ORIGINAL RESEARCH | Annals of Internal Medicine

Combination Therapy With Telaprevir for Chronic Hepatitis C Virus Genotype 1 Infection in Patients With HIV

A Randomized Trial

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Background: Telaprevir (TVR) plus peginterferon-α2a (PEG-IFN-α2a) and ribavirin substantially increases treatment efficacy for genotype 1 chronic hepatitis C virus (HCV) infection versus PEG-IFN-α2a–ribavirin alone. Its safety and efficacy in patients with HCV and HIV-1 are unknown.

Objective: To assess the safety and efficacy of TVR plus PEG-IFN-α2a–ribavirin in patients with genotype 1 HCV and HIV-1 and to evaluate pharmacokinetics of TVR and antiretrovirals during coadministration.

Design: Phase 2a, randomized, double-blind, placebo-controlled study. (ClinicalTrials.gov: NCT00983853)

Setting: 16 international multicenter sites.

Patients: 62 patients with HCV genotype 1 and HIV-1 who were HCV treatment–naive and receiving 0 or 1 of 2 antiretroviral regimens were randomly assigned to TVR plus PEG-IFN-α2a–ribavirin or placebo plus PEG-IFN-α2a–ribavirin for 12 weeks, plus 36 weeks of PEG-IFN-α2a–ribavirin.

Measurements: HCV RNA concentrations.

Results: Pruritus, headache, nausea, rash, and dizziness were higher with TVR plus PEG-IFN-α2a–ribavirin during the first 12 weeks. During this period, serious adverse events occurred in 5% (2 in 38) of those receiving TVR plus PEG-IFN-α2a–ribavirin and 0% (0 in 22) of those receiving placebo plus PEG-IFN-α2a–ribavirin; the same number in both groups discontinued treatment due to adverse events. Sustained virologic response occurred in 74% (28 in 38) of patients receiving TVR plus PEG-IFN-α2a–ribavirin and 45% (10 in 22) of patients receiving placebo plus PEG-IFN-α2a–ribavirin. Rapid HCV suppression was seen with TVR plus PEG-IFN-α2a–ribavirin (68% [26 in 38 patients] vs. 0% [0 in 22 patients] undetectable HCV RNA levels by week 4). Two patients had on-treatment HCV breakthrough with TVR-resistant variants. Patients treated with antiretroviral drugs had no HIV breakthroughs; antiretroviral exposure was not substantially modified by TVR.

Limitation: Small sample size and appreciable dropout rate.

Conclusion: In patients with HCV and HIV-1, more adverse events occurred with TVR versus placebo plus PEG-IFN-α2a–ribavirin; these were similar in nature and severity to those in patients with HCV treated with TVR. With or without concomitant antiretrovirals, sustained virologic response rates were higher in patients treated with TVR versus placebo plus PEG-IFN-α2a–ribavirin.

Primary Funding Source: Vertex Pharmaceuticals and Janssen Pharmaceuticals.

Ann Intern Med. 2013;159:86-96. www.annals.org
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This article was published at www.annals.org on 17 May 2013.

With the development of effective therapies against HIV, hepatitis C virus (HCV) infection has emerged as a major cause of morbidity and mortality among patients with HIV (1). In patients with only HCV and those with both HCV and HIV, HCV treatment resulting in sustained virologic response (SVR) has been associated with decreased likelihood of end-stage liver disease, hepatocellular carcinoma, and death (2–4). Accordingly, practice guidelines recommend that HCV treatment should be given to patients with both HCV and HIV in whom the likelihood of serious liver disease and achieving SVR is judged to outweigh the risk for adverse events (AEs) (5–9).

The efficacy of peginterferon-α2a (PEG-IFN-α2a) and ribavirin is low for patients with both HCV and HIV compared with patients with genotype 1 HCV alone, ranging from 14% to 29% (10, 11). In patients with HCV genotype 1 alone, the addition of an HCV NS3/4A protease inhibitor, either telaprevir (TVR) or boceprevir, to PEG-IFN-α2a–ribavirin substantially increased the SVR rate (12–16), leading to the recommendation for routine use of these agents in patients with HCV (17). Despite the potential benefit of HCV protease inhibitor–based therapy in the treatment of HCV in patients with HIV, potential concerns for patients with both HCV and HIV include increased AEs (such as anemia, gastrointestinal symptoms, and rash); antiviral drug resistance; and the demonstration, in healthy volunteers, of potentially clinically significant drug interactions with antiretrovirals through inhibition of cytochrome P_{450} 3A4 (CYP3A4) (18). To date, very few case reports on the use of HCV protease inhibitors in patients with HIV have been published (19, 20).

The objectives of this study were to assess the safety, tolerability, and efficacy of TVR plus PEG-IFN-α2a–ribavirin in patients with both HCV genotype 1 and HIV and to evaluate the pharmacokinetics of TVR and selected antiretroviral medications during coadministration.

METHODS

Design Overview

This study (VX08-950-110) was a phase 2a, randomized, double-blind (through week 24), placebo-controlled, multicenter study. Patients were required to be receiving

no antiretrovirals (part A) or 1 of 2 specified antiretroviral regimens (part B), including either efavirenz or ritonavir-boosted atazanavir. Patients in part A were randomly assigned in a 1:1 ratio and patients in part B were randomly assigned in a 2:1 ratio to receive TVR or placebo, both in combination with PEG-IFN-α2a–ribavirin. Randomization was done using an interactive Web response system and was blocked and stratified to optimize balance among the treatment groups with regard to baseline viral load (HCV RNA levels <800 000 IU/mL or ≥800 000 IU/mL). In part B, randomization was also stratified to optimize balance between the protocol-specified antiretroviral regimens. A blinded statistician from Vertex Pharmaceuticals (Cambridge, Massachusetts) created the randomization code, which was kept on a protected server. Telaprevir or placebo was administered orally every 8 hours with food, 180 μg of PEG-INF-α2a (Pegasys, Hoffmann-La Roche, Nutley, New Jersey) was injected subcutaneously once weekly, and ribavirin (Copegus, Hoffmann-La Roche, Nutley, New Jersey) was administered by mouth twice daily for the first 12 weeks, followed by an additional 36 weeks of PEG-IFN-α2a–ribavirin. On the basis of drug interaction studies in healthy volunteers, patients receiving efavirenz-based antiretroviral therapy received 1125 mg of TVR every 8 hours, whereas all others received 750 mg every 8 hours (18). Ribavirin was administered at 800 mg daily according to the recommendations for dosing in patients with both HIV and HCV in the United States and Canada (21, 22), which are based on a large, randomized, controlled trial that showed similar SVR and lower incidence of anemia with this dose compared with higher, weight-based doses (23). In France and Germany, ribavirin was administered at 1200 mg daily for patients weighing 75 kg or greater and 1000 mg daily for those weighing less than 75 kg (24); country-specific amendments were made based on local practice guidelines (25).

Setting and Participants

Patients with both HCV and HIV ($n = 62$) were enrolled at 16 investigational sites in 4 countries (United States [$n = 48$], Spain [$n = 9$], Germany [$n = 3$], and France [$n = 2$]). Key inclusion criteria included age of 18 to 65 years, genotype 1 chronic HCV infection, chronic HIV-1 infection, no previous HCV treatment, and hemoglobin levels of 120 g/L or greater in women and 130 g/L or greater in men. Patients were required to have stable HIV disease defined as follows: Part A (no antiretroviral therapy) participants had CD4 counts of 0.500×10^9 cells/L or greater and HIV RNA levels of 100 000 copies/mL or less, and part B (antiretroviral therapy for >12 weeks) participants had CD4 counts of 0.300×10^9 cells/L or greater and HIV RNA levels less than 50 copies/mL. For part B, permissible antiretroviral regimens were efavirenz, tenofovir, and emtricitabine, or ritonavir-boosted atazanavir, tenofovir, and either emtricitabine or lamivudine. Exclusion criteria for patients in all parts included hepatic decompensation; other causes of significant liver disease, cancer within 5 years, significant cardiac dysrhythmia, and active AIDS-related conditions within 6 months. All patients had liver biopsies within 1 year unless previous biopsies indicated cirrhosis; histologic assessment according to the METAVIR scoring system was done by a local pathologist.

Context

In patients with genotype 1 hepatitis C virus (HCV), adding telaprevir to peginterferon-α2a (PEG-IFN-α2a) and ribavirin produces a greater sustained virologic response than with PEG-IFN-α2a–ribavirin alone. Patients with HCV often also have HIV.

Contribution

In a small, randomized trial of patients with both genotype 1 HCV and HIV, treatment with telaprevir plus PEG-IFN-α2a–ribavirin achieved a greater sustained virologic response than PEG-IFN-α2a–ribavirin alone and with a magnitude similar to that seen in patients with only HCV. No HIV breakthroughs took place.

Caution

The number of withdrawals was appreciable. Adverse events were more common in groups receiving treatment with telaprevir plus PEG-IFN-α2a–ribavirin than with PEG-IFN-α2a–ribavirin alone. Only certain HIV antiretroviral regimens were permitted.

Implication

The role of direct-acting antivirals in the treatment of HCV and HIV warrants further study.

—The Editors

Outcomes and Follow-up

Safety

Adverse events were recorded for all patients who received at least 1 dose of a study drug through 30 days after the last dose. Except for rash, the severity of all AEs was graded according to the Division of AIDS Table 1 for Grading the Severity of Adult and Pediatric Adverse Events, version 1.0. Planned safety reviews were conducted by independent statistical and data monitoring committees. Patient-specific HCV RNA response was monitored by an unblinded independent reviewer until week 24 and then by the study site investigators (**Appendix 1**, available at www.annals.org) after HCV RNA unblinding (from week 24 onward). The results of HCV RNA data before week 24 and treatment assignments were unblinded only after all patients completed week 24. Virologic breakthrough was defined as an increase greater than 1 $\log_{10}$ in HCV RNA above nadir or greater than 100 IU/mL if previously undetected. Patients with HCV RNA levels greater than 1000 IU/mL at week 4 were required to discontinue treatment with TVR and continue PEG-IFN-

Table 1. **Baseline Characteristics of Study Patients, by Treatment Group***

Characteristic	Part A: Participants Not Receiving Antiretroviral Therapy		Part B: Participants Receiving Efavirenz, Tenofovir, and Emtricitabine	
	TVR/P–R (*n* = 7)	P–R (*n* = 6)	TVR/P–R (*n* = 16)	P–R (*n* = 8)
Median age (range), *y*	39 (34–50)	48 (42–65)	48 (31–57)	47 (31–53)
Median BMI (range), kg/m^2	29 (22–37)	31 (26–37)	24 (21–32)	23 (19–28)
Male sex, *n*	6	4	16	7
Race, *n*†				
White	2	3	12	5
Black	4	3	3	3
Other	1	0	1	0
Ethnicity, *n*†				
Hispanic or Latino	3	2	5	1
Not Hispanic or Latino	4	4	10	7
Not collected per local regulations	0	0	1	0
HCV genotype 1 subtype, *n*‡				
1a	3	3	12	6
1b	4	2	4	1
Other subtype	0	1	0	1
Mean HCV RNA (SD), log_{10} *IU/mL*§	6.7 (0.5)	6.2 (0.5)	6.5 (0.5)	6.5 (0.7)
HCV RNA ≥800 000 IU/mL, *n*§	7	5	13	7
Stage of fibrosis and cirrhosis, *n*				
No or minimal fibrosis	2	2	5	4
Portal fibrosis	4	4	7	3
Bridging fibrosis	1	0	2	1
Cirrhosis	0	0	2	0
Median HIV RNA (range), *copies/mL*‖	1495 (193–53 450)	267 (25–21 950)	Undetectable	Undetectable
Median $CD4^+$ count (range), $\times 10^9$ *cells/L*	0.604 (0.496–0.758)	0.672 (0.518–1.189)	0.533 (0.298–0.984)	0.514 (0.323–1.034)

BMI = body mass index; HCV = hepatitis C virus; P–R = peginterferon-α2a–ribavirin alone for 48 wk; TVR/P–R = telaprevir combined with peginterferon-α2a–ribavirin for 12 wk, followed by peginterferon-α2a–ribavirin for an additional 36 wk.

* Patients received telaprevir (750 mg/8 h) for 12 wk in combination with peginterferon-α2a (180 μg/wk) and ribavirin (800 mg/d) for a total of 48 wk. When the antiretroviral therapy included efavirenz, telaprevir dosage was 1125 mg/8 h. Five patients in part B (telaprevir plus atazanavir-based therapy, *n* = 3; placebo plus atazanavir-based therapy, *n* = 1; and telaprevir plus efavirenz-based therapy, *n* = 1) received weight-based ribavirin (1200 mg/d) in accordance with country requirements (France and Germany). Antiretroviral medications were administered according to clinical practice.

† Self-reported and not mutually exclusive. "Other" category includes Native American, Alaska Native, Native Hawaiian, or other Pacific Islander and other self-reported races.

‡ Determined using the Versant HCV Genotype 2.0 Assay (LiPA) (Siemens Medical Solutions, Malvern, Pennsylvania). Two patients receiving P–R (1 in part A, 1 in part B receiving efavirenz, tenofovir, and emtricitabine treatment) were neither genotype 1a nor 1b.

§ Measured with Cobas TaqMan HCV assay, version 2.0 (Roche Molecular Systems, Branchburg, New Jersey), which has a lower limit of quantitation of 25 IU/mL.

‖ According to inclusion criteria, baseline HIV-1 RNA levels were <50 copies/mL for part B. HIV RNA copies were measured with the Ultrasensitive Cobas Amplicor assay (Roche Molecular Systems, Branchburg, New Jersey).

α2a–ribavirin. All study medications were discontinued in patients with virologic breakthrough or at treatment week 12 in patients with a decrease less than 2 log_{10} in HCV RNA from baseline or at weeks 24 or 36 in patients with quantifiable HCV RNA. No placebo was administered to patients once study medications were discontinued.

Efficacy

Hepatitis C virus RNA levels were assessed using the Cobas TaqMan HCV Test, version 2.0 (Roche Molecular Systems, Branchburg, New Jersey), which has a lower limit of quantitation (LLOQ) of 25 IU/mL and a lower limit of detection of 15 IU/mL. The LLOQ was used to define SVR, and the lower limit of detection was used to assess on-treatment response. A patient was defined as achieving SVR if HCV RNA levels were less than the LLOQ at posttreatment weeks 12 (SVR_{12}) or 24 (SVR_{24}). Relapse was defined as HCV RNA levels less than the LLOQ at the actual end-of-treatment window but subsequent HCV RNA levels greater than or equal to the LLOQ. To be eligible for relapse, a patient's HCV RNA levels had to be less than the LLOQ at the actual end of treatment or during the next treatment visit window (**Appendix 2**, available at www.annals.org). The primary efficacy end point was HCV RNA level at week 12. Secondary end points were HCV RNA levels at week 4, proportion of patients with undetectable HCV RNA levels at weeks 4 and 12, and unquantifiable HCV RNA levels at end of treatment and at posttreatment weeks 12 (SVR_{12}) and 24 (SVR_{24}). For patients with no HCV RNA assessment at posttreatment week 24, the SVR_{12} assessment was imputed for SVR_{24}. For all end-of-treatment, relapse, and SVR win-

Table 1—**Continued**

Part B: Participants Receiving Ritonavir-Boosted Atazanavir, Tenofovir, and Either Emtricitabine or Lamivudine		Total	
TVR/P–R (*n* = 15)	P–R (*n* = 8)	TVR/P–R (*n* = 38)	P–R (*n* = 22)
52 (36–59)	39 (26–53)	46 (31–59)	44 (26–65)
25 (23–33)	25 (22–30)	25 (21–37)	26 (19–37)
13	7	35	18
13	7	27	15
2	1	9	7
0	0	2	0
3	3	11	6
12	5	26	16
0	0	1	0
12	5	27	14
3	3	11	6
0	0	0	2
6.4 (0.9)	6.5 (0.6)	6.5 (0.7)	6.4 (0.6)
12	7	32	19
3	5	10	11
12	2	23	9
0	1	3	2
0	0	2	0
Undetectable	Undetectable	Undetectable (undetectable–53 450)	Undetectable (undetectable–21 950)
0.514 (0.254–0.874)	0.535 (0.302–0.772)	0.570 (0.254–0.984)	0.586 (0.302–1.189)

dows, the last available HCV RNA assessment in the study treatment window was used (**Appendix 2**).

Pharmacokinetics

Antiretrovirals

Ratios of mean predose concentrations (C_{trough}) during HCV treatment (weeks 1, 2, 4, and 12) to the C_{trough} before HCV treatment (day −1) were calculated within individual patients; the median (25th to 75th percentiles) was calculated for all patients in a treatment group.

Telaprevir

Week-4 intensive TVR concentration–time profiles were collected before and at 1, 2, 3, 4, 6, and 8 hours after dose. Steady-state pharmacokinetic parameters of TVR minimum, average, and maximum concentrations (C_{min}, C_{avg}, and C_{max}, respectively) were determined through standard noncompartmental analysis (WinNonlin, version 5.3, Pharsight, Mountain View, California).

Interim Analysis

Four interim analyses were conducted. The first 2 were protocol-specified by the independent statistical and data monitoring committee and were conducted after 20 and 40 patients (enrolled in parts A or B) completed 8 weeks of dosing with study treatment (or discontinued treatment earlier). These first 2 interim analyses were blinded at the individual-patient level and were unblinded by overall treatment group to the study sponsor for regulatory purposes only after the interim analysis was completed. A third interim analysis was warranted to evaluate the efficacy and safety and information for a phase 3 study and regulatory purposes. It included all data in the clinical database at the time of the data cutoff, including data collected through week 24 and safety data for the 62 patients who were randomly assigned. A fourth interim analysis included data through 12 weeks after the last dose of a study drug. The third and fourth analyses were unblinded because all patients had reached protocol treatment week 24, at which time the study was no longer blinded.

Statistical Analysis

Sample size was selected to provide data regarding the safety, pharmacokinetic, and antiviral activity of TVR plus PEG-IFN-α2a–ribavirin to inform the design of subsequent studies; no formal sample size calculation was done in this pilot study.

All patients who were administered at least 1 dose of placebo or TVR were included in safety and efficacy summaries. No formal hypothesis testing was conducted. Patients with missing on-treatment HCV RNA assessments

in the specific study visit window were counted as being nonrespondent even if they ultimately achieved SVR.

Role of the Funding Source

This study was funded by Vertex Pharmaceuticals and Janssen Pharmaceuticals. The protocol was approved by the institutional review boards of all study centers and was done in accordance with Good Clinical Practice guidelines, as described in the International Conference on Harmonisation Guideline E6 and the Declaration of Helsinki. All patients provided written informed consent. The protocol was designed by the pharmaceutical sponsors in collaboration with the principal investigator, who is not employed by Vertex Pharmaceuticals, had unrestricted access to the data, and wrote the first draft of the manuscript. Subsequent drafts of the manuscript reflect comments from all coauthors. The study and data analysis were conducted and the decision to submit the manuscript was made by the pharmaceutical sponsors in collaboration with the principal investigator. All authors reviewed and approved the final manuscript and assume responsibility for the accuracy and completeness of the data reported. The National Institutes of Health had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, and approval of the manuscript.

RESULTS

Baseline Characteristics

Of 113 patients screened, 60 were randomly assigned and received at least 1 dose of TVR ($n = 38$) or placebo ($n = 22$). Thirteen patients did not receive antiretroviral therapy, and 47 patients received efavirenz-containing ($n = 24$) or ritonavir-boosted, atazanavir-containing ($n = 23$) antiretroviral therapy (**Figure 1**). Most patients were men (88%); were white (70%); had HCV genotype 1, subtype a (68%); had high levels of HCV RNA (≥800 000 IU/mL [85%]); and were enrolled in the United States (77%) (**Table 1**). Overall, 7 patients (12%) had bridging fibrosis or cirrhosis. Among patients not taking antiretrovirals, the median HIV RNA level was 1495 copies/mL and CD4 cell count was 0.652×10^9 cells/L. Among patients taking antiretrovirals, HIV RNA levels were less than 50 copies/mL and the median CD4 cell count was 0.518×10^9 cells/L.

Adverse Events and Tolerability

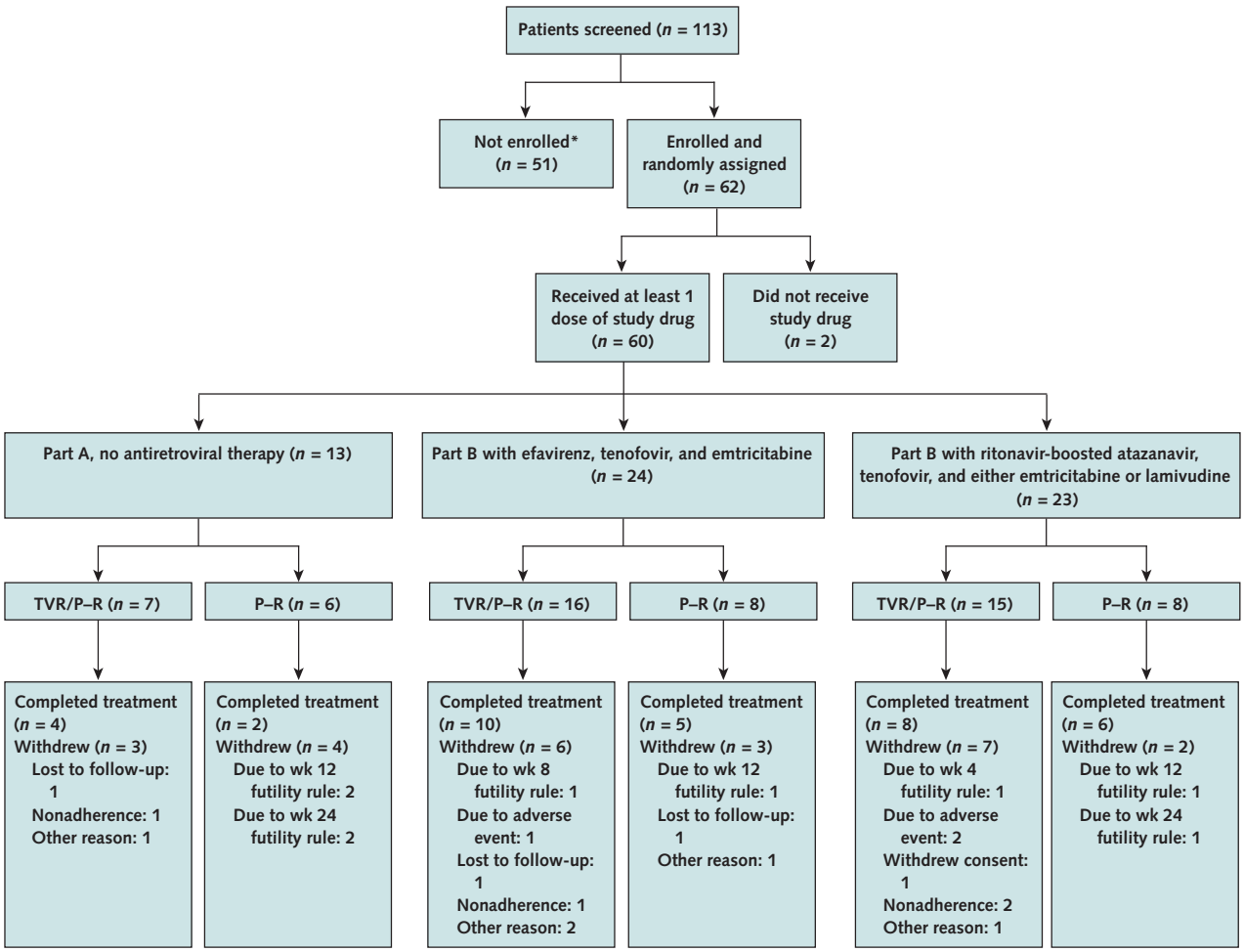
During the TVR versus placebo phase (weeks 1 through 12), patients treated with TVR had a higher incidence (difference of >10 percentage points compared with placebo) of pruritus, headache, nausea, rash, and dizziness (**Table 2**). During this phase, rash was seen in 11 of 38 (29%) and 4 of 22 (18%) patients treated with TVR and placebo, respectively; no patients had severe or life-threatening rash or discontinued treatment with TVR due to rash. Topical corticosteroids were used to manage rash; no patients received systemic corticosteroids. Anorectal symptoms were reported in 5 of 38 (13%) and 1 of 22 (5%) patients treated with TVR and placebo, respectively. Abdominal pain occurred more frequently in the TVR plus PEG-IFN-α2a–ribavirin groups (≥10–percentage point difference) compared with PEG-IFN-α2a–ribavirin, but occurred in fewer than 15% of patients.

During the overall treatment phase (weeks 1 through 48), AEs were consistent with those seen during the first 12 weeks (**Appendix Table 1**, available at www.annals.org). Although most AEs were mild to moderate in severity, 9 patients had serious AEs (TVR, $n = 7$; placebo, $n = 2$); 2 AEs occurred during the initial 12 weeks of treatment (both in the TVR group). Three patients in the TVR group discontinued all study medications because of an AE (vomiting, $n = 1$; anemia, $n = 1$; and cholelithiasis, $n = 1$), and 1 patient taking ritonavir-boosted atazanavir discontinued TVR because of jaundice. Among patients taking ritonavir-boosted atazanavir, grade 3 and 4 hyperbilirubinemia (predominantly indirect bilirubin) occurred in 13 of 15 (87%) TVR recipients and 5 of 8 (63%) placebo recipients during the first 12 weeks of therapy; such increases were not seen in patients who did not receive antiretroviral therapy or in those receiving efavirenz. Anemia was common, with a decrease in hemoglobin levels to less than 100 g/L in 12 of 38 (32%) TVR recipients and 5 of 22 (23%) placebo recipients. Anemia was managed with blood transfusion in 5 patients (TVR, $n = 4$; and placebo, $n = 1$) and administration of epoetin-α in 4 patients (TVR, $n = 3$; and placebo, $n = 1$). Grade 3 or greater neutropenia was seen in 6 of 38 (16%) and 6 of 22 (27%) patients treated with TVR and placebo, respectively. As in previous studies of patients with both HCV and HIV treated with PEG-IFN-α2a–ribavirin (11), absolute CD4 cell count decreased in all patients; however, the percentage of the $CD4^+$ lymphocytes was unchanged during treatment. No deaths or AIDS-defining illnesses were seen during the study.

Efficacy

Of the 60 patients who received study medications, 35 (58%) completed 48 weeks of treatment and 25 (42%) discontinued treatment early because of protocol-defined virologic failure (TVR, $n = 2$, weeks 4 or 8; placebo, $n = 7$, weeks 12 or 24), AEs (TVR, $n = 3$, at or before weeks 4, 24, or 36; placebo, $n = 0$), loss to follow-up (TVR, $n = 2$, at or before weeks 36 or 48; placebo, $n = 1$, at or before week 24), withdrawal of consent (TVR, $n = 1$, at or before week 4; placebo, $n = 0$), or other reasons (nonadherence, $n = 4$; lack of response, $n = 1$; thought they completed therapy, $n = 1$; moved, $n = 1$; patient decision, $n = 2$) (**Figure 1**). The decreases in HCV RNA levels from baseline were more rapid in TVR recipients than in placebo recipients (**Figure 2**), with mean changes in $\log_{10}$ HCV RNA levels from baseline to week 12 of −5.8 IU/mL and −3.8 IU/mL, respectively (**Table 3**). By week 4, HCV RNA levels were not detected in 26 of 38 (68%) patients

Figure 1. **Study flow diagram.**



Part A patients did not receive concomitant antiretroviral therapy. Part B patients were assigned 1 of 2 HIV treatment regimens: efavirenz, tenofovir, and emtricitabine, or ritonavir-boosted atazanavir with tenofovir and either emtricitabine or lamivudine. Patients were assigned to receive either TVR/P–R or P–R. Patients in part A were randomly assigned in a 1:1 ratio and the 2 groups of patients in part B were randomly assigned in a 2:1 ratio to receive TVR/P–R or P–R. HCV = hepatitis C virus; P–R = peginterferon-α2a–ribavirin alone for 48 wk; TVR/P–R = telaprevir combined with peginterferon-α2a–ribavirin for 12 wk, followed by peginterferon-α2a–ribavirin for an additional 36 wk.

* The most common reasons for exclusion were low CD4 cell count, low creatinine clearance, low or undetectable HCV viral load, low absolute neutrophil count, high HIV viral load, high α-fetoprotein level, positive hepatitis B test result, or out of treatment window.

in the TVR group and 0 of 22 (0%) patients in the placebo group (difference, 68 percentage points [95% CI, 54 to 83 percentage points]). By week 12, HCV RNA levels were undetectable in 30 of 38 (79%) TVR recipients and 6 of 22 (27%) placebo recipients (difference, 52 percentage points [CI, 29 to 74 percentage points]) (**Table 3**). Sustained virologic response at posttreatment weeks 12 and 24 was higher in patients treated with TVR plus PEG-IFN-α2a–ribavirin (28 of 38 patients [74%]) than in those treated with PEG-IFN-α2a–ribavirin alone (10 of 22 patients [45%]) (difference, 29 percentage points [CI, 3 to 53 percentage points]). Among black patients, SVR was achieved in 8 of 9 persons who received TVR and 3 of 7 who received placebo. Evaluation of SVR according to genotype 1 subtype and interleukin-28B genotype was limited by small numbers of patients (subtype 1b) and incomplete data (interleukin-28B) (**Appendix Table 2**, available at www.annals.org). After treatment discontinuation, HCV viral relapse occurred in 1 of 32 (3%) TVR recipients and 2 of 13 (15%) placebo recipients; HCV viremia was detected at posttreatment week 4 in all 3 patients.

Virology

At baseline, TVR-resistant variants were not seen in patients who received TVR. Two patients with HCV subtype 1a had virologic breakthrough while receiving TVR (1 receiving ritonavir-boosted atazanavir at week 4; 1 receiving efavirenz at week 12); both had variants with the combination of TVR-resistant amino acid substitutions at NS3 positions 36 (V36M) and 155 (R155K). No substitutions

Table 2. **Summary of AEs Reported by Patients in Any Treatment Group***

AEs	TVR Treatment Phase (Weeks 1–12)			Overall Treatment Phase (Weeks 1–48)		
	TVR/P–R (*n* = 38)	P–R (*n* = 22)	Difference (95% CI)	TVR/P–R (*n* = 38)	P–R (*n* = 22)	Difference (95% CI)
Overall						
Any AE	37 (97)	21 (95)	2 (−8 to 12)	38 (100)	22 (100)	–
AEs leading to death	0 (0)	0 (0)	–	0 (0)	0 (0)	–
Serious AEs	2 (5)	0 (0)	5 (−2 to 12)	7 (18)	2 (9)	9 (−8 to 26)
AEs leading to treatment discontinuation	2 (5)	0 (0)	5 (−2 to 12)	3 (8)	0 (0)	8 (−1 to 16)
Special interest						
Pruritus†	13 (34)	1 (5)	30 (12 to 47)	15 (39)	2 (9)	30 (11 to 50)
Rash†	11 (29)	4 (18)	11 (−11 to 32)	13 (34)	5 (23)	11 (−12 to 35)
Anemia†	5 (13)	4 (18)	−5 (−24 to 14)	7 (18)	4 (18)	0.2 (−20 to 20)
Anorectal discomfort†	5 (13)	1 (5)	9 (−5 to 22)	5 (13)	2 (9)	4 (−12 to 20)

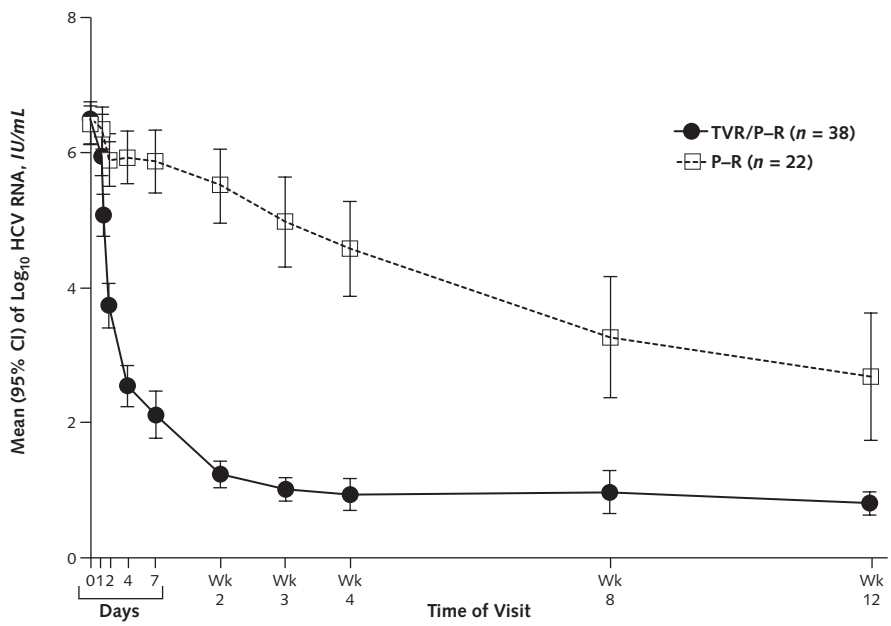
AE = adverse event; P–R = peginterferon-α2a–ribavirin alone for 48 wk; TVR/P–R = telaprevir combined with peginterferon-α2a–ribavirin for 12 wk, followed by peginterferon-α2a–ribavirin for an additional 36 wk.
* All values are numbers (percentages) unless otherwise indicated.
† Pruritus, rash, anemia, and anorectal discomfort were assessed with the use of a group of related terms to identify all dermatologic, anemia, and anorectal events, respectively.

were detected in the 2 patients who discontinued treatment with TVR prematurely. In the 1 TVR recipient with posttreatment HCV relapse, the resistant variant V36M was detected at relapse but not at subsequent testing 14 weeks later. Among patients not receiving antiretroviral therapy, HIV RNA level decreased in both TVR (−1.16 $\log_{10}$ at week 4) and placebo (−0.91 $\log_{10}$ at week 4) recipients. Among patients taking antiretroviral therapy, HIV breakthrough was not seen.

Pharmacokinetics of TVR and Antiretroviral Drugs

Plasma concentrations were available for 36 of 38 TVR recipients and all patients who received efavirenz (*n* = 24), atazanavir (*n* = 23), or tenofovir (*n* = 47). The

Figure 2. **Mean (95% CI) $\log_{10}$ HCV RNA levels from baseline through 12 wk, by treatment group.**



HCV RNA levels were assessed at 0, 1, 2, 4, and 7 d and at 2, 3, 4, 8, and 12 wk. The numbers of patients with HCV RNA measures at each time point are shown. HCV = hepatitis C virus; P–R = peginterferon-α2a–ribavirin alone for 48 wk; TVR/P–R = telaprevir combined with peginterferon-α2a–ribavirin for 12 wk, followed by peginterferon-α2a–ribavirin for an additional 36 wk.

Table 3. **Virologic Response During and After the Treatment Period, by Treatment Group**

Virologic Response*	Part A: Participants Not Receiving Antiretroviral Therapy		Part B: Participants Receiving Efavirenz, Tenofovir, and Emtricitabine		Part B: Participants Receiving Ritonavir-Boosted Atazanavir, Tenofovir, and Either Emtricitabine or Lamivudine		Total	
	TVR/P–R (*n* = 7)	P–R (*n* = 6)	TVR/P–R (*n* = 16)	P–R (*n* = 8)	TVR/P–R (*n* = 15)	P–R (*n* = 8)	TVR/P–R (*n* = 38)	P–R (*n* = 22)
Participants with response, *n*								
4 wk	5	0	12	0	9	0	26	0
12 wk	6	2	14	2	10	2	30	6
4 and 12 wk (extended rapid virologic response)	4	0	12	0	7	0	23	0
End of treatment	4	2	11	4	8	5	23	11
12 wk after end of treatment (SVR_{12})	5	2	11	4	12	4	28	10
24 wk after end of treatment (SVR_{24})	5	2	11	4†	12†	4	28	10
Participants with relapse, *n/N*‡	1/6§	0/2	0/14	0/5	0/12	2/6	1/32	2/13
HCV RNA levels								
4 wk								
Patients, *n*	7	6	15	8	14	8	36	22
Mean change from baseline (SD), log_{10} *IU/mL*‖	−5.9 (0.3)	−1.4 (1.0)	−5.7 (0.6)	−1.8 (1.6)	−5.4 (1.0)	−2.2 (1.1)	−5.6 (0.8)	−1.8 (1.2)
No assessment, *n*	0	0	0	0	0	0	0	0
Discontinued treatment, *n*	0	0	1	0	1	0	2	0
12 wk								
Patients, *n*	7	6	15	8	11	7	33	21
Mean change from baseline (SD), log_{10} *IU/mL*‖	−6.0 (0.6)	−3.3 (2.3)	−5.6 (0.8)	−3.7 (2.0)	−5.9 (0.8)	−4.3 (1.6)	−5.8 (0.7)	−3.8 (1.9)
No assessment, *n*	0	0	0	0	0	1	0	1
Discontinued treatment, *n*	0	0	1	0	4	0	5	0

HCV = hepatitis C virus; P–R = peginterferon-α2a–ribavirin alone for 48 wk; SVR = sustained virologic response; TVR/P–R = telaprevir combined with peginterferon-α2a–ribavirin for 12 wk, followed by peginterferon-α2a–ribavirin for an additional 36 wk.

* HCV RNA levels were measured at 1, 2, and 4 d; at 1, 2, 3, 4, 8, 12, 16, 20, 24, 36, and 48 wk; and at posttreatment follow-up visits.

† Before visit at 24 wk, 2 patients with SVR at 12 wk (SVR_{12}) were lost to follow-up. For these patients, SVR_{12} results were imputed for the SVR_{24} visit for this analysis. The protocol-specified definition of SVR_{24} was met by 3 of 8 (38%) for efavirenz-based P–R and 11 of 15 (73%) for atazanavir-based TVR/P–R.

‡ Defined as HCV RNA levels greater than or equal to the lower limit of quantitation (LLOQ) relative to the actual end-of-treatment window. The number of patients with levels <LLOQ at the end-of-treatment visit window, or those whose next level observed after the actual end-of-treatment window was <LLOQ, was used as the denominator for relapse calculations.

§ 1 patient receiving TVR/P–R from part A did not have HCV RNA assessment available at the end of treatment.

‖ HCV RNA levels were measured with Cobas TaqMan HCV assay, version 2.0 (Roche Molecular Systems, Branchburg, New Jersey), which has an LLOQ of 25 IU/mL.

median ratios of antiretroviral trough concentrations during and before TVR treatment were 6% lower for efavirenz and 16% higher for atazanavir (**Table 4**). The median ratios of tenofovir concentrations during and before TVR treatment varied according to concurrent administration of atazanavir (25% lower) or efavirenz (6% higher), but the median trough concentrations of tenofovir were similar in the TVR (116 ng/mL; range, 63.7 to 233 ng/mL) and placebo (98.8 ng/mL; range, 38.5 to 257 ng/mL) groups. Telaprevir concentrations with and without concurrent antiretroviral therapy were similar with the exception that the minimum TVR concentration was 31% higher in patients taking ritonavir-boosted atazanavir; however, no corresponding increase in the average or maximum TVR concentration was seen in this group.

DISCUSSION

Treatment with HCV protease inhibitors in combination with PEG-IFN-α2a–ribavirin is recommended for patients with only genotype 1 chronic HCV infection (17). However, the use of these regimens in patients with both HCV and HIV has been limited by the absence of data about the safety and efficacy of HCV protease inhibitors and their effect on the metabolism of antiretroviral drugs (16, 26, 27). In this preliminary study, TVR plus PEG-IFN-α2a–ribavirin in patients with HCV genotype 1 and HIV was associated with a higher virologic response and more AEs than PEG-IFN-α2a–ribavirin alone.

The nature and severity of AEs were similar to those seen in larger studies of patients with only HCV, including skin rash, gastrointestinal symptoms, and anemia (13, 15). Compared with those treated with placebo, patients with both HCV and HIV treated with TVR were more likely to have mild and moderate rashes or pruritus. Although serious cutaneous adverse reactions, including fatal outcomes, have been reported with TVR combination therapy (26), severe or treatment-limiting rash was not seen in the 38 patients treated with TVR in this small study. Anemia has also been seen in patients treated with TVR plus PEG-IFN-α2a–ribavirin. Although the incidence of anemia in this study was similar in patients treated with TVR and placebo, management of treatment-related anemia with

Table 4. **Summary of Pharmacokinetics of Antiretroviral Therapy and Telaprevir in Patients With Both HCV and HIV**

Analyte	Parameter	Median C_{trough} Ratio (25th–75th Percentiles)*	
		TVR/P–R	P–R
Effect of telaprevir on antiretroviral medication exposure			
Atazanavir	C_{trough}	1.16 (1.04–2.48) (n = 14)	1.03 (0.87–1.47) (n = 7)
Efavirenz	C_{trough}	0.94 (0.84–1.25) (n = 15)	0.79 (0.63–1.14) (n = 8)
Tenofovir (with efavirenz)	C_{trough}	1.06 (0.90–1.47) (n = 15)	0.64 (0.42–1.10) (n = 8)
Tenofovir (with atazanavir)	C_{trough}	0.75 (0.62–1.56) (n = 14)	0.93 (0.84–1.15) (n = 7)
		GLSMR (90% CI)†	
Effect of antiretroviral medications on telaprevir exposure			
Telaprevir (with efavirenz)	C_{min}	0.88 (0.55–1.43)	
	C_{avg}	0.96 (0.66–1.40)	
	C_{max}	1.01 (0.73–1.39)	
Telaprevir (with atazanavir)	C_{min}	1.31 (0.80–2.14)	
	C_{avg}	1.09 (0.75–1.60)	
	C_{max}	1.01 (0.73–1.40)	

GLSMR = geometric least square mean ratio; HCV = hepatitis C virus; P–R = peginterferon-α2a–ribavirin alone for 48 wk; TVR/P–R = telaprevir combined with peginterferon-α2a–ribavirin for 12 wk, followed by peginterferon-α2a–ribavirin for an additional 36 wk.

* C_{trough} ratio = arithmetic mean predose concentrations on wk 1, 2, 4, and 12 (mean C_{trough} during telaprevir or placebo exposure) ÷ predose concentration on day −1 for individual patients (C_{trough} before telaprevir or placebo exposure).

† GLSMR = pharmacokinetic parameter during antiretroviral therapy ÷ pharmacokinetic parameter without antiretroviral therapy. Telaprevir pharmacokinetic samples were available for 15 patients receiving efavirenz and 13 patients receiving atazanavir. GLSMRs and 90% CIs for C_{avg}, C_{max}, and C_{min} for telaprevir with and without antiretrovirals were calculated using WinNonlin, version 5.3 (Pharsight, Mountainview, California). The no-effect range of the 90% CIs for the GLSMR was 0.8–1.25 (32).

epoetin-α or blood transfusion was more common in patients treated with TVR. Nonetheless, only 1 patient treated with TVR discontinued therapy because of anemia. Compared with previous studies, the severity of anemia in this study may have been alleviated by the administration of low fixed-dose ribavirin (800 mg/d) to most patients, which was associated with similar SVR and less anemia compared with higher, weight-based ribavirin in the study by Rodriguez-Torres and colleagues (23) and by the exclusion of the patients taking the antiretroviral drug zidovudine, which worsens anemia related to PEG-IFN-α2a–ribavirin therapy (28–30). Although we did not detect a difference in safety or tolerability of TVR compared with previous studies of patients with only HCV (26), larger studies of TVR plus PEG-IFN-α2a–ribavirin are needed to fully characterize the profile of TVR in patients with both HCV and HIV.

In this small preliminary study, 74% of patients with both genotype 1 HCV and HIV treated with TVR plus PEG-IFN-α2a–ribavirin achieved SVR compared with 45% of those treated with PEG-IFN-α2a–ribavirin alone. The observed safety and tolerability of TVR in this small preliminary study were consistent with that previously reported in patients with only HCV (26, 31). It is important to note that no adverse effect on HIV infection or its treatment with antiretroviral drugs was detected. The addition of TVR to PEG-IFN-α2a–ribavirin led to robust and rapid HCV suppression, with two thirds of patients achieving undetectable HCV RNA levels after 4 weeks compared with none of the patients treated with placebo. This is consistent with the viral kinetics seen in larger studies of patients with only HCV (13, 15, 16). For most patients with both HCV and HIV treated with TVR, this early HCV suppression was sustained during and after treatment. Although interpretation is limited by the small sample size and appreciable dropout rate, there was a 29–percentage point difference in SVR in patients treated with TVR compared with those treated with placebo, and virologic breakthrough with TVR-resistant variants was uncommon, occurring in only 2 patients. The increase in efficacy with TVR compared with placebo was similar to that seen in clinical trials of patients with only HCV (13, 15). This finding was not expected because the efficacy of HCV treatment with PEG-IFN-α2a–ribavirin has been markedly lower in patients with both HCV and HIV compared with patients with only HCV in previous studies (10, 11, 23), suggesting blunted interferon responsiveness in patients with HIV. Although preliminary, our data suggest that drugs directly targeting HCV may overcome the effect of HIV infection on treatment response and support larger, ongoing confirmatory studies of TVR plus PEG-IFN-α2a–ribavirin in patients with both HCV and HIV.

Because TVR is metabolized by and is a strong inhibitor of CYP3A4 (18), interactions with antiretroviral drugs that inhibit or induce, or are metabolized by, CYP3A4 were anticipated. On the basis of the results of interaction studies completed in healthy volunteers (18, 26), antiretroviral regimens were limited to ritonavir-boosted atazanavir with a standard dose of TVR or efavirenz with a higher dose of TVR to overcome induction of CYP3A4. In this study of patients with both HCV and HIV, the pharmacokinetics of TVR and antiretroviral drugs was carefully assessed to determine the applicability of the data derived from healthy volunteers. Considering the high degree of variability of antiretroviral drug exposure, the coadministration of TVR did not have a clinically meaningful effect

on the antiretroviral drugs studied. The lack of HIV breakthrough provides additional support for coadministration of TVR with the selected antiretroviral regimens. Similarly, compared with patients with both HCV and HIV who were not taking antiretrovirals, concurrent antiretroviral therapy did not seem to alter the HCV response during TVR administration. Finally, as predicted from healthy volunteer studies, the higher dose of TVR (1125 mg every 8 hours) seemed to compensate for the induction effect of efavirenz on TVR metabolism (18). Taken together, these data underscore the value of conducting interaction studies with novel anti-HCV and antiretroviral drugs before treating patients with both HCV and HIV in clinical trials or practice.

This study has several important limitations. It was small, limiting the interpretation of safety and efficacy findings. In addition, because we enrolled patients who had not been previously treated for HCV and those who had stable HIV disease and high CD4 cell counts; as such, these results are not generalizable to patients with both HCV and HIV who had previous HCV treatment failure or those with more advanced HIV infection. Similarly, because we included only patients taking specific antiretroviral drugs for which interactions with TVR were predicted to be acceptable, these results cannot be extended to patients receiving other antiretroviral regimens. However, the pharmacokinetic data from this study were consistent with predications derived from interaction studies in healthy volunteers, indicating that interaction data derived from such studies are informative.

In conclusion, the addition of TVR to PEG-IFN-α2a–ribavirin led to a higher virologic response in this preliminary study in patients with both genotype 1 HCV and HIV. The observed safety and tolerability of TVR was consistent with the profile seen in patients with only HCV. Although drug interactions between TVR and antiretroviral drugs metabolized by CYP3A4 limited the antiretroviral therapy regimens that were studied, no adverse effect on HIV disease or its treatment was seen. These findings support the conduct of larger, ongoing, confirmatory phase 3 studies of TVR plus PEG-IFN-α2a–ribavirin in patients with both genotype 1 HCV and HIV.

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Acknowledgment: The authors thank the coordinators, nurses, and patients involved in the study; Theorem Clinical Research, Oracle Health Sciences Global Business Unit, i3 Research and i3 Global, Covance Laboratories, Quest Pharmaceuticals, and ICON Central Laboratories for coordinating and implementing various aspects of the study; Christina (Tina) Karunaratne for clinical project management; Eileen Zhang, PhD, for virology analyses; Min Chen, MS, for statistical programming; Yang Dai, PhD, for pharmacokinetic data analysis; Jonathan Kirk for graphic design support; Leslie Lescale-Matys, PhD, for study conduct and data analysis; and Kristin Stephan, PhD, Frances Smith, PhD, Karen Eisenhauer, PhD, and Mrudula Donepudi, PhD, for medical writing and editorial assistance (all from Vertex Pharmaceuticals). The authors also thank the site investigators (see **Appendix 1**, available at www.annals.org).

Grant Support: By the National Institute on Drug Abuse (K24DA034621 and R01DA16065), National Institute of Allergy and Infectious Diseases (P30AI094189), National Center for Research Resources and the National Institutes of Health Roadmap for Medical Research (UL1RR025005), National Institute of Diabetes and Digestive Kidney Diseases (K24 DK070528), Hickey Foundation–HONE Project (GCO 09-0395), and the National Institute of Mental Health (R34 MH099930-01A1). Funding was also provided by the Fundación Investigación y Educación en SIDA, European AIDS Treatment Network (LSHM-CT-2006-037570), European Community's Seventh Framework Program FP7/2007-2013 Collaborative HIV and Anti-HIV Drug Resistance Network (Project 223131), and Red de Investigación en SIDA (ISCIII-RETIC-RD12/0017/0031).

Potential Conflicts of Interest: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M13-0291.

Reproducible Research Statement: *Study protocol:* Available from Dr. Rubin (e-mail, raymond_rubin@vrtx.com). *Statistical code and data set:* Not available.

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Appendix 1: List of Clinical Trial Investigators

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Appendix 2: Supplemental Methods: Efficacy Outcomes and Follow-up

For relapse, the number of patients with levels less than the LLOQ at the end-of-treatment visit window, or those whose next level seen after the actual end-of-treatment window was less than the LLOQ, is used as the denominator for relapse calculations. To be eligible for relapse, a patient's HCV RNA levels had to have been such that the last level in the actual end-of-treatment window was less than the LLOQ or no levels were available in the actual end-of-treatment window, but the last level in the next window was less than the LLOQ.

Appendix Table 1. **Incidence of All AEs Reported in All Patients During the Overall Treatment Phase, by Treatment Group***

AEs	TVR/P–R (*n* = 38), *n (%)*	P–R (*n* = 22), *n (%)*
General disorders and administration site conditions		
Fatigue	16 (42)	9 (41)
Chills	6 (16)	4 (18)
Pyrexia†	8 (21)	2 (9)
Flulike illness	5 (13)	3 (14)
Irritability	5 (13)	3 (14)
Pain†	1 (3)	3 (14)
Injection site erythema	2 (5)	1 (5)
Malaise	2 (5)	0 (0)
Catheter site erythema	0 (0)	1 (5)
Catheter site pain	0 (0)	1 (5)
Injection site pain	1 (3)	0 (0)
Injection site pruritus	1 (3)	0 (0)
Injection site reaction	1 (3)	0 (0)
Nodule	0 (0)	1 (5)
Noncardiac chest pain	1 (3)	0 (0)
Peripheral edema	1 (3)	0 (0)
Gastrointestinal disorders		
Nausea†	13 (34)	5 (23)
Diarrhea	9 (24)	4 (18)
Vomiting	7 (18)	2 (9)
Upper abdominal pain†	5 (13)	0 (0)
Gastroesophageal reflux disease†	0 (0)	3 (14)
Anogenital dysplasia	0 (0)	2 (9)
Anorectal discomfort	1 (3)	1 (5)
Cheilitis	2 (5)	0 (0)
Constipation	1 (3)	1 (5)
Dry mouth	2 (5)	0 (0)
Dyspepsia	1 (3)	1 (5)
Hemorrhoids	2 (5)	0 (0)
Rectal hemorrhage	1 (3)	1 (5)
Abdominal distention	1 (3)	0 (0)
Abdominal pain	1 (3)	0 (0)
Anal pruritus	1 (3)	0 (0)
Anal skin tags	0 (0)	1 (5)
Aphthous stomatitis	1 (3)	0 (0)
Flatulence	1 (3)	0 (0)
Gingival bleeding	0 (0)	1 (5)
Hematochezia	1 (3)	0 (0)
Dry lips	1 (3)	0 (0)
Oral disorder	0 (0)	1 (5)
Painful defecation	1 (3)	0 (0)
Parotid inflammation	1 (3)	0 (0)
Peritonitis	0 (0)	1 (5)
Proctalgia	0 (0)	1 (5)
Retching	1 (3)	0 (0)
Toothache	0 (0)	1 (5)
Nervous system disorders		
Headache	14 (37)	6 (27)
Dizziness	8 (21)	3 (14)
Disturbance in attention	1 (3)	1 (5)
Paraesthesia	0 (0)	2 (9)
Cognitive disorder	1 (3)	0 (0)
Dysesthesia	1 (3)	0 (0)
Dysgeusia	1 (3)	0 (0)
Hyperesthesia	1 (3)	0 (0)
Lethargy	1 (3)	0 (0)
Parosmia	1 (3)	0 (0)
Syncope	0 (0)	1 (5)
Tremor	1 (3)	0 (0)

Appendix Table 1—Continued

AEs	TVR/P–R (*n* = 38), *n (%)*	P–R (*n* = 22), *n (%)*
Skin and subcutaneous tissue disorders		
Pruritus†	15 (39)	2 (9)
Rash	5 (13)	2 (9)
Alopecia	4 (11)	2 (9)
Dermatitis	1 (3)	2 (9)
Dry skin	2 (5)	1 (5)
Night sweats	2 (5)	1 (5)
Acne	1 (3)	1 (5)
Erythema	2 (5)	0 (0)
Generalized rash	1 (3)	1 (5)
Contact dermatitis	1 (3)	0 (0)
Drug eruption	0 (0)	1 (5)
Eczema	1 (3)	0 (0)
Hyperhidrosis	1 (3)	0 (0)
Prurigo	1 (3)	0 (0)
Purpura	1 (3)	0 (0)
Maculopapular rash	0 (0)	1 (5)
Papular rash	1 (3)	0 (0)
Skin irritation	1 (3)	0 (0)
Skin lesion	0 (0)	1 (5)
Skin ulcer	0 (0)	1 (5)
Stasis dermatitis	1 (3)	0 (0)
Psychiatric disorders		
Depression†	8 (21)	2 (9)
Insomnia†	5 (13)	5 (23)
Anxiety	3 (8)	1 (5)
Depressed mood†	1 (3)	3 (14)
Affect lability	2 (5)	0 (0)
Decreased libido	2 (5)	0 (0)
Disorientation	1 (3)	0 (0)
Emotional disorder	1 (3)	0 (0)
Mood swings	1 (3)	0 (0)
Sleep disorder	1 (3)	0 (0)
Suicidal ideation	1 (3)	0 (0)
Infections		
Nasopharyngitis	2 (5)	1 (5)
Fungal skin infection	2 (5)	0 (0)
Oral candidiasis	1 (3)	1 (5)
Respiratory tract infection	1 (3)	1 (5)
Sinusitis	2 (5)	0 (0)
Upper respiratory tract infection	1 (3)	1 (5)
Acarodermatitis	1 (3)	0 (0)
Acute sinusitis	0 (0)	1 (5)
Anal abscess	1 (3)	0 (0)
Anal tinea	1 (3)	0 (0)
Anogenital warts	0 (0)	1 (5)
Appendicitis	0 (0)	1 (5)
Bronchitis	1 (3)	0 (0)
Staphylococcal cellulitis	1 (3)	0 (0)
Infective conjunctivitis	1 (3)	0 (0)
Furuncle	0 (0)	1 (5)
Groin infection	1 (3)	0 (0)
Herpangina	1 (3)	0 (0)
Influenza	1 (3)	0 (0)
Lower respiratory tract infection	0 (0)	1 (5)
Onychomycosis	0 (0)	1 (5)
Acute otitis media	1 (3)	0 (0)
Paronychia	1 (3)	0 (0)
Pharyngitis	1 (3)	0 (0)
Pilonidal cyst	1 (3)	0 (0)
Pneumonia	0 (0)	1 (5)
Postoperative wound infection	0 (0)	1 (5)
Acute pyelonephritis	1 (3)	0 (0)
Secondary syphilis	1 (3)	0 (0)

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Appendix Table 1—Continued

AEs	TVR/P–R (*n* = 38), *n* (%)	P–R (*n* = 22), *n* (%)
Staphylococcal abscess	1 (3)	0 (0)
Staphylococcal infection	1 (3)	0 (0)
Subcutaneous abscess	0 (0)	1 (5)
Tinea barbae	0 (0)	1 (5)
Tonsillitis	0 (0)	1 (5)
Tooth infection	1 (3)	0 (0)
Urinary tract infection	1 (3)	0 (0)
Bacterial urinary tract infection	0 (0)	1 (5)
Blood and lymphatic system disorders		
Neutropenia	9 (24)	5 (23)
Anemia	6 (16)	3 (14)
Hemolytic anemia	1 (3)	0 (0)
Thrombocytopenia	1 (3)	0 (0)
Musculoskeletal and connective tissue disorders	12 (32)	8 (36)
Laboratory abnormalities	12 (32)	6 (27)
Metabolism and nutrition disorders	12 (32)	5 (23)
Respiratory, thoracic, and mediastinal disorders†	6 (16)	7 (32)
Eye disorders	2 (5)	3 (14)
Cardiac disorders	3 (8)	1 (5)
Hepatobiliary disorders†	4 (10)	0 (0)
Renal and urinary disorders†	4 (10)	0 (0)
Ear and labyrinth disorders	2 (5)	1 (5)
Injury, poisoning, and procedural complications	3 (8)	0 (0)
Vascular disorders†	0 (0)	3 (14)
Endocrine disorders	2 (5)	0 (0)
Congenital, familial, and genetic disorders	1 (3)	0 (0)
Benign, malignant, and unspecified neoplasms	0 (0)	1 (5)
Reproductive system and breast disorders	1 (3)	0 (0)

AE = adverse event; P–R = peginterferon-α2a–ribavirin alone for 48 wk; TVR/P–R = telaprevir combined with peginterferon-α2a–ribavirin for 12 wk, followed by peginterferon-α2a–ribavirin for an additional 36 wk.
* Includes all individual rash, anemia, anorectal discomfort, and pruritus events assessed with the use of a group of related terms in **Table 2**.
† Events occurred at ≥10–percentage point difference between groups.

Appendix Table 2. Rates of SVR, by Patient and Treatment Subgroups

SVR*	Part A: Participants Not Receiving Antiretroviral Therapy		Part B: Participants Receiving Efavirenz, Tenofovir, and Emtricitabine		Part B: Participants Receiving Ritonavir-Boosted Atazanavir, Tenofovir, and Either Emtricitabine or Lamivudine		Total	
	TVR/P–R (*n* = 7)	P–R (*n* = 6)	TVR/P–R (*n* = 16)	P–R (*n* = 8)	TVR/P–R (*n* = 15)	P–R (*n* = 8)	TVR/P–R (*n* = 38)	P–R (*n* = 22)
HCV genotype 1 subtype, *n/N*								
1a	1/3	1/3	9/12	2/6	10/12	1/5	20/27	4/14
1b	4/4	1/2	2/4	0/1	1/3	3/3	7/11	4/6
Other subtype	0	0/1	0	1/1	0	0	0	1/2
IL-28B genotype, *n/N*†								
CC	0	0	5/5	0	4/4	1/1	9/9	1/1
CT	2/2	2/2	4/4	3/6	3/3	3/6	9/9	8/14
TT	1/2	0/1	1/1	0	0/1	0	2/4	0/1
No IL-28B assessment	2/3	0/3	1/6	0/2	4/7	0/1	7/16	0/6

HCV = hepatitis C virus; IL-28B = interleukin-28B; P–R = peginterferon-α2a–ribavirin alone for 48 wk; SVR-sustained virologic response; TVR/P–R = telaprevir combined with peginterferon-α2a–ribavirin for 12 wk, followed by peginterferon-α2a–ribavirin for an additional 36 wk.
* HCV RNA levels were measured at 1, 2, and 4 d; at 1, 2, 3, 4, 8, 12, 16, 20, 24, 36, and 48 wk; and at posttreatment follow-up visits.
† IL-28B genotype was retrospectively determined for patients who provided specific informed consent and was not available in all patients.