−7.0 to 0)
First instance of alkaline phosphatase levels >3 times the upper limit of normal	0 (0)	0 (0)	0 (0)	0 (−3.7 to 1.9)
Tier 2 AEs				
Any AE	166 (82.6)	83 (83.0)	69 (72.6)	−0.3 (−8.8 to 9.5)
Drug-related AEs†	83 (41.3)	34 (34.0)	25 (26.3)	7.4 (−4.4 to 18.5)
Discontinuations due to AE	1 (0.5)	1 (1.0)	0 (0)	−0.5 (−5.0 to 1.9)
Serious AEs	7 (3.5)	4 (4.0)	3 (3.2)	−0.6 (−6.7 to 3.7)
Serious drug-related AEs†	1 (0.5)	1 (1.0)	0 (0)	−0.5 (−5.0 to 1.9)
Deaths	0 (0)	1 (1.0)	0 (0)	NA
AEs ≥10%‡				
Fatigue	32 (15.9)	20 (20.0)	13 (13.7)	NA
Headache	25 (12.4)	13 (13.0)	12 (12.6)	NA
Nausea	22 (10.9)	9 (9.0)	7 (7.4)	NA
Laboratory abnormalities				
Bilirubin level >2.6 times the upper limit of normal	0 (0)	0 (0)	0 (0)	NA
Hemoglobin level <8.5 g/dL	1 (0.5)	1 (1.0)	1 (1.1)	NA
Creatinine level >2.5 times the baseline level	0 (0)	0 (0)	0 (0)	NA

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; DTG = deferred-treatment group; ITG = immediate-treatment group; NA = not available.
* The difference is shown for the initial treatment period and the first 14 d of follow-up. The 95% CI for the difference was determined by the method of Miettinen and Nurminen (17).
† Includes events determined by the investigator to be drug related.
‡ Includes events with an incidence of ≥10% in 1 or both treatment groups.

this is the first trial of DAA agents for HCV treatment that did not specifically exclude patients who were actively using drugs with high abuse potential. Previously, interferon-free HCV therapy trials excluded patients with illicit drug use because of concerns regarding visit and medication adherence and interactions with nonprescription drugs. The SVR12 rates observed in this trial are similar to the results of the C-EDGE Treatment-Naive and C-EDGE Co-Infection trials, which excluded patients currently using drugs (14, 15).

Subgroup analysis showed comparable response rates among patients with GT1a, GT1b, and GT4 infections. In the few patients with GT6 infection, the SVR12 rate was much lower than in those with any other GT. The GT6 strain is found primarily in southern China, Hong Kong, Taiwan, and Southeast Asia. Of the 9 GT6-infected patients enrolled, 5 in the ITG and 3 in the DTG were from Taiwan, and 1 patient in the DTG was from Australia. Two of the 5 GT6-infected patients with viral recurrence had findings consistent with probable reinfection.

Despite reservations concerning HCV treatment in patients who use drugs, this study demonstrated excellent treatment adherence in a population receiving stable OAT despite ongoing drug use among most participants. Treatment adherence in this study was similar to that in other interferon-free DAA trials in the general HCV population, which excluded patients with illicit drug use. Drug use also did not seem to affect elbasvir–grazoprevir efficacy. These outcomes support the previously reported evidence from interferon-containing regimen studies that people who use drugs can achieve HCV treatment outcomes similar to those of the general HCV population (19). In the United States, most states restrict Medicaid-based access to sofosbuvir-based therapy to patients without evidence of ongoing illicit drug use (20). The results of this study suggest that access to interferon-free DAA therapy should be expanded to patients receiving OAT, including the removal of drug use–based restrictions, providing further support for international guidelines (21–23).

Of considerable clinical and public health interest is the potential effect of HCV reinfection after successful treatment of high-risk populations, including PWID (24, 25). High levels of HCV reinfection might compromise benefit from both the individual patient and public health perspectives. Preliminary data from this study indicate that HCV reinfection in the early posttreatment period (to 24 weeks) may occur, with 6 cases of probable HCV reinfection detected, 3 of which were identified at 1 clinical site. The observation that 4 of 6 patients with reinfections had positive results on opioid testing during posttreatment follow-up suggests that injection drug use was the probable source of reinfection. An ongoing extension of this study will evaluate drug use behaviors and the incidence and outcome of

HCV reinfection over a 3-year period after treatment. Of interest, 3 of the 6 patients categorized as having HCV reinfection subsequently had undetectable HCV RNA levels without additional HCV treatment, indicating that not all reinfection cases develop viral persistence and drawing attention to the possible role of an augmented HCV-specific immune response after DAA therapy (26, 27). Ultradeep sequencing confirmed that the patients with probable reinfection did not have baseline mixed HCV infection, with potential nonclearance of the nondominant strain.

Resistance-associated variants did not seem to affect efficacy in GT1- or GT4-infected patients, because high SVR rates were achieved in patients with and without NS3 or NS5A RAVS. In consideration of the U.S. Food and Drug Administration's prescribing information, few GT1a-infected patients with baseline NS5A RAVs (n = 3) would meet the treatment guideline for 16 weeks of elbasvir–grazoprevir plus ribavirin.

This study has limitations. First, although illicit drug use was monitored by UDS before and during treatment, we do not have data on injection drug use behaviors. A key focus of the posttreatment observational study is the collection of such data. Second, the adherence monitoring tool may have promoted adherence. Further studies are required to evaluate potential interventions to support adherence in patients who use drugs. Third, these results may not be generalizable to the broader population of people who use drugs, most of whom are not in addiction treatment programs. The generalizability also is limited regarding GTs other than GT1 and GT4; only a few patients with GT6 infection were enrolled, and persons with GT2, GT3 (shown to be highly prevalent in PWID), and GT5 infections were not studied in this trial. Additional evaluation of interferon-free DAA therapy is required in these populations.

In conclusion, these findings document that elbasvir–grazoprevir is effective and well tolerated for treating HCV infection in PWID who are receiving OAT. The risk for reinfection warrants further study.

From The Kirby Institute, UNSW Australia, Sydney, Australia; Yale School of Medicine, New Haven, Connecticut; Montefiore Medical Center, Bronx, New York; Akershus University Hospital, Lorenskog, Norway; Auckland Clinical Studies, Auckland, New Zealand; Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; University of California, San Francisco, San Francisco, California; ID Care, Hillsborough, New Jersey; China Medical University, Taichung, Taiwan; Vancouver Infectious Diseases Centre, Vancouver, British Columbia, Canada; and Merck & Co., Inc., Kenilworth, New Jersey.

Note: All authors vouch for the completeness and accuracy of the data and data analyses and for the fidelity of this report to the study protocol. The first author wrote the first draft of the manuscript. All authors reviewed the manuscript and provided input. Editorial assistance was provided by employees of Merck.

Disclaimer: The opinions expressed in this report represent the consensus of the authors and do not necessarily reflect the formal position of Merck or the authors' affiliated universities.

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Reproducible Research Statement: *Study protocol:* See Supplement 2. *Statistical code:* Not available. *Data set:* Merck's data sharing policy, including restrictions, is available at http://engagezone.merck.com/ds_documentation.php. Requests for access to the study data can be submitted through the EngageZone site or at dataaccess@merck.com.

Requests for Single Reprints: Gregory J. Dore, MD, The Kirby Institute, Wallace Wurth Building, UNSW Australia, UNSW, NSW 2052, Australia; e-mail, gdore@kirby.unsw.edu.au.

Current author addresses and author contributions are available at www.annals.org.

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Current Author Addresses: Drs. Dore and Grebely: The Kirby Institute, Wallace Wurth Building, UNSW Australia, UNSW, NSW 2052, Australia.
Dr. Altice: Yale School of Medicine, 135 College Street, Suite 323, New Haven, CT 06510.
Dr. Litwin: Montefiore Medical Center, 1510 Waters Place, Bronx, NY 10461.
Dr. Dalgard: Sykehusveien 25, Infeksjonsmedisinsk poliklinikk, Akershus University Hospital, 1478 Lorenskog, Norway.
Dr. Gane: Auckland Clinical Studies, Medacs House, 3 Ferncroft Street, Ground Floor, Grafton, Auckland 1150, New Zealand.
Dr. Shibolet: Tel Aviv Sourasky Medical Center, Gastrointestinal and Liver Disease, 6 Waitzmann Street, Tel Aviv, 64239, Israel.
Dr. Luetkemeyer: University of California, 995 Potrero Avenue, Box 0874, Building 80, Fourth Floor, San Francisco, CA 94110.
Dr. Nahass: ID Care, 105 Raider Boulevard, Suite 101, Hillsborough, NJ 08844.
Dr. Peng: School of Medicine, China Medical University, 2 Yuh-Der Road, Taichung 40447, Taiwan.
Dr. Conway: Vancouver Infectious Diseases Centre, 201–1200 Burrard Street, Vancouver, BC, Canada V6Z 2C7.
Dr. Howe: British Columbia Centre for Excellence in HIV/AIDS, St. Paul's Hospital, 608–1081 Burrard Street, Vancouver, BC, Canada V6Z 1Y6.
Mr. Gendrano: Merck & Co., Inc., 126 East Lincoln Avenue, PO Box 2000, RY34-A474, Rahway, NJ 07065.
Mr. Chen: Merck & Co., Inc., 126 East Lincoln Avenue, PO Box 2000, RY34-A316, Rahway, NJ 07065.
Dr. Huang: Merck & Co., Inc., 2000 Galloping Hill Road, PO Box 539, K-15-4-D402, Kenilworth, NJ 07033.
Dr. Dutko: Merck & Co., Inc., 351 North Sumneytown Pike, UG3C-06, North Wales, PA 19454.
Dr. Nickle: Merck Sharp & Dohme Corp., 33 Avenue Louis Pasteur, Boston, MA 02115.
Dr. Nguyen: Merck & Co., Inc., 351 North Sumneytown Pike, UG4C-06, North Wales, PA 19454.
Dr. Wahl: Merck & Co. Merck & Co., Inc., 126 East Lincoln Avenue, PO Box 2000, RY34-A484, Rahway, NJ 07065.
Dr. Barr: Merck & Co., Inc., 351 North Sumneytown Pike, UG3C-96, North Wales, PA 19454.
Dr. Robertson: Merck & Co., Inc., 351 North Sumneytown Pike, UG3D-056, North Wales, PA 19454.
Dr. Platt: Merck & Co., Inc., 351 North Sumneytown Pike, North Wales, PA 19454.

Author Contributions: Conception and design: G.J. Dore, A.H. Litwin, O. Dalgard, J. Grebely, A.Y.M. Howe, I.N. Gendrano, B.Y. Nguyen, J. Wahl, E. Barr, M.N. Robertson, H.L. Platt.
Analysis and interpretation of the data: G.J. Dore, F. Altice, A.H. Litwin, O. Dalgard, O. Shibolet, A. Luetkemeyer, R. Nahass, C.Y. Peng, B. Conway, J. Grebely, A.Y.M. Howe, I.N. Gendrano, E. Chen, H.C. Huang, F.J. Dutko, D.C. Nickle, B.Y. Nguyen, J. Wahl, E. Barr, M.N. Robertson, H.L. Platt.
Drafting of the article: G.J. Dore, F. Altice, A.H. Litwin, A. Luetkemeyer, R. Nahass, B. Conway, I.N. Gendrano, H.C. Huang, F.J. Dutko, B.Y. Nguyen, E. Barr, M.N. Robertson, H.L. Platt.
Critical revision for important intellectual content: G.J. Dore, F. Altice, A.H. Litwin, O. Dalgard, O. Shibolet, C.Y. Peng, B. Conway, J. Grebely, B.Y. Nguyen, J. Wahl, E. Barr, M.N. Robertson, H.L. Platt.
Final approval of the article: G.J. Dore, F. Altice, A.H. Litwin, O. Dalgard, E.J. Gane, O. Shibolet, A. Luetkemeyer, R. Nahass, C.Y. Peng, B. Conway, J. Grebely, A.Y.M. Howe, I.N. Gendrano, E. Chen, H.C. Huang, F.J. Dutko, D.C. Nickle, B.Y. Nguyen, J. Wahl, E. Barr, M.N. Robertson, H.L. Platt.
Provision of study materials or patients: G.J. Dore, A.H. Litwin, O. Shibolet, R. Nahass, C.Y. Peng, B. Conway, B.Y. Nguyen.
Statistical expertise: E. Chen, D.C. Nickle.
Obtaining of funding: B.Y. Nguyen.
Administrative, technical, or logistic support: I.N. Gendrano, B.Y. Nguyen.
Collection and assembly of data: G.J. Dore, A.H. Litwin, O. Dalgard, O. Shibolet, A. Luetkemeyer, R. Nahass, C.Y. Peng, A.Y.M. Howe, I.N. Gendrano, H.C. Huang, E. Barr, H.L. Platt.

Appendix: Members of the C-EDGE CO-STAR Study Group

Members of the C-EDGE CO-STAR Study Group who authored this work: Gregory J. Dore, MD (The Kirby Institute, UNSW Australia, Sydney, Australia); Frederick Altice, MD (Yale School of Medicine, New Haven, Connecticut); Alain H. Litwin, MD (Montefiore Medical Center, Bronx, New York); Olav Dalgard, MD (Akershus University Hospital, Lorenskog, Norway); Edward J. Gane, MD (Auckland Clinical Studies, Grafton, Auckland, New Zealand); Oren Shibolet, MD (Tel Aviv Sourasky Medical Center, Tel Aviv, Israel); Anne Luetkemeyer, MD (University of California, San Francisco, California); Ronald Nahass, MD (ID Care, Hillsborough, New Jersey); Cheng-Yuan Peng, MD (China Medical University, Taichung, Taiwan); Brian Conway, MD (Vancouver Infectious Diseases Centre, Vancouver, British Columbia, Canada); Jason Grebely, PhD (The Kirby Institute, UNSW Australia, Sydney, Australia); Anita Y.M. Howe, PhD*; Isaias N. Gendrano, MPH*; Erluo Chen, MPH*; Hsueh-Cheng Huang, PhD*; Frank J. Dutko, PhD*; David C. Nickle, PhD*; Bach-Yen Nguyen, MD*; Janice Wahl, MD*; Eliav Barr, MD*; Michael N. Robertson, MD*; and Heather L. Platt, MD*.

Members of the C-EDGE CO-STAR Study Group who contributed to this work but did not author it:

Australia: David Iser, MBBS (Hons), BMedSc, PhD (The Alfred Hospital, Melbourne, Victoria); Joseph Sasadeusz, MBBS, PhD (The Royal Melbourne Hospital, Melbourne, Victoria); and Martin Weltman, MBBCh, PhD (UNSW Australia, Sydney, New South Wales).

Canada: Roger P. LeBlanc, MD, and Daniele Longpre, MD (Clinique l'Actuel, Montreal, Quebec).

France: Jean-Pierre Bronowicki, MD, PhD (University Hospital of Nancy, Vandoeuvre-les-Nancy); Joseph Moussalli, MD (Pitie Salpetriere Hospital, Paris), and Fabien Zoulim, MD, PhD (Hospices Civils de Lyon, Lyon).

Germany: Andreas Trein, MD (Clinic for Infectious Diseases, Stuttgart); and Albrecht Stoehr, MD, PhD (Asklepios Klinik St. Georg, Hamburg).

Netherlands: Hendrik W. Reesink, MD, PhD (Academic Medical Center, Amsterdam).

Norway: Hege Kileng, MD (University Hospital of North Norway, Tromsø).

Romania: Adrian Octavian Abagiu, MD, PhD (National Institute for Infectious Diseases, Bucharest); Emanoil Ceausu, MD, PhD (Victor Babes Clinical Hospital for Infectious and Tropical Diseases, Bucharest); and Adrian Streinu-Cercel, MD, PhD (Carol Davila University of Medicine and Pharmacy, Bucharest).

Spain: Juan Ignacio Arenas Ruiz-Tapiador, MD (Hospital Universitario Donostia, San Sebastián); Jose Luis Calleja Panero, MD, PhD (Hospital la Luz, Madrid); Juan Antonio Pineda, MD, PhD (Hospital Universitario de Valme, Seville); Conrado Fernandez Rodriguez, MD, PhD (Hospital Universitario Fundación Alcorcon, Madrid); and Juan Turnes Vazquez, MD (Complejo Hospitalario de Pontevedra, Pontevedra).

Taiwan: Wan-Long Chuang, MD, PhD (Kaohsiung Medical University, Kaohsiung); and Sheng-Shun Yang, MD, PhD (Taichung Veterans General Hospital, Taichung).

United Kingdom: Kosh Agarwal, MD (King's College Hospital, London); David Bell, MD (Gartnavel General Hospital, Glasgow, Scotland); Ashley Brown, MD (St. Mary's and Hammersmith Hospitals, London); John Dillon, MBBS, MD (University of Dundee, Dundee, Scotland); Daniel M.H. Forton, BSc, PhD, MBBS (St. George's University, London); and Andrew Ustianowski, PhD (North Manchester General Hospital, Manchester).

United States: David Michael Asmuth, MD (University of California, Davis Medical Center, Sacramento, California); Kathleen K. Casey, MD (Jersey Shore University Medical Center, Neptune City, New Jersey); James N. Cooper, MD (Inova Fairfax Hospital, Falls Church, Virginia); Stuart C. Gordon, MD (Henry Ford Hospital, Detroit, Michigan); Paul Y. Kwo, MD (Indiana University School of Medicine, Indianapolis, Indiana); Jacob Paul Lalezari, MD (California Pacific Medical Center, San Francisco, California; William M. Lee, MD (University of Texas Southwestern Medical Center, Dallas, Texas); Andrew J. Muir, MD (Duke University Medical Center, Durham, North Carolina); Grisell Ortiz-Lasanta, MD (Fundación de Investigación de Diego, Santurce, Puerto Rico); K. Rajender Reddy, MD (Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania); Kenneth E. Sherman, MD, PhD (University of Cincinnati College of Medicine, Cincinnati, Ohio); Jihad Slim, MD (Newark Beth Israel Medical Center, Newark, New Jersey); Mark S. Sulkowski, MD (Johns Hopkins University School of Medicine, Baltimore, Maryland); Andrew H. Talal, MD, MPH (Jacobs School of Medicine and Biomedical Sciences, Buffalo, New York); and Joseph Leo Yozviak, DO (Lehigh Valley Health Network, Allentown, Pennsylvania).

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