Effectiveness of Hepatitis C Treatment with Pegylated Interferon and Ribavirin in Urban Minority Patients

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Randomized controlled trials of hepatitis C virus (HCV) therapy with pegylated interferon and ribavirin have demonstrated sustained viral response rates (SVRs) of 54%-63% (efficacy). Treatment results in clinical practice (effectiveness) may not be equivalent. The goal of this study was to assess the effectiveness of HCV treatment with pegylated interferon and ribavirin in a treatment-naïve, human immunodeficiency virus (HIV)-negative, United States urban population with many ethnic minority patients. We evaluated 2,370 outpatients for HCV therapy from 2001 to 2006 in the Faculty Practice of the Albert Einstein College of Medicine or the attending-supervised Montefiore Medical Center Liver Clinic. Care was supervised by one experienced physician under conditions of everyday clinical practice, and appropriate ancillary resources were made available to all patients. Two hundred fifty-five patients were treated with a mean age of 50 years (60% male, 40% female; 58% Hispanic, 20% African American, 9% Caucasian, 13% other; 68% genotype 1, the remainder genotypes 2 or 3). Patients had at least one liver biopsy. Intention-to-treat analysis (ITT) showed SVR in 14% of genotype 1 patients and 37% in genotype 2/3 patients ($P < 0.001$). SVR was significantly higher in faculty practice (27%) than in clinic patients (15%) by intention-to-treat ($P = 0.01$) but not per-protocol analysis (46% faculty practice, 34% clinic). 3.3% of 1,656 treatment-naïve, HIV antibody–negative individuals ultimately achieved SVR. Current hepatitis C therapies may sometimes be unavailable to, inappropriate for, and ineffective in United States urban patients. Treatment with pegylated interferon and ribavirin was less effective in this population than is implied by multinational phase III controlled trials. New strategies are needed to care for such patients. (HEPATOLOGY 2010;51: 1137-1143.)

In multinational phase III randomized controlled trials of hepatitis C therapy with combination pegylated interferon and ribavirin, intention-to-treat (ITT) analysis has consistently shown sustained viral response rates of 54%-63%.[1-3] Often, however, treatment results comparable to those of registration trials are not achieved in daily clinical practice.[4] Industry-sponsored trials are conducted with the advantage of extraordinary resources to ensure that all aspects of therapy with a study drug are accurately controlled, observed, and documented. Trial subjects undergo unusually frequent outpatient assessments, and their adherence to a protocol is closely observed by trained research coordinators who distribute study drugs and document their use, and who are able to intervene rapidly in the event of a side effect that may impair continued subject participation. Furthermore, patients enrolled in registration trials are carefully selected to exclude coexisting medical problems that may have confounding effects on treatment and its outcome. The motivation and other unquantifiable characteristics of study subjects may differ substantially from those of individuals who present for care in ordinary practice settings. Finally, members of ethnic groups treated in clinical practice may not have the same response to therapy as persons of different ethnicity studied in registration trials. The vast majority of these individuals were reported to have been

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus; ITT, intention-to-treat; SVR, sustained virologic reponse.

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Received August 27, 2009; accepted November 8, 2009.

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Published online in Wiley InterScience (www.interscience.wiley.com).

DOI 10.1002/hep.23429

Potential conflict of interest: Nothing to report.

Table 1. Comparison of Results with Sentinel Trials

Variable	Current	Fried et al.[1]	Manns et al.[2]	Hadziyannis et al.[3]
Screened, n	1,656*	1,459	2,316	1,736
Excluded, n	1,401	338	786	452
ITT analysis, n (male/female)†	255 (152/103)†	453 (324/129)†	511 (321/190)†	436 (287/149)†
Mean age, years	50.0 ± 8.6	42.8 ± 10.1	43 (21-68)	43.0 ± 10.1
Ethnicity, W/H/AA/O‡	23/149/52/31	372/0/27/54	Unknown	394/0/11/31
Mean weight, kg	84.4 ± 18.9	79.8 ± 17.5	82 (43-159)	77.3 ± 16.0
Mean viral load, log copies/mL§	Unknown¶	6.0 ± 7.3	2.7	6.1 ± 6.8
Mean baseline alanine aminotransferase, U/L	98.0 ± 97.0	90.2 ± 65.2	2.3 × Normal (0.81-13.3)	87.0 ± 60.9
Risk factor, D/T/O#	169/37/49	190/85/178	315/114/82	163/80/131
Lost or withdrew, n (genotype 1/genotype 2/3)	96 (68/28)	119	14	117
Completed Rx at follow-up, n (%)	131 (51%)	334 (74%)	497 (97%)	319 (73%)
SVR, n (%)	54 (21%)	255 (56%)	274 (54%)	275 (63%)
Genotype 1, n (%)	173 (68%)	298 (66%)	348 (68%)	271 (62%)
SVR genotype 1, n (%)	24 (14%)	138 (46%)	145 (42%)	141 (52%)
SVR genotypes 2 and 3, n (%)	30 (37%)	116 (76%)	129 (79%)	122 (80%)
Cirrhosis, n (%)	73 (29%)	56 (12%)	136 (27%)	115 (26%)
SVR in cirrhosis, n (%)	9 (12%)	24 (43%)	60 (44%)	(41%-73%)μ

Statistical analysis was not possible because the source data are not in the public domain.

*Total screened (2,370) less previously treated (236) and HIV coinfected (478) patients.

†Intention-to-treat, standard treatment arm.

‡W/H/AA/O, white/Hispanic/African American/other.

§Mean viral load at commencement of therapy.

¶Quantitative results reported as >750,000 copies/mL in many patients. #Likely source of infection; D/T/O, percutaneous drug use/transfusion/other. □Genotype 1, 41%; genotypes 2 and 3, 73%.

white (82%[1] to 90%[3]), none were Hispanic, and very few were African American (3%[3] to 6%[1]), whereas 58% of the patients treated at our urban medical center were Hispanic and 20% were African American (Table 1).

Nevertheless, efficacy data from randomized controlled therapeutic trials are commonly used to make important treatment decisions. In the care of hepatitis C, this type of data is used widely by clinicians and patients to make the complex decision to embark on a long course of treatment that may be complicated by a variety of potentially significant side effects, may prove to be ineffective, and may be unnecessary. For these reasons, it is desirable for practitioners to know not only the efficacy of combination therapy as demonstrated in phase III registration trials, but also its effectiveness: the outcome of treatment in patients like their own receiving ordinary clinical care. Aspects of this question have been examined by a Canadian,[5] an Australian,[6] and three European[7-9] groups, all of whom found the effectiveness of combination therapy to be comparable to its proven efficacy. A United States group treating predominantly Caucasian patients in a Midwestern university hospital setting had the same results.[10] Studies have shown, however, that African American and Hispanic patients infected with hepatitis C virus (HCV) are less likely to have a sustained viral response (SVR) to treatment than non-Hispanic whites.[11-15] We assess the effectiveness of hepatitis C therapy in a mixed United States urban population, including large numbers of ethnic minority patients who were underrepresented in HCV treatment registration trials, and qualitatively compare our results to the predicted efficacy of therapy based on published studies. It is our hypothesis that results of hepatitis C therapy in urban minority patients treated in an ordinary clinical practice setting (effectiveness) are inferior to those reported from registration trials for reasons of ethnic differences, poor toleration, inadequate adherence, and other intangible factors.

Materials and Methods

Between April 2001 and June 2006, we evaluated 2,370 outpatients with hepatitis C for possible therapy with combination pegylated interferon and ribavirin. Patients were seen in the private faculty practice of the Albert Einstein College of Medicine or the attending-supervised Liver Clinic at Montefiore Medical Center, Bronx, New York. Evaluation and treatment of all patients was under the supervision of one physician with over 15 years of experience as a full-time clinical hepatologist in an academic medical center; general treatment requirements are listed in Table 2. The decision to treat any individual patient was made by the supervising physician in accordance with the general requirements for treatment (Table

Table 2. General Treatment Requirements

1. Consent to treatment
2. Ability to adhere to therapy with the support of the clinical staff in opinion of supervising physician
3. No intrauterine pregnancy and use of effective birth control
4. No end-stage renal disease or expectation of need for hemodialysis (ribavirin dose adjusted for increased serum Cr)
5. No history of renal transplantation
6. No clinical hemoglobinopathy
7. No symptomatic pulmonary disease
8. No symptomatic cardiovascular disease
9. No active autoimmune or other inflammatory disease
10. Six months of abstinence from active substance abuse
11. Adequately treated psychiatric disease when present by history or clinical evaluation
12. Platelet count ' 35,000 per μL (splenic embolization as necessary)
13. Reasonable expectation of benefit from treatment in opinion of supervising physician based on age, comprehensive medical evaluation

2) and under conditions of everyday clinical practice. All patients meeting these requirements (and no others) were offered therapy. Medication doses, with the exception of doses of pegylated interferon-α-2a, which was prescribed in the standard amount of 180 μg/week, were adjusted for weight in all patients according to treatment guidelines. Initial doses were only reduced if growth factors were ineffective in maintaining blood counts above minimally acceptable levels as follows, and patients had intractable symptomatic anemia requiring multiple transfusions (hemoglobin $<$10 g/dL), an absolute granulocyte count of less than 500 per μL, or a platelet count of less than 20,000 per μL. Patients with genotype 1 infection were treated for a total of 48 weeks, as were patients with genotype 3 infection with greater than Metavir stage 2 fibrosis and cirrhotic patients with genotype 2 infection. Noncirrhotic patients with genotype 2 infection and patients with genotype 3 infection with less than or equal to Metavir stage 2 fibrosis were treated for a total of 24 weeks. Patients were given appointments to be seen at least monthly, but more often if necessary to treat side effects, and were followed for an additional 24 weeks after completion of therapy to determine the presence or absence of SVR. Appointments were given on demand, not according to a rigid weekly or monthly schedule. Patients were questioned regarding adherence; treatment was discontinued if, in the judgment of the supervising physician, a patient had missed two or more weekly interferon injections or consistently missed ribavirin doses or altered the prescribed regimen. Every effort was made to help patients complete treatment, including psychosocial support when deemed appropriate and palliation of side effects with selective serotonin reuptake inhibitors, methylphenidate, nonsteroidal anti-inflammatory drugs, gabapentin and other medications. Comprehensive clinical and demographic data were collected retrospectively by chart review at the commencement of the study in 2005 and prospectively thereafter; data were recorded in an Excel (Microsoft, Seattle, WA) database by a single data manager. Ethnicity data were recorded according to hospital policy on a voluntary basis when patients registered for initial outpatient visits; the category "other" includes patients who identified themselves as Asian, of Pacific Rim origin, or declined to declare ethnicity.

Data concerning all treatment-naïve outpatients with hepatitis C were retrieved from the database. Patients with human immunodeficiency virus (HIV) infection and those who were not given medication because they did not meet general requirements for treatment were excluded from the ITT analysis (effectiveness). Results of the effectiveness analysis were then compared with similar analyses performed in published trials (efficacy).[1-3] Data were stratified for faculty practice (predominantly managed care) and liver clinic (predominantly Medicaid) patients. This project was approved by the Institutional Review Board of the Montefiore Medical Center.

Statistical Analysis. Following completion of data collection, the Excel database was exported into SPSS 16.0 for Windows (SPSS Inc, Chicago, IL). Data for all patients who received one or more doses of medication were included in the ITT analysis, while data for all patients completing therapy and returning for evaluation 6 months after treatment completion were included in the per-protocol analysis. Quantitative baseline descriptive variables are expressed as means with standard error of the mean. Qualitative variables are expressed as absolute numbers and proportions. The χ^2 statistic was used to compare categorical variables while continuous variables were compared using the Mann-Whitney U test. A two-sided P value of <0.05 was considered statistically significant. Statistical analysis of compared effectiveness and efficacy data was not possible because registration trial raw data is not in the public domain.

Results

Eligibility for Therapy. Of 2,370 patients with hepatitis C evaluated during the period under review, 2,134 were treatment-naïve. Clinical data from 1,879 patients were excluded from analysis: 478 patients with HIV infection and 1,401 patients who in the opinion of the supervising physician did not meet general treatment requirements (Table 2) and did not take medications (Fig. 1). The reasons that individuals did not meet general treatment requirements could not be accurately determined in every instance, because in some cases documentation of the supervising physician's decision by liver clinic fellows was inconsistent and possibly incomplete,

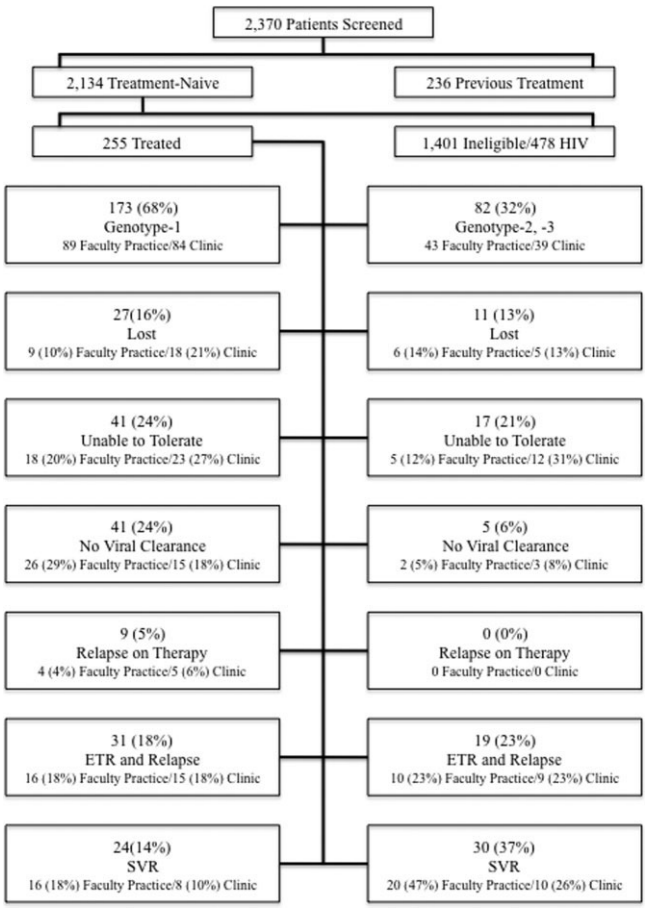

Fig. 1. Results of patient evaluation and treatment. Left column: genotype 1 patients. Right column: genotype 2 and 3 patients.

and therefore these results are not reported here. Many persons failed to return for follow-up before completion of preliminary testing. The majority of ineligible patients had multiple contraindications to therapy with interferon and ribavirin. Ultimately, 255 patients, 10.8% of those referred for evaluation and 15.4% of the HIV-negative treatment-naïve group, received at least one dose of both pegylated interferon and ribavirin. This ITT cohort included 173 (68%) persons with genotype 1 and 82 (32%) persons with genotype 2 or 3 virus infection.

Demographic and Clinical Features of Treated Patients. Demographic and clinical features of ITT patients are shown in Table 3. There were more males (152) than females (103) in this group. The mean weight of patients was 84.4 ± 18.9 kg, and the mean serum alanine aminotransferase level prior to therapy was 98.0 ± 97.0 U/L. Likely sources of infection included percutaneous drug use in 169 (66%) patients, transfusion in 37 (15%) patients, and other or undefined in 49 (19%) patients. Seventy-three individuals (29%) had cirrhosis. The majority of study patients were Hispanic (149), followed by African American (52), other (31), and Caucasian (23). Eighty-nine percent of treated Liver-Clinic patients were minorities, versus only 70% of faculty practice patients ($P = 0.18$).

Response to Therapy. Outcomes are from the ITT analysis unless specifically noted to be from the per-protocol analysis.

One hundred thirty-one patients (51%) completed treatment and returned 6 months later for follow-up laboratory testing: 53% of those with genotype 1 infection who began therapy and 49% of those with genotype 2 or 3 infection who began therapy. Sixty-six patients (26%) did not present for followup after initiation of treatment or lost insurance and were unable to obtain medications, and 58 individuals (23%) discontinued therapy prematurely because of side effects.

SVR was achieved in 54 patients (ITT: 14% genotype 1, 37% genotypes 2/3 [$P < 0.001$]; per-protocol: 23% genotype 1, 61% genotypes 2/3 [$P < 0.001$]) (Table 4, Fig. 1). Nine patients (12%) with histological cirrhosis or cirrhosis on the basis of cross-sectional imaging with associated clinical evidence of portal hypertension had an SVR, while 17 (23%) did not respond to therapy (primary nonresponse) and 40 (55%) were unable to complete therapy. Of those individuals achieving SVR, 63% were Hispanic, 8% were African American, and 17% were Caucasian (Table 5). Primary nonresponse was observed significantly more often in persons infected with genotype 1 virus (24%) than in those with genotype 2 or

Table 3. Demographic and Clinical Features of the ITT Cohort

	Genotype 1	Genotype 2/3	P Value	Faculty Practice	Liver Clinic	*P* Value
Male/Female (%)	104/69 (60/40)	48/34 (59/41)	0.81	79/53 (60/40)	73/50 (59/41)	0.93
Mean age, years	50.4 ± 8.5	50.6 ± 9.0	0.86	50.6 ± 8.3	50.3 ± 9.0	0.79
Mean weight, kg	83.9 ± 19.7	85.6 ± 16.9	0.55	85.0 ± 18.3	83.7 ± 19.6	0.61
Hispanic, n (%)	97 (56%)	52 (63%)	0.24	62 (47%)	87 (71%)	>0.01
African American, n (%)	46 (27%)	6 (7%)	>0.01	30 (23%)	22 (18%)	0.06
Caucasian, n (%)	16 (9%)	7 (9%)	0.85	15 (11%)	8 (7%)	0.18
Other ethnicity, n (%)	14 (8%)	17 (21%)	0.33	25 (19%)	6 (4%)	0.17
Mean baseline alanine aminotransferase, U/L	87 ± 66.6	120 ± 139	0.01	109 ± 105	86 ± 86	0.06

Table 4. Treatment Outcomes (ITT Cohort) Divided by Genotype and Practice Setting

	Genotype 1	Genotype 2/3	P Value	Faculty Practice	Liver Clinic	*P* Value
SVR	24 (14%)	30 (37%)	<0.001	36 (27%)	18 (15%)	0.01
Unable to tolerate	41 (24%)	17 (21%)	0.819	23 (17%)	35 (28%)	0.04
No response	41 (24%)	5 (6%)	0.001	28 (21%)	18 (15%)	0.17
Withdrawn	41 (24%)	25 (30%)	0.38	31 (23%)	35 (28%)	0.56
Relapse on therapy	9 (5%)	0 (0%)	0.29	4 (3%)	5 (4%)	0.97
Relapse after therapy	17 (10%)	5 (6%)	0.24	10 (8%)	12 (10%)	0.66

Values are presented as the number of patients (%).

3 virus infection (6%; $P = 0.001$). There was no significant difference in treatment toleration based on genotype ($P = 0.8$) (Table 4).

The proportion of treated patients with genotype 1 virus infection was similar in both practice settings (faculty practice, 67%; liver clinic, 68%) (Fig. 1). The SVR (ITT) was significantly higher in faculty practice patients (27%) than in liver clinic patients (15%) ($P = 0.01$), however, this was not the case when only patients who completed therapy were considered; the per-protocol SVR rate was 46% in the faculty practice and 34% in the liver clinic ($P = 0.20$). Liver clinic patients were significantly more likely than faculty practice patients to stop treatment because of side effects (28% versus 17%; [$P = 0.04$]). More faculty practice than liver clinic patients had a primary nonresponse to therapy (21 versus 15% [$P = 0.17$]), although the difference was not significant.

Discussion

HCV infection is particularly common in the United States urban minority populace.[18] Published reports suggest that therapy is less effective in such individuals than in persons enrolled in registration trials, which include mostly patients of western European ancestry.[11-16] This hypothesis is confirmed by our data: the overall SVR rate in our patients was one-third to less than one-half that predicted on the basis of registration trials. This discrepancy does not appear to be accounted for by other factors, including patient demographics and features of infection (Table 1). The mean age of our patients was approximately 7 years older than that of patients in the registration trials. There appears to be no appreciable difference in weight, mean baseline alanine aminotransferase level, distribution of infection genotype, or percentage with cirrhosis between members of our cohort and those of the efficacy cohorts, with the exception that more than twice as many of our patients had cirrhosis than did those studied by Fried et al.[1] We are unable to report the mean baseline viral load of our patients because of variations in testing methodologies used to evaluate them in the practice settings.

Ethnic background is known to influence HCV kinetics during treatment and SVR rates after standard therapies. SVR rates in African American patients reported by authors of several trials using a variety of methodologies are 19%-28% for individuals with genotype 1 infection and 57% for individuals with genotype 2 or 3 infection.[12,13,19-21] African American patients treated at our center had roughly comparable outcomes (Table 5): somewhat worse in patients with genotype 1 disease and somewhat better in patients with genotype 2 or 3 disease. In contrast, our Hispanic patients had notably worse SVR rates than those reported by other investigators regardless of infection genotype (Table 5). Published SVR rates in Hispanic patients are 34%-47% for individuals with genotype 1 infection and 66% for individuals with genotype 2 or 3 infection;[16,22] some authors have suggested that poor therapeutic response in Hispanic patients is due to higher than normal rates of treatment discontinuation.[23] In addition to these results, we found that the

Table 5. Outcomes Based on Ethnicity

Group	SVR	Unable to Tolerate	No Response	Withdrawn	Relapsed on Therapy	Relapsed After Therapy
Genotype 1						
Hispanic (n = 92)	10.9%	31.5%	14.1%	22.8%	17.4%	3.3%
African American (n = 51)	13.7%	7.8%	41.2%	7.9%	19.6%	9.8%
Caucasian (n = 16)	25.0%	31.2%	18.8%	6.2%	18.8%	0.0%
Genotypes 2/3						
Hispanic (n = 36)	30.6%	25.0%	5.6%	8.2%	30.6%	0.0%
African American (n = 6)	66.7%	16.7%	0.0%	16.7%	0.0%	0.0%
Caucasian (n = 16)	33.3%	33.3%	0.0%	16.7%	16.7%	0.0%

SVR rate in our Caucasian study patients was much less than predicted, even when measured on a per-protocol basis.

These data imply that treatment of urban patients with hepatitis C, regardless of ethnic background, may be adversely affected by social factors and factors related to the care environment. We evaluated the effectiveness of therapy in patients treated in two care environments depending on insurance coverage, and by implication, socioeconomic status, but according to the same widely used treatment algorithm. We found that liver clinic patients were significantly more likely than faculty practice patients to discontinue therapy because of side effects, and that individuals insured by managed care companies had a significantly higher SVR rate based on ITT analysis. This difference in SVR rate, however, disappeared when outcome was evaluated using a per-protocol analysis. Importantly, almost all patients treated in this urban medical center, with the exception of African Americans, had substantially worse than predicted outcomes regardless of care environment.

Conceivably, the reason for the poor SVR rate in our patients was suboptimal clinical care. In this regard, clinical outcomes were unaffected by whether or not patients primarily were treated directly by the supervising attending physician or by trainees. Patients receiving care in both the attending-supervised liver clinic and the private faculty practice had the same liberal access to treating physicians and their therapy was similarly supported by ancillary services, for example psychiatric consultation. These resources were felt to equal or exceed in quality and availability those accessible to non–hospital-based private practice patients. In addition, the same aggressive approach to side effect management was used in both practice settings, and dose reductions were avoided unless drug side effects could be managed in no other way. In contrast, dose reductions were mandated by protocol in efficacy trials. Although our patients may have been less adherent to therapy than individuals enrolled in efficacy trials, any person suspected on the basis of history or laboratory test results of consistently missing medication doses or who consistently missed follow-up appointments had treatment discontinued by the supervising physician. The remaining patients still had a poor SVR rate as determined by per-protocol analysis. More vigorous and accurate monitoring of adherence particularly in Hispanic patients, if possible, might have improved per-protocol outcomes.

In our opinion, the most disturbing finding of this study is the very low therapeutic yield in terms of SVR rate of referrals for evaluation of hepatitis C. Only 3.3% of 1,656 treatment-naïve, HIV antibody–negative individuals who presented for possible therapy ultimately completed evaluation and treatment, and achieved SVR. A major reason for this result is that 84.6% of our patients did not meet the general treatment requirements, which were based on widely used criteria to determine eligibility for HCV therapy. (We are studying why urban patients often fail to meet treatment eligibility requirements and also the outcomes of treatment denial.) Furthermore, 26% of patients who might have been treated were unable to obtain medicine or ultimately failed to keep follow-up appointments. Another 23% of patients selected for therapy stopped taking medicines because of side effects. Overall, only 51% of our ITT patients completed treatment and follow-up as compared with 73%-97% of individuals in efficacy trials. These data justify the highly restrictive selection of patients for randomization in registration trials, but also emphasize the differences between such trials and the real-world practice setting.

On the basis of all our findings, current hepatitis C therapies may sometimes be unavailable to, inappropriate for, and ineffective in United States urban patients. Real-world evaluation of patients similar to ours should be informed not only by efficacy trials with relatively high SVR rates, but also by effectiveness results of this kind. Better therapeutic strategies, drug regimens, and insurance coverage are essential to improve our ability to successfully treat hepatitis C in urban settings with a high prevalence of this disease and, by implication, related morbidity and mortality.

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