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The Influence of Abacavir and Other Antiretroviral Agents on Virologic Response to Hepatitis C Virus Therapy Among Antiretroviral-Treated HIV-Infected Patients

Valerianna K. Amorosa[1,2], **Jihad Slim**[3], **Karam Mounzer**[4], **Christopher Bruno**[5], **Margaret Hoffman-Terry**[6], **Zachariah Dorey-Stein**[1], **Thomas Ferrara**[2], **Jay R. Kostman**[1], and **Vincent Lo Re III**[1,2,7,8]

[1]Division of Infectious Diseases, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA

[2]Infectious Diseases Section, Philadelphia Veterans Affairs Medical Center, Philadelphia, PA

[3]Division of Infectious Diseases, St. Michael's Hospital, Newark, NJ

[4]Jonathan Lax Treatment Center, Philadelphia, PA

[5]Division of Infectious Diseases, Drexel University School of Medicine, Philadelphia, PA

[6]Division of Infectious Diseases, Lehigh Valley Hospital, Allentown, PA

[7]Department of Biostatistics and Epidemiology and Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, PA

[8]Center for Education and Research on Therapeutics, University of Pennsylvania School of Medicine, Philadelphia, PA

Abstract

Background—It remains unclear if certain antiretroviral medications, particularly abacavir, compromise response to hepatitis C virus (HCV) therapy. Such data can inform selection of appropriate antiretrovirals in HIV/HCV-coinfected patients.

Objectives—To determine if use of abacavir, as well as other antiretrovirals, was associated with reduced response to pegylated (PEG) interferon plus ribavirin.

Methods—A cohort study was performed among antiretroviral-treated HIV/HCV patients initiating PEG-interferon plus ribavirin between January 2001 and June 2007 at 6 U.S. sites. Abacavir and other antiretrovirals represented exposures of interest. Study outcomes included: 1) early virologic

Address Correspondence to: V. Lo Re III, M.D., M.S.C.E., Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, 809 Blockley Hall, 423 Guardian Drive, Philadelphia, PA 19104-6021, vincentl@mail.med.upenn.edu, Tel: 215-573-5964; Fax: 215-349-5111.

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response (≥2 log IU/mL decrease in HCV viral load at 12 weeks), and 2) sustained virologic response (undetectable HCV viral load 24 weeks after treatment discontinuation).

Results—Among 212 antiretroviral-treated patients, 74 (35%) received abacavir. For genotype 1 and 4 patients, no differences were observed between abacavir users and non-users in early virologic response (26 [40%] versus 53 [44%]; adjusted OR, 1.00; 95% CI, 0.50 – 2.00) or sustained virologic response (8 [13%] versus 13 [12%]; adjusted OR, 1.34; 95% CI, 0.50 – 3.62). Among genotype 2 and 3 patients, rates of early virologic response (7 [78%] versus 16 [89%]; OR, 0.44; 95% CI, 0.05 – 3.76) and sustained virologic response (3 [33%] versus 8 [44%]; OR, 0.63; 95% CI, 0.12 – 3.32) were also similar between abacavir users and non-users. No association was found between other antiretrovirals and lack of early or sustained response.

Conclusions—Use of abacavir or other antiretroviral medications was not associated with reduced early or sustained virologic response rates.

Keywords

hepatitis C; HCV therapy; abacavir; antiretroviral therapy; virologic response

INTRODUCTION

Liver disease due to chronic hepatitis C virus (HCV) infection is a major cause of morbidity and mortality among HIV-infected patients in the developed world [1]. HCV therapy with 48 weeks of combination pegylated (PEG) interferon plus ribavirin is the current standard intervention that can cure chronic HCV [2–4] and can reduce the risk of liver-related complications [5–8]. Although a number of factors have been shown to affect virologic response to HCV therapy among coinfected patients, notably HCV genotype, baseline HCV viral load, dosage of antiviral therapy, and adherence [2–4,9,10], the impact of antiretroviral medications on early and sustained virologic response remains unknown.

Existing studies examining the association between antiretroviral medications and HCV virologic response have focused mainly on the guanosine analogue abacavir [11–14], which has been hypothesized to compete intracellularly with ribavirin, another guanosine analogue, for enzymes involved in ribavirin's phosphorylation, interfering with this drug's antiviral effect [14]. However, these studies included only European subjects, included few subjects on abacavir, often did not restrict analyses to patients receiving antiretroviral therapy (ART), and reported conflicting results. As a result, it remains unclear if abacavir is associated with reduced HCV virologic response. Furthermore, the effect of other antiretroviral medications on HCV treatment response has not been well evaluated [15]. Since antiretroviral agents may possibly affect the chances of achieving virologic response to combination HCV therapy in coinfected patients, the results of such studies can help inform decisions about medication choices in this population.

To address this issue, we determined if use of abacavir was associated with reduced early and sustained virologic response among antiretroviral-treated HIV/HCV-coinfected patients who received PEG-interferon plus ribavirin in clinical practice. In secondary analyses, we examined whether other antiretroviral medications reduced HCV treatment response.

METHODS

Study Design and Subjects

A retrospective cohort study was conducted among antiretroviral-treated HIV/HCV-coinfected patients initiating HCV therapy with PEG-interferon alfa-2a or −2b plus ribavirin between January 1, 2001 and June 30, 2008 at six coinfection clinics (Penn Presbyterian Medical Center,

Philadelphia, PA; Philadelphia Veterans Affairs (VA) Medical Center, Philadelphia, PA; Jonathan Lax Treatment Center, Philadelphia, PA; Hahnemann Hospital, Philadelphia, PA; St. Michael's Hospital, Newark, NJ; Lehigh Valley Hospital, Allentown, PA). Patients were eligible for inclusion if they: 1) had detectable HCV RNA levels prior to HCV therapy, 2) received an initial course of PEG-interferon plus ribavirin, 3) had evidence of HIV infection, and 4) were receiving ART (defined as 3 antiretroviral medications from at least two different drug classes [16]) at the start of HCV therapy. Patients who were treated with PEG-interferon monotherapy or who did not receive ART were excluded.

Potentially eligible subjects were identified by reviewing lists of coinfected patients who received PEG-interferon plus ribavirin at the sites during the observation period. All eligible patients were included. The study was approved by the Institutional Review Boards of the University of Pennsylvania, Philadelphia VA Medical Center, Jonathan Lax Treatment Center, Drexel University, St. Michael's Hospital, and Lehigh Valley Hospital.

Main Study Outcomes

The main study outcome was early virologic response, defined as a decrease in HCV RNA of ≥2 log IU/mL at 12 weeks of HCV therapy [17–19]. Patients who prematurely withdrew from HCV therapy prior to 12 weeks of treatment were considered not to have had early virologic response.

Secondary outcomes included: 1) change from baseline of HCV viral load at 12 weeks of HCV therapy; 2) end of treatment response, defined as a negative HCV viral load result at 48 weeks of HCV therapy; and 3) sustained virologic response, defined as a negative HCV viral load result obtained at least 24 weeks after cessation of HCV therapy [17–19]. Patients who prematurely withdrew from HCV therapy prior to 48 weeks of treatment were considered not to have had end-of-treatment or sustained virologic responses, unless they had a documented negative HCV viral load at least 24 weeks after treatment discontinuation.

Data Collection

Data were abstracted from patients' charts and recorded onto structured data collection forms. Baseline demographic (age; sex; race; ethnicity; height; body weight), clinical (risk factors for HIV transmission; diabetes mellitus [based on physician's diagnosis and/or use of anti-diabetic medications]; medication use and dosages; HCV treatment withdrawal and reason), and laboratory data (CD4 T lymphocyte count; HIV viral load [Versant HIV-1 RNA 3.0 Assay, Bayer Diagnostics: detection limit of 75 copies/mL]; hepatitis B surface antigen [Elecsys 2010, Roche Diagnostics, Indianapolis, IN]; HCV genotype [Invader HCV Assay 1.0; Third Wave Technologies; Madison, WI]; quantitative HCV viral load [Cobas Amplicor HCV Monitor, Roche Diagnostics, Branchburg, NJ: detection limit of <600 IU/mL; Cobas TaqMan, Roche Diagnostics, Pleasanton, CA: detection limit of <10 IU/mL; Versant HCV RNA 3.0 Quantitative Assay, Bayer Diagnostics, Tarrytown, NY: detection limit of <615 IU/mL, according to the available technique at each site]; and liver biopsy results [if available]) were abstracted from dates closest but prior to the date of HCV treatment initiation. Liver fibrosis staging was assessed via METAVIR score in all patients for whom a liver biopsy had been performed prior to initiating HCV therapy [20]. Advanced fibrosis was defined by the presence of bridging fibrosis or cirrhosis (i.e., METAVIR stages 3 or 4). A 10% random chart re-abstraction was performed to validate the accuracy of data collection.

PEG-interferon alfa-2a dosages were categorized as 180 μg/week or less, while alfa-2b dosages were categorized as <1.1, 1.2–1.3, or ≥1.4 μg/kg/wk to allow for clinician rounding of patient body weight. Ribavirin was categorized as at or above recommended levels as follows: genotypes 1 or 4, 1,000 mg/day for patients ≤75 kg and 1,200 mg/day for patients >75 kg;

genotypes 2 or 3, 800 mg/day, irrespective of weight [18,21]. Subjects' progress notes were examined for PEG-interferon and ribavirin dose reductions during therapy. Those who were not prescribed recommended dosages either at baseline or during follow-up were classified as having received suboptimal dosages of these medications.

Statistical Analysis

Median declines in log HCV RNA between baseline and week 12 were compared between abacavir users and non-users with Wilcoxon rank-sum tests. Early and sustained virologic response was compared between abacavir users and non-users with chi-square tests. Multivariable logistic regression evaluated the association (odds ratios [ORs]; 95% confidence intervals [CIs]) between abacavir use and early virologic response, end-of-treatment response, and sustained virologic response. Potential confounders evaluated included age; sex; race; body mass index; site; HIV/HCV risk factors; baseline CD4 count; baseline HIV viral load; degree of liver fibrosis; and zidovudine use. We assessed the impact of confounding by examining the change in ORs for each comparison as potential confounders were included in the model [22]. Analyses were stratified by HCV genotype. We also performed analyses stratified by site, but results were unchanged (data not shown). Additionally, given the importance of weight-based dosing on virologic response, we evaluated outcomes among patients who maintained weight-based PEG-interferon and ribavirin doses throughout their treatment course. We also examined whether use of other antiretrovirals was associated with lack of early or sustained virologic response.

Assuming a type 1 error rate of 0.05, a 2:1 ratio of unexposed:exposed, an overall early virologic response rate of 55% [23], and that 35% of subjects would receive abacavir, a sample size of 180 patients was targeted to provide 80% power to detect a 20% difference in early virologic response rate between abacavir users and non-users. All data were analyzed using STATA 10.1 (STATA Corp, College Station, TX).

RESULTS

Patient Characteristics

A total of 265 coinfected patients were prescribed PEG-interferon plus ribavirin during the observation period. Of these, 51 patients were not prescribed ART at the time HCV treatment was initiated, and 2 had no baseline HCV viral load result (Figure 1). The final sample included 212 subjects (74 [35%] received abacavir). Patients prescribed abacavir more commonly were female, African-American, and had a history of injection drug use. There were no significant differences by abacavir use with regard to age, ethnicity, body mass index, diabetes mellitus, zidovudine use, HCV genotype, CD4 cell count, HIV viral load, and HCV viral load (Table 1).

Thirteen patients completed 12 weeks of HCV therapy but were still on treatment at the time of analysis. As such, they were not included in analyses evaluating end-of-treatment or sustained virologic responses.

A total of 121 (57%) patients prematurely withdrew from therapy. Withdrawal rates were higher among patients who received abacavir (49 [66%] versus 70 [51%]; p=0.03). Comparing abacavir users to non-users, the most common reasons for HCV treatment discontinuation were lack of virologic response (19 [26%] versus 33 [24%]; p=0.8), influenza-like symptoms (7 [9%] versus 8 [6%]; p=0.4), and depression (6 [8%] versus 9 [7%]; p=0.7) (Figure 1).

Medication Dosing

One hundred fifty-eight subjects (75%) were treated with PEG-interferon alfa-2a, 149 (94%) of whom initiated the recommended dose of 180 μg/week. An additional 5 patients had their PEG-interferon alfa-2a dose decreased during follow-up so that overall 14 (9%) received a suboptimal PEG-interferon alfa-2a dose. Fifty-four subjects (25%) were treated with PEG-interferon alfa-2b, 50 (93%) of whom started on at least 1.4 μg/kg/wk. The remaining 4 (7%) started on at least 1.2 μg/kg/wk. No subjects had peg-interferon alfa-2b dose reductions during follow-up. Thus, a total of 18 subjects received suboptimal PEG-interferon dosages during their HCV treatment.

Among subjects with genotype 1 or 4, 63 (34%) were prescribed a reduced ribavirin dosage. An additional 5 patients had their ribavirin dose decreased during follow-up so that overall 68 (37%) received a suboptimal ribavirin dosage. All subjects with genotypes 2 or 3 started and remained on at least 800 mg of ribavirin.

HCV viral load declines at 12 weeks

Overall, the median decline in HCV viral load at 12 weeks were similar for patients prescribed abacavir compared to those not receiving this medication (1.15 versus 1.94 log IU/mL; p=0.5). Among patients with HCV genotypes 1 or 4, median viral load declines at 12 weeks were similar between abacavir users and non-users (0.93 versus 1.50 log IU/mL; p=0.8). For patients with HCV genotypes 2 or 3, median viral load declines were smaller for those who received abacavir (3.60 versus 5.93 log IU/mL; p=0.06).

When we performed a sub-analysis excluding the 68 patients who received suboptimal ribavirin doses during the initial 12 weeks of HCV therapy, viral load declines were not statistically different by abacavir use (1.80 versus 2.30 log IU/mL; p=0.7). Among subjects with genotypes 1 or 4 who received optimal ribavirin doses over the initial 12 weeks, median declines in HCV viral load at 12 weeks were similar among abacavir-users and non-users (1.15 versus 1.56 log IU/mL; p=0.6).

Early virologic response

A total of 102 patients (48%; 79 genotype 1 or 4; 23 genotype 2 or 3) experienced early virologic response. Overall, early virologic response rates were similar between abacavir users and non-users overall (33 [45%] versus 69 [50%]; p=0.5), among patients with genotypes 1 or 4 (26 [40%] versus 53 [44%]; p=0.5), and for subjects with genotypes 2 or 3 (7 [78%] versus 16 [89%]; p=0.4). After controlling for age, sex, race, fibrosis stage, methadone use, zidovudine use, baseline CD4 count, and baseline HCV viral load, abacavir use was not associated with a reduced risk of early virologic response overall (adjusted OR, 0.99; 95% CI, 0.53 – 1.84) or for genotype 1 or 4 patients (adjusted OR, 1.00; 95% CI, 0.50 – 2.00). Sample sizes for genotypes 2 or 3 were insufficient for multivariable analyses. In sub-analyses performed among patients who maintained optimal ribavirin dosages, abacavir remained not associated with a reduced risk of early virologic response (Table 2).

End-of-treatment response

Fifty-eight (27%) patients had an end-of-treatment response (14 [19%] for abacavir users versus 44 [32%] for non-users; p = 0.05). The end-of-treatment response rate was lower, but not statistically significantly at conventional levels, among abacavir users with HCV genotypes 1 and 4 (16% versus and 27%; p=0.1) and genotypes 2 and 3 (44% versus 63%; p=0.4). After adjustment for age, sex, race, fibrosis stage, methadone use, zidovudine use, baseline CD4 count, and baseline HCV viral load, there remained no significant association between abacavir use and end-of-treatment response among genotype 1 and 4 infected subjects (adjusted OR,

1.08; 95% CI, 0.41 – 2.55). Sample sizes for genotypes 2 or 3 were insufficient for multivariable analyses.

Sustained virologic response

Among 199 patients who had completed their HCV treatment course at the time of analysis, 32 (16%) achieved sustained virologic response (21/173 [12%] with genotype 1 or 4; 11/26 [42%] with genotype 2 or 3). The rates of sustained virologic response were not significantly different between abacavir users and non-users overall or among genotype 1 and 4 patients (Table 3).

Other antiretroviral agents and virologic response

The nucleoside analogues zidovudine, tenofovir, lamivudine, and emtricitabine were not associated with reduced 12-week HCV viral load declines, lack of early virologic response, or lack of sustained virologic response (Table 4). Use of non-nucleoside reverse transcriptase inhibitor or protease inhibitor antiretroviral classes was also not associated with these outcomes.

DISCUSSION

In this study, use of abacavir was not associated with reduced early or sustained virologic response, either overall or by HCV genotype. Among genotype 1- and 4-infected patients, median declines in HCV viral load over the initial 12 weeks of PEG-interferon plus ribavirin therapy were similar between abacavir users and non-users. In addition, in analyses performed among patients prescribed weight-based ribavirin dosages, no differences were observed in median HCV viral load declines at 12 weeks between abacavir users and non-users. In contrast, median declines in HCV viral load at 12 weeks for genotype 2 and 3 patients, all of whom received 800 mg/day of ribavirin, were substantially smaller among patients on abacavir, though there were no significant differences in early or sustained virologic response. Further, no other antiretroviral medications were associated with lack of virologic response.

Our results are consistent with a prior cohort study of 244 coinfected patients treated with PEG-interferon plus ribavirin at four hospitals in Spain (85% on ART; 49 on abacavir; 97% prescribed ≥13.2 mg/kg/day of ribavirin), which reported that patients receiving abacavir in the setting of weight-based ribavirin achieved similar sustained virologic response rates compared to non-users (46.2% versus 46.7%; OR, 1.03; 95% CI, 0.55 – 1.94) [13]. The results of these studies suggest that the putative competitive effect between abacavir and ribavirin can be overcome with optimal weight-based ribavirin dosages.

Our findings differed from several other studies examining the association between abacavir use and HCV virologic response. A retrospective analysis of 154 coinfected subjects (22 receiving abacavir) enrolled in the French National Agency for Research on AIDS and Viral Hepatitis (ANRS) HC02-Ribavic trial reported that abacavir use was an independent predictor of early virologic failure to combination HCV therapy (adjusted OR, 4.9; 95% CI, 1.5–16.1) [11]. However, all patients in this trial received 800 mg/day of ribavirin. In addition, a retrospective cohort study of 493 coinfected patients (78% on ART; 115 receiving abacavir) prescribed PEG-interferon plus ribavirin at 10 Spanish hospitals also suggested that abacavir use reduced sustained virologic response rates (adjusted OR, 2.22; 95% CI, 0.9 – 5.4), particularly in the setting of low (<2.3 μg/mL) ribavirin plasma levels measured at 4 weeks of treatment (adjusted OR, 7.63; 95% CI, 1.4 – 41.7) [14]. A second Spanish cohort study among 256 coinfected who received PEG-interferon plus ribavirin compared sustained virologic response rates between patients prescribed a nucleos(t)ide background consisting of abacavir plus lamivudine (70 patients) with tenofovir plus lamivudine or emtricitabine (186 patients)

[13]. Sustained virologic response rates were significantly lower in patients prescribed abacavir than tenofovir (20 [29%] versus 83 [45%]; adjusted OR, 2.6; 95% CI, 1.1 – 6.9) and particularly among those prescribed <13.2 mg/kg/day of ribavirin (3/15 [20%] versus 22/42 [52%]; p=0.03). Differences in ribavirin dosing and the study populations, which were exclusively European, might account for the disparate results between studies. Additionally, some studies were not restricted to subjects only receiving ART, which makes those results subject to confounding by indication [24].

We observed that the initial 12-week HCV viral load decline in patients infected with HCV genotypes 2 or 3 was substantially smaller among abacavir users. Since these patients were all prescribed non-weight-based ribavirin dosages (i.e., 800 mg/day), it is possible that abacavir may interfere with ribavirin's activity at these lower ribavirin dosages. The relatively small number of patients with genotypes 2 or 3 in this study limits our ability to draw definitive conclusions. Additional studies in coinfected patients with genotype 2 or 3 should be performed to examine if use of weight-based dosages of ribavirin can increase the viral load decline at 12 weeks.

Our analyses demonstrated that no other antiretroviral medications compromised early or sustained virologic responses to HCV therapy. In particular, our findings did not corroborate an earlier study reporting that use of ritonavir was associated with reduced early and sustained virologic response rates [25]. In addition, elevations in pre-treatment total bilirubin have been reported to increase the risk of early virologic failure (adjusted OR, 4.5; 95% CI, 1.5 – 13.4) [11]. Since the antiretroviral medication, atazanavir, can cause hyperbilirubinemia, use of this medication might reduce the risk of early virologic response. However, we found no association between atazanavir and HCV virologic non-response. Moreover, no other antiretroviral medication or classes were associated with lack of virologic response.

Our study had several limitations. First, the retrospective design of the study did not allow all potential confounders to be collected. Although a number of variables were evaluated and controlled for analytically, multivariable analyses may not entirely eliminate residual confounding from additional unmeasured factors, as is always true for all observational studies. In particular, we did not have information on the duration of HCV infection, since this was not routinely collected in medical records, and were unable to measure adherence to PEG-interferon and ribavirin therapy [10], as pharmacy refill data were not available at all sites. We therefore could not examine the relationship between these variables and response to HCV therapy.

Second, although this study drew patients from six sites, some secondary analyses had small sample sizes. There was also a high overall rate of HCV treatment discontinuation, which contributed to the low sustained virologic response rates observed in this study. These factors limited our ability to identify potentially important associations. Our results should be interpreted with caution since early virologic response was the primary outcome, and the main strength of ribavirin is in the prevention of relapse, which is mainly reflected by rates of sustained virologic response. As additional studies of similar design are reported, formal methods of meta-analysis could be used to combine results across studies and perhaps add to the precision of our findings.

Third, patients who received abacavir more frequently prematurely discontinued HCV therapy, and the most common reason for withdrawal was virologic non-response. This increased rate of HCV treatment discontinuation might have been due to abacavir interfering with the antiviral activity of ribavirin, ultimately resulting in virologic non-response and withdrawal from therapy.

Finally, the study only included patients from the United States, and these results may not be generalizable to coinfected patients in other areas.

In conclusion, our study found that use of abacavir as well as other antiretrovirals was not associated with a lack of early or sustained virologic response. Additional studies are needed to determine if weight-based dosages of ribavirin can enhance HCV viral load declines among genotype 2 and 3 abacavir users.

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V.K.A. and V.L.R. participated in the conception and design of the study. J.S., K.M., C.B., M.H.T., Z.D.S., T.F., and J.R.K. participated in data collection at each of the sites. V.K.A. and V.L.R. performed data cleaning and statistical analyses. V.K.A. and V.L.R. collaborated on initial drafts of the manuscript.

REFERENCES

1. Weber R, Sabin CA, Friis-Moller N, Reiss P, El-Sadr WM, Kirk O, Dabis F, Law MG, Pradier C, De Wit S, Akerlund B, Calvo G, Monforte A, Rickenbach M, Ledergerber B, Phillips AN, Lundgren JD. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. Arch Intern Med 2006;166:1632–1641. [PubMed: 16908797]
2. Carrat F, Bani-Sadr F, Pol S, Rosenthal E, Lunel-Fabiani F, Benzekri A, Morand P, Goujard C, Pialoux G, Piroth L, Salmon-Ceron D, Degott C, Cacoub P, Perronne C. Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial. Jama 2004;292:2839–2848. [PubMed: 15598915]
3. Chung RT, Andersen J, Volberding P, Robbins GK, Liu T, Sherman KE, Peters MG, Koziel MJ, Bhan AK, Alston B, Colquhoun D, Nevin T, Harb G, van der Horst C. Peginterferon Alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. N Engl J Med 2004;351:451–459. [PubMed: 15282352]
4. Torriani FJ, Rodriguez-Torres M, Rockstroh JK, Lissen E, Gonzalez-Garcia J, Lazzarin A, Carosi G, Sasadeusz J, Katlama C, Montaner J, Sette H Jr, Passe S, De Pamphilis J, Duff F, Schrenk UM, Dieterich DT. Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. N Engl J Med 2004;351:438–450. [PubMed: 15282351]
5. Barreiro P, Labarga P, Martin-Carbonero L, Amor A, Ruiz-Sancho A, Castellares C, Gonzalez-Lahoz J, Soriano V. Sustained virological response following HCV therapy is associated with non-progression of liver fibrosis in HCV/HIV-coinfected patients. Antivir Ther 2006;11:869–877. [PubMed: 17302249]
6. De Bona A, Galli L, Gallotta G, Guzzo A, Alagna L, Lazzarin A, Uberti-Foppa C. Rate of cirrhosis progression reduced in HIV/HCV co-infected non-responders to anti-HCV therapy. New Microbiol 2007;30:259–264. [PubMed: 17802905]
7. Labarga P, Soriano V, Vispo ME, Pinilla J, Martin-Carbonero L, Castellares C, Casado R, Maida I, Garcia-Gasco P, Barreiro P. Hepatotoxicity of antiretroviral drugs is reduced after successful treatment of chronic hepatitis C in HIV-infected patients. J Infect Dis 2007;196:670–676. [PubMed: 17674307]
8. Pineda JA, Garcia-Garcia JA, Aguilar-Guisado M, Rios-Villegas MJ, Ruiz-Morales J, Rivero A, del Valle J, Luque R, Rodriguez-Bano J, Gonzalez-Serrano M, Camacho A, Macias J, Grilo I, Gomez-Mateos JM. Clinical progression of hepatitis C virus-related chronic liver disease in human immunodeficiency virus-infected patients undergoing highly active antiretroviral therapy. Hepatology 2007;46:622–630. [PubMed: 17659577]
9. Backus, LI.; Boothroyd, DS.; Mole, LA. Digestive Disease Week (DDW 2009). Chicago: 2009 May 30. Predictors of sustained virologic response to pegylated interferon and ribavirin in a national cohort of male HIV/HCV-coinfected veterans in routine medical care. June 4 [Abstract M1785]

10. Lo Re V 3rd, Amorosa VK, Localio AR, O'Flynn R, Teal V, Dorey-Stein Z, Kostman JR, Gross R. Adherence to hepatitis C virus therapy and early virologic outcomes. Clin Infect Dis 2009;48:186–193. [PubMed: 19086908]
11. Bani-Sadr F, Denoeud L, Morand P, Lunel-Fabiani F, Pol S, Cacoub P, Perronne C, Carrat F. Early virologic failure in HIV-coinfected hepatitis C patients treated with the peginterferon-ribavirin combination: does abacavir play a role? J Acquir Immune Defic Syndr 2007;45:123–125. [PubMed: 17460476]
12. Laufer N, Laguno M, Perez I, Cifuentes C, Murillas J, Vidal F, Bonet L, Veloso S, Gatell JM, Mallolas J. Abacavir does not influence the rate of virological response in HIV-HCV-coinfected patients treated with pegylated interferon and weight-adjusted ribavirin. Antivir Ther 2008;13:953–957. [PubMed: 19043930]
13. Mira JA, Lopez-Cortes LF, Barreiro P, Tural C, Torres-Tortosa M, de Los Santos Gil I, Martin-Rico P, Rios-Villegas MJ, Hernandez-Burruezo JJ, Merino D, Lopez-Ruz MA, Rivero A, Munoz L, Gonzalez-Serrano M, Collado A, Macias J, Viciana P, Soriano V, Pineda JA. Efficacy of pegylated interferon plus ribavirin treatment in HIV/hepatitis C virus co-infected patients receiving abacavir plus lamivudine or tenofovir plus either lamivudine or emtricitabine as nucleoside analogue backbone. J Antimicrob Chemother 2008;62:1365–1373. [PubMed: 18854330]
14. Vispo E, Barreiro P, Pineda JA, Mira JA, Maida I, Martin-Carbonero L, Rodriguez-Novoa S, Santos I, Lopez-Cortes LF, Merino D, Rivero A, Soriano V. Low response to pegylated interferon plus ribavirin in HIV-infected patients with chronic hepatitis C treated with abacavir. Antivir Ther 2008;13:429–437. [PubMed: 18572756]
15. Pineda JA, Mira JA, Gil Ide L, Valera-Bestard B, Rivero A, Merino D, Giron-Gonzalez JA, Rios-Villegas MJ, Gonzalez-Serrano M, Collado A, Garcia-Garcia JA, Carrillo-Gomez R, Lopez-Cortes LF, Gomez-Mateos J. Influence of concomitant antiretroviral therapy on the rate of sustained virological response to pegylated interferon plus ribavirin in hepatitis C virus/HIV-coinfected patients. J Antimicrob Chemother 2007;60:1347–1354. [PubMed: 17938129]
16. Hammer SM, Eron JJ Jr, Reiss P, Schooley RT, Thompson MA, Walmsley S, Cahn P, Fischl MA, Gatell JM, Hirsch MS, Jacobsen DM, Montaner JS, Richman DD, Yeni PG, Volberding PA. Antiretroviral treatment of adult HIV infection: 2008 recommendations of the International AIDS Society-USA panel. Jama 2008;300:555–570. [PubMed: 18677028]
17. Soriano V, Puoti M, Sulkowski M, Cargnel A, Benhamou Y, Peters M, Mauss S, Brau N, Hatzakis A, Pol S, Rockstroh J. Care of patients coinfected with HIV and hepatitis C virus: 2007 updated recommendations from the HCV-HIV International Panel. AIDS 2007;21:1073–1089. [PubMed: 17502718]
18. Strader DB, Wright T, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C. Hepatology 2004;39:1147–1171. [PubMed: 15057920]
19. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 2009;49:1335–1374. [PubMed: 19330875]
20. Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. Hepatology 1996;24:289–293. [PubMed: 8690394]
21. Tien PC. Management and treatment of hepatitis C virus infection in HIV-infected adults: recommendations from the Veterans Affairs Hepatitis C Resource Center Program and National Hepatitis C Program Office. Am J Gastroenterol 2005;100:2338–2354. [PubMed: 16181388]
22. Rothman, KJ.; Greenland, S. Modern Epidemiology. Philadelphia: Lippincott Williams and Wilkins; 1998.
23. Chung, RT.; Umbleja, T.; Butt, AA.; Goodman, ZD.; Andersen, JW.; Koziel, MJ.; Alston, B.; Peters, M.; Sulkowski, M.; Sherman, KE. SLAM-C (ACTG 5178): Role of early virologic response in extended therapy with PEG-interferon and weight-based ribavirin in HCV/HIV coinfection; 16th Conference on Retroviruses and Opportunistic Infections (CROI); 2009 Feb 8–11. [Abstract 103LB]
24. Walker AM, Stampfer MJ. Observational studies of drug safety. Lancet 1996;348:489. [PubMed: 8757145]
25. Talwani, R.; Reisler, R.; Polk, C., et al. Ritonavir-boosted PI and not abacavir adversely impacts HCV treatment; 48th International Conference on Antimicrobial Agents and Chemotherapy (ICAAC 2008); October 25–28, 2008;

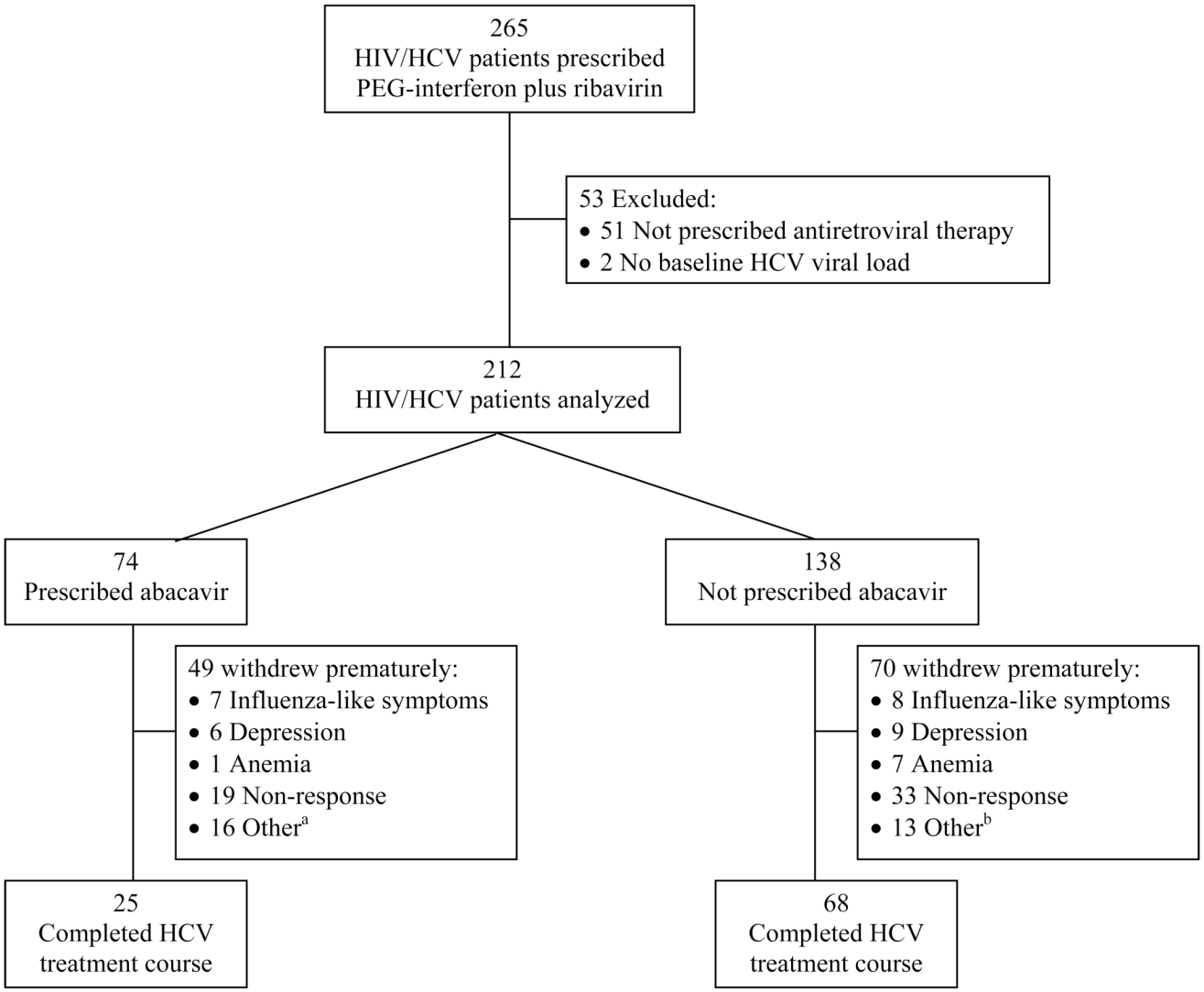

Figure 1. Selection of HIV/hepatitis C virus-coinfected patients for inclusion in the study

a Other includes: Death (hepatic failure [1]; motor vehicle accident [1]), relapse of substance abuse [3], rash [1], infection [1], loss to follow-up [4], non-adherence [2], and patient's request to withdraw [3].

b Other includes: Loss to follow-up [4], infection [2], non-adherence [2], incarceration [1], hyperbilirubinemia [1], hospitalization for unrelated condition [1], lactic acidosis [1], and thrombocytopenia [1].

Table 1

Patient characteristics, overall and by receipt of abacavir.

Characteristic	All Subjects (n=212)	Abacavir Non-users (n=138)	Abacavir Users (n=74)	P-Value
Median age (yrs, IQR)	48 (43–52)	48 (42–52)	49 (45–53)	0.1
Sex (no., %)				
Male	158 (75%)	112 (81%)	46 (62%)	0.002
Female	54 (25%)	26 (19%)	28 (38%)	
Race (no., %)				0.07*
African-American	121 (57%)	72 (52%)	49 (66%)	
White	82 (39%)	61 (44%)	21 (28%)	
Other	9 (4%)	5 (4%)	4 (5%)	
Hispanic (no., %)	33 (16%)	24 (17%)	9 (12%)	0.3
Median body mass index (kg/m^2, IQR)	26.4 (23.3–29.7)	26.7 (23.5–29.7)	25.7 (22.9–29.6)	0.4
HIV and/or HCV risk factors (no., %)‡				
Injection drug use	139 (66%)	84 (61%)	55 (74%)	0.05
Heterosexual sex	87 (41%)	57 (41%)	30 (41%)	0.9
MSM	22 (10%)	15 (11%)	7 (9%)	0.7
Intranasal cocaine use	11 (5%)	8 (6%)	3 (4%)	0.6*
Transfusion	8 (3%)	6 (4%)	2 (3%)	0.5*
Other	15 (7%)	9 (7%)	6 (8%)	0.7
Median CD4 cell count (cells/mm^3, IQR)	487 (355–675)	482 (340–674)	489 (380–676)	0.9
CD4 cell count <200 cells/mm^3 (no., %)	14 (7%)	9 (7%)	5 (7%)	0.9*
Median HIV RNA level (copies/mL, IQR)	75 (50–400)	75 (50–400)	93 (50–400)	0.6
HIV RNA <50 copies/mL (no., %)	152 (72%)	98 (71%)	54 (73%)	0.8
HCV genotype (no., %)				0.9
1 or 4	185 (87%)	120 (87%)	65 (88%)	
2 or 3	27 (13%)	18 (13%)	9 (12%)	
HCV viral load > 800,000 IU/mL (no., %)	137 (65%)	92 (67%)	45 (61%)	0.4
METAVIR stage 3–4 hepatic fibrosis (no., %)	69 (33%)	43 (31%)	26 (35%)	0.6
Chronic hepatitis B virus coinfection (no., %)	10 (5%)	9 (7%)	1 (1%)	0.09*
Active methadone use (no., %)	14 (7%)	10 (7%)	4 (5%)	0.6*
PEG-interferon (no., %)				0.2
alfa-2a	158 (75%)	98 (71%)	59 (79%)	

Characteristic	All Subjects (n=212)	Abacavir Non-users (n=138)	Abacavir Users (n=74)	P-Value
alfa-2b	54 (25%)	40 (29%)	15 (21%)	
Baseline ribavirin dosage prescribed (no., %)				0.2*
600 mg/d	2 (1%)	0 (0%)	2 (3%)	
800 mg/d	50 (23.5%)	34 (25%)	16 (22%)	
1,000 mg/d	70 (33%)	45 (33%)	25 (34%)	
1,200 mg/d	89 (42%)	59 (43%)	30 (41%)	
1,400 mg/d	1 (5%)	0 (0%)	1 (1%)	
PI use (no., %)	119 (56%)	84 (61%)	35 (47%)	0.06
Atazanavir	37 (17%)	25 (18%)	12 (16%)	0.7
Lopinavir	43 (20%)	28 (20)	15 (20%)	0.9
Nelfinavir	16 (8%)	12 (9%)	4 (5%)	0.6*
NNRTI use (no., %)	83 (39%)	56 (41%)	27 (36%)	0.6
Efavirenz	60 (28%)	42 (30%)	18 (24%)	0.3
Nevirapine	22 (10%)	14 (10%)	8 (11%)	0.9
NRTI use (no., %)				
Tenofovir	116 (55%)	92 (67%)	24 (32%)	<0.001
Zidovudine	40 (19%)	24 (17%)	16 (22%)	0.4

‡Subjects may have had more than one risk factor.

*P-value determined using Fisher's exact test.

HIV=human immunodeficiency virus; HCV=hepatitis C virus; IQR=interquartile range; MSM=men who have sex with men; NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor

Table 2

Early virologic response rates according to use of abacavir, by genotype, and among patients receiving optimal dosages of PEG-interferon and ribavirin.

Population	Early Virologic Response			Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)*
	Overall	On Abacavir	Off Abacavir		
All patients	102/212 (48%)	33/74 (45%)	69/138 (50%)	0.80 (0.46 – 1.42)	0.99 (0.53 – 1.84)
Genotype 1 or 4	79/185 (43%)	26/65 (40%)	53/120 (44%)	0.84 (0.46 – 1.56)	1.00 (0.50 – 2.00)
Genotype 2 or 3	23/27 (85%)	7/9 (78%)	16/18 (89%)	0.44 (0.05 – 3.76)	**
Optimal PEG-interferon	95/194 (49%)	32/68 (47%)	63/126 (50%)	0.94 (0.52 – 1.71)	1.13 (0.59 – 2.18)
Optimal ribavirin	77/144 (53%)	27/55 (49%)	50/89 (56%)	0.79 (0.40 – 1.55)	0.90 (0.42 – 1.93)
Genotype 1 or 4 plus optimal ribavirin	53/118 (45%)	19/45 (42%)	34/73 (47%)	0.84 (0.40 – 1.77)	0.96 (0.38 – 2.39)

*Odds ratios were adjusted for age, sex, race, fibrosis stage, methadone use, zidovudine use, baseline CD4 cell count, and baseline HCV viral load.

**Sample size for genotypes 2 or 3 were insufficient for analyses.

Table 3

Sustained virologic response rates according to use of abacavir, by genotype.

Population	Sustained Virologic Response			Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)*
	Overall (n=199)	On Abacavir (n=71)	Off Abacavir (n=128)		
All patients	32 (16%)	11 (15%)	21 (16%)	0.89 (0.40 – 1.98)	1.11 (0.48 – 2.59)
Genotype 1 or 4	21 (12%)	8 (13%)	13 (12%)	1.07 (0.42 – 2.75)	1.34 (0.50 – 3.62)
Genotype 2 or 3	11 (41%)	3 (33%)	8 (44%)	0.63 (0.12 – 3.32)	**

* Odds ratios were adjusted for age, sex, and race.

** Sample size for genotypes 2 or 3 were insufficient for analyses.

Table 4

Median declines in hepatitis C viral load at 12 weeks, early virologic response rates, and sustained virologic response rates among HIV/hepatitis C-coinfected patients who received particular antiretroviral medications or classes during PEG-interferon plus ribavirin therapy.

		Median Decline in HCV Viral Load at 12 Weeks			Early Virologic Response			Sustained Virologic Response		
Antiretroviral Drug or Class	**No. (%) Patients**	**Drug or Class Present (log IU/mL)**	**Drug or Class Absent (log IU/mL)**	**P-Value**	**Drug or Class Present No. (%)**	**Drug or Class Absent No. (%)**	**P-Value**	**Drug or Class Present No. (%)**	**Drug or Class Absent No. (%)**	**P-Value**
Zidovudine	40 (19%)	−2.18	−1.58	0.6	22 (55%)	80 (47%)	0.3	5 (13%)	27 (17%)	0.5
Tenofovir	116 (55%)	−1.58	−1.96	0.5	53 (46%)	49 (51%)	0.4	13 (14%)	19 (18%)	0.5
Lamivudine or emtricitabine	178 (84%)	−1.61	−1.63	0.5	87 (49%)	15 (44%)	0.6	24 (15%)	8 (24%)	0.2
NNRTI	83 (39%)	−1.95	−1.56	0.7	40 (48%)	62 (48%)	0.9	12 (16%)	20 (17%)	0.9
PI	119 (56%)	−1.59	−1.81	0.9	58 (49%)	44 (47%)	0.8	20 (18%)	12 (14%)	0.4
Atazanavir	37 (17%)	−2.25	−1.56	0.08	20 (54%)	82 (47%)	0.4	6 (18%)	26 (16%)	0.7
Ritonavir	55 (26%)	−2.51	−1.57	0.07	28 (51%)	74 (47%)	0.6	13 (27%)	19 (17%)	0.2

HCV=hepatitis C virus; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor