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# Sustained Long-term Antiviral Maintenance Therapy in HCV/HIV Coinfected Patients (SLAM-C)

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## Abstract

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**Background—**HCV/HIV coinfection treatment is suboptimal with low SVR rates to standard therapies. A multicenter randomized clinical trial designed to assess the efficacy/safety of pegylated-interferon maintenance therapy was performed by the NIH-funded ACTG network.

**Methods—**HCV treatment naïve and non-responding interferon-experienced subjects with confirmed HCV and HIV, CD4>200 cells/mm$^3$, and at least Stage 1 fibrosis were enrolled, and treated for 12 weeks with pegylated interferon alfa 2a 180 mcg/week (PEG) + weight-based ribavirin to determine response status. Non-responder subjects (failure to clear HCV RNA or achieve 2-log drop) underwent liver biopsy and were randomized to receive full dose PEG or observation only for 72 weeks. Paired biopsies were evaluated by a central pathologist.

**Results—**330 subjects were enrolled; median age was 48 years; 43% White, 37% Black, non-Hispanic; 83% male; CD4+ 498 cells/mm$^3$; 32% were interferon experienced; 74% had entry HIV RNA<50 cp/ml. EVR was observed in 55.9% and 42.5% achieved cEVR. A planned interim analysis of occurred when 84 subjects were randomized. With data on 40 paired biopsies available, a safety monitoring board stopped the trial due to lack of fibrosis progression (median = 0 Metavir units/year) in the observation arm.

**Conclusion—**Lack of fibrotic progression in the control arm was unexpected, and may represent a short-term PEG/ribavirin therapy effect, high levels of HIV viral suppression and use of antiretroviral regimens that may be less toxic than prior generations of therapy.

### Keywords

HCV; HIV; Maintenance; Racial Disparity; Fibrosis

## INTRODUCTION

Hepatitis C infection is a primary etiology of liver injury in patients with HIV infection, though other factors including drug hepatoxicity, steatosis and other coinfections may also play a role.1 HCV/HIV coinfection is associated with increased rates of fibrotic progression, higher rates of cirrhosis in cross-sectional analyses and more rapid progression to end-stage liver disease compared to those with either HCV or HIV monoinfection.2–7 An analysis comparing HCV monoinfected and coinfected hemophilics showed that coinfection was associated with higher fibrosis scores and a higher proportion of advanced fibrosis/cirrhosis after controlling for age, demographic features or other laboratory parameters.8 Treatment of HCV in the setting of HCV/HIV coinfection yields suboptimal results with a significant decrement in sustained viral response compared to those with HCV monoinfection who undergo interferon-based therapies.9

For the last decade, there has been considerable interest in the concept of viral suppressive therapy in HCV treatment non-responders as a means of ameliorating fibrotic progression in subjects who were classified as treatment non-responders. Multicenter clinical trials designed to test this concept in patients with HCV monoinfection included HALT-C, EPIC-3 and COPILOT. In 2004 the National Institute of Allergy and Infectious Diseases (NIAID)-funded Aids Clinical Trials Group (ACTG) embarked on a randomized, controlled trial designed to elucidate the role of maintenance therapy in HCV treatment non-responders with HCV/HIV coinfection.

## SUBJECTS & METHODS

### Study Design

Enrollment of the A5178 clinical trial began in August 2004 and the last subject entered the study in April 2007. In total, 330 subjects were enrolled in this prospective, randomized,

open-label, controlled trial (National Institutes of Health Registration number NCT00078403) designed to determine the effects of PEG maintenance therapy on fibrotic progression in HCV/HIV coinfected subjects. The overall schema is shown in Figure 1. All eligible subjects were initially treated with pegylated interferon alfa 2a 180 mcg SQ per week (PEG) plus weight based ribavirin (WBR) administered orally in divided doses according to body weight (1000 mg for ≤75 kg; 1200 mg for >75 kg). The initial treatment period of twelve weeks was used primarily to provide classification of early virologic responder (EVR) vs. non-responder (NR) status prior to randomization of NR to maintenance therapy vs. untreated control. This period was called “Step 1”. Between Week 12 and 18, study medications were continued pending classification of response status. HCV RNA was determined based upon the Week 12 collection; subjects who had at least a two log decrease in HCV RNA from baseline or who were virus undetectable (<600 IU/ml) were EVRs and all other were NRs. NR subjects underwent liver biopsy and were then randomized via a centralized process to receive full-dose PEG for 72 additional weeks (maintenance), or observation with no treatment (control or observation). This period was defined as “Step 2” of the protocol. At Step 2 completion all subjects discontinued treatment, and underwent repeat liver biopsy. Subjects who responded to Step 1 therapy entered an unrandomized 72 week treatment cycle (Step 3) whose outcome will be described in subsequent publications.

## Subject Eligibility

Step 1 of the study enrolled subjects of either gender at least 18 years old who were coinfected with HCV and HIV. HIV-1 infection was documented by a positive ELISA assay confirmed by western blot, HIV-1 culture, HIV-1 antigen, or HIV-1 RNA. All subjects were required to have HIV-1 RNA <50,000 copies/ml and a CD4 count of >200 cells/$mm^3$. HCV viremia, defined as detectable levels of HCV RNA by RT-PCR or bDNA was also required. All study subjects underwent liver biopsy within 104 weeks prior to Step 1 and were required to have at least Stage 1 fibrosis as determined by the local pathologist. Biopsies required for Step 1 entry were not centrally reviewed, and are not available for further assessment and scoring. Subjects could be either HCV treatment naïve or experienced. Laboratory criteria required for entry included: ANC≥1000/$mm^3$; hemoglobin ≥11 for men and ≥10 g/dl for women; platelets ≥70,000/$mm^3$; creatinine ≤1.5 mg/dl; INR <1.5; ALT and AST and alkaline phosphatase ≤10× upper limit of normal (ULN); direct bilirubin <1.5 mg/dl; lipase ≤1.5× ULN; and a normal TSH (or normal thyroid function on full thyroid panel). Female and male subjects with reproductive potential agreed to use two forms of approved contraception. Subjects were eligible for Step 2 if they met the definition for NR in Step 1, or if they were treated outside of Step 1 with a pegylated interferon and ribavirin that fulfilled the same criteria as required of subjects directly enrolling from Step 1. In an amendment, a rollback option was incorporated which permitted subjects from Step 3 who had up to 42 weeks of PEG/WBR and were HCV positive to enroll in Step 2 after obtaining an entry liver biopsy.

Subjects were excluded if they had AIDS-defining opportunistic infections within 12 weeks prior to Step 1 or Step 2 entry. Key exclusion criteria for both Step 1 and Step 2 included: evidence of decompensated liver disease or other significant liver disease (including hepatitis B, acute hepatitis A, hemochromatosis, or homozygotic alpha-1 antitrypsin deficiency); recent steroid use; active drug/alcohol abuse that would interfere with study adherence, uncontrolled seizure disorders; uncontrolled active depression; history of autoimmune processes that could be exacerbated by the treatment regimen; or history of major organ transplantation.

## Recruitment and Clinical Assessments

Subjects were enrolled at 36 ACTG Clinical Units within the United States providing a broad geographic representation of enrolled subjects. Following Step 1 entry, subjects were seen at Weeks 2, 4, 8 and 12. Study medications were continued during the six week period when HCV RNA from Week 12 was used to determine response status. During this period a liver biopsy was performed if the subject was classified as a NR. Following Step 2 randomization, subjects were seen at Weeks 2, 4, 8, 12, 16, 24, 32, 40, 48, 56, 64 and 72 from that time point. Thus total time of drug exposure was planned to be 12 + 2–6 + 72 weeks for subjects randomized to PEG maintenance. Routine clinical and laboratory assessments for safety were performed at study visits. Following completion of dosing (Maintenance) or observation (Controls), a liver biopsy was performed at Week 72.

Liver biopsies from Step 2 entry and completion were transferred to a central site where they were de-identified and coded. Biopsies were then shipped to the central pathologist (ZDG) at the Armed Forces Institute of Pathology where they were evaluated in a blinded manner using the Metavir and Ishak scoring criteria.

HCV RNA was tested using Roche Cobas Amplicor assay with a lower detection limit of 600 IU/ml for the quantitative assay (used on Step 1) and 60 IU/ml for the qualitative assay (used on Step 2). HIV RNA was tested at a central laboratory using Roche Ultrasensitive HIV RT PCR with a lower limit of quantification of 50 copies/ml.

## Sample Size, Randomization and Statistical Analysis

The sample size was based on the Step 2 design. Published data from Benhamou et al. suggested that untreated subjects would progress 0.18 Metavir fibrosis units/year or 0.27 units in 18 months.2 A clinically significant difference in fibrosis was assumed to be reduction in the rate by 0.05 fibrosis units/year. Assuming a standard deviation of 0.107 Metavir units/year and use of Wilcoxon rank-sum test, 134 subjects would be needed to provide 80% power with a one sided alpha of 0.05. This allowed for an overall dropout rate of 10% of subjects enrolled in Step 2. To meet the target sample size in Step 2, we initially estimated a Step 1 lead-in enrollment of 180 subjects. However, early monitoring revealed a higher proportion of EVRs than expected and a lower rate of subjects directly enrolling from non-Step 1 treatments than anticipated. This led the study team to increase the Step 1 enrollment to a maximum of 330 subjects. Step 2 was randomized with permuted blocks stratified by pre HCV treatment CD4 <200, ≥200, unknown. The randomization was performed at a central site, and the sites and subjects were not blinded to the assigned treatment arm.

Statistical analysis was performed using Statistical Analysis System, Version 9.2 (SAS Institute Inc). Wilcoxon rank-sum tests were used to test statistical significance of differences between treatment arms in continuous measures, including the primary endpoint, change in Metavir fibrosis score scaled by time between the Step 2 entry and exit biopsies. Changes within group in continuous measures used Wilcoxon signed rank tests. Comparisons of categorical measures between two groups used Fisher's exact tests. EVR was evaluated using intention-to-treat (ITT) criteria wherein subjects without Week 12 HCV RNA data were considered failures. EVR rate was summarized with a two-sided 95% exact binomial confidence interval to allow comparisons with EVR rates observed in previous studies. Age, race, gender, prior IFN use, HCV genotype, cirrhosis on pre-Step 1 liver biopsy, injection drug use history, and baseline BMI, CD4 cell count, HIV RNA, HCV RNA, ALT, AST, alkaline phosphatase, ANC and hemoglobin were chosen a priori to be studied as predictors of EVR. In addition to using contingency tables and Fisher's exact tests, EVR predictors were assessed in simple and multi-covariate logistic regression. As

specified by the protocol, a one-sided alpha of 0.05 was used for the primary endpoint (rate of fibrosis progression on Step 2). For all the other comparisons, two-sided p-values <0.05 were considered statistically significant.

### Ethical Issues

The clinical protocol was reviewed and approved by NIAID and FDA. All subjects were provided informed consent which was IRB approved at all clinical sites. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. An independent Safety Monitoring Committee provided oversight during the conduct of the trial.

## RESULTS

### Demographic and Baseline Characteristics

Three hundred thirty subjects enrolled in Step 1; 329 received at least one dose of study medications. Demographics are summarized in Table 1. The majority of subjects were male (83%). The median age was 48 years. Race was self-reported; 43% were white, non-Hispanic, 37% black, 15% Hispanic. Thirty-two percent had previous interferon experience and 74% had undetectable HIV-1 (RNA<50 copies/ml). The median CD4 was 498 cells/$mm^3$. The entry liver biopsy was obtained within less than six months prior to enrollment in 66% of subjects and within 12 months in 82%. Cirrhosis was present in 13% of subjects who entered Step 1. The median baseline HCV RNA titer was $3.98 \times 10^6$ IU/ml. HCV genotype 1 or 4 was present in 86% of subjects.

### Step 1 Outcomes: Early Viral Response

The observed early viral response (EVR) was 55.9% (95% CI: 50.4% – 61.4%). Univariate analysis of factors associated with EVR is shown in Table 2. EVR was much more common in subjects with Genotype 2,3 (90.7%, 39/43) vs. those with Genotype 1,4 (50.5%, 143/283; p<0.0001). Race was also an important factor in univariate analysis of treatment response. As shown in Figure 2, African-Americans and Hispanics were much less likely than Caucasians to achieve EVR (p<0.001). Interestingly, males were more likely to have EVR than females, p=0.03). This and other univariate associations were explored using multicovariate logistic regression models. There were complex associations between race, gender, and ANC. In some models, an influence of body weight in women but not men was observed. The sparse data available at this level of analysis, especially in subsets of women, precludes drawing definitive conclusions regarding the analysis of predictors. Complete EVR, defined as undetectable HCV RNA (<600 IU/ml) following 12 weeks of therapy was observed in 42.5% of the subjects (ITT). Highly significant differences in cEVR were also observed when comparison between Caucasians, African Americans and Hispanics was performed (p<0.001, Figure 2)

### Step 2 Outcomes: Maintenance Therapy for Non-responders

Of the 297 subjects who completed 12 weeks of initial therapy in Step 1, 113 were classified as treatment non-responders, and could have been considered for Step 2, the maintenance therapy vs. untreated control portion of the study. One additional subject was thought to be eligible from Step 1, but was subsequently found to have had a 2-log drop in HCV viral load from baseline. Another 5 subjects were admitted to Step 2 randomization by either direct admission (n=3) or Step 3 rollback (n=2). Thirty-three subjects went off study without entering Step 2 (details in *Tolerability and Safety*), leaving 86 subjects who underwent liver biopsy, Step 2 entry and randomization; 44 subjects in the Maintenance arm and 42 subjects in the Observation arm.

In April 2007, the SMC reviewed study progress. As noted above, our hypothesis assumed fibrosis progression of 0.18 Metavir units/year in the observation arm and that the PEG maintenance therapy would reduce the rate of fibrosis progression. At the time of the SMC review, no fibrosis progression was observed in the observation arm. Statistical extrapolation of possible outcomes indicated that it was highly unlikely that continuation to full enrollment would result in a statistically meaningful difference between study arms. Therefore, the SMC recommended the randomized component of SLAM-C be closed to further enrollment and the study team discontinued scheduling and performance of pending Step 2 entry and exit liver biopsies to prevent risk exposure in those subjects. There were no safety concerns.

To ensure uniform follow-up, the primary report was based upon 62 subjects (33 in the maintenance, 29 in the observation arm) who entered Step 2 at least 72 weeks prior to the Step 2 closure or had paired biopsy data available. The two treatment arms were similar with respect to age (median 49 and 48 years in the PEG vs. observation arm, respectively), gender (73% vs. 72% male), race (52% vs. 55% black, 33% vs. 28% white and 15% vs. 14% Hispanic), HIV<50 (67% vs. 79%), CD4 (median 389 vs. 373 cells/$mm^3$), HCV RNA (median 5.8 vs. 5.6 log IU/mL), HCV genotype (97% vs. 93% had genotype 1 or 4), cirrhosis (15% vs. 28%) and prior interferon treatment (55% vs. 34%). The arms were also comparable in terms of Step 2 entry Metavir fibrosis scores; 43% had a score of 0–1; 28% with 2; 15% scored 3; and 13% with 4.

Of the 62 subjects, 47 had paired liver biopsy data available for the final analysis; 26 in the maintenance and 21 in the observation arm. The median change in Metavir fibrosis score was 0 in both arms (p= 0.84), with a range of −1.43 fibrosis units to + 1.44 fibrosis units/year in the maintenance arm, and −0.73 to 1.31 in the untreated control arm. The results of the paired biopsy comparison between the maintenance and observation arms are graphically summarized in Figure 3. Various sensitivity analyses were performed to incorporate data from subjects lacking evaluable biopsy information (15 subjects of the 62); all yielded results consistent with the results from complete cases provided above. Multiple analyses of subgroups defined by demographic, virologic and clinical criteria failed to find any meaningful differences in fibrosis level. Though the primary hypothesis was based upon change in the Metavir fibrosis score, the central pathologist also provided staging using the Ishak scoring system, which provides more granularity at the level of advanced fibrosis. Use of Ishak fibrosis scores did not change the outcome.

Among subjects with paired biopsy data, the inflammatory activity on biopsy was similar at the initiation of Step 2 (median of 5 vs. 6 Ishak score in the PEG vs. observation arm; p=0.22). However, inflammation increased in untreated subjects randomized to the control arm (median change of +1.31 units on Ishak inflammatory score scale, p<0.01), and was stable (median change of 0) among subjects in the maintenance arm. However, this difference between arms failed to reach statistical significance with a pre-defined two-tailed test (p= 0. 10). ALT was not associated with change in the inflammatory score.

### Retention, Tolerability & Safety

Figure 4 shows the overall subject flow in the study including stage of discontinuation. During the first 12 weeks of lead-in treatment during Step 1, 32 subjects (9.7%) discontinued treatment prior to reaching the decision point at Week 12. These include three deaths, including one judged to be likely related to the use of ddI (didanosine) and ribavirin leading to development of fatal pancreatitis. Eight subjects withdrew consent, and another eight reported severe debilitation that led to their withdrawal. Five subjects were not adherent and five met an endpoint requiring withdrawal from the study. Of the latter group, 4/5 had non-protocol defined low grade toxicities, but refused to re-challenge with drug and

one had a protocol defined toxicity of Grade 3 absolute neutrophil count despite protocol mandated drug hold of 28 days. Three subjects were lost during this period to miscellaneous reasons related to travel and follow-up issues. Of 113 NRs, 33 went off study without registering to Step 2. Nearly 1/3 of these (n=9) went off study due to the SMC recommended closure of Step 2. Among the remaining 24 subjects, there were multiple reasons for being ineligible for Step 2: severe debilitation (1), thrombocytopenia (1), missed doses in Step 1 (2), inability to get liver biopsy (6), fibrosis score of zero (1), Child-Pugh B (1), opportunistic infection (1), seizures (1), depression with suicidal ideation (1) and inability to randomize during required window (3). The remaining 6 withdrew consent (5) or were unable to travel to the clinic (1). Among subjects who were randomized and followed in Step 2, four subjects in the maintenance arm and three subjects in the observation arm failed to continue per protocol. These include one subject in the control arm who died on study Week 66 from overdose of trazodone. Three subjects in the Step 2 maintenance arm and one subject in the observation arm were unwilling to adhere to study requirements, one subject in the control arm withdrew consent and one subject in the maintenance arm was severely debilitated.

Figure 5 shows the distribution of observed laboratory toxicity grades between the two Step 2 arms. The protocol required reporting of signs and symptoms and laboratory toxicities that were Grade≥3 or led to a change in treatment regardless of grade. Finding of “any toxicity” was more common in the treatment arm (n=28 of 33), than in the control arm (n= 17 of 29). However, most toxicities were mild/moderate (Grade 2–3). There were 7 grade 4 toxicities reported in the maintenance arm and 3 in the observation arm. In the maintenance arm, three were related to low absolute neutrophil counts, three to high gamma-glutamyl transpeptidase (GGT) and one to high fasting blood sugar. In the observation arm, high uric acid, high glucose and high ALT were observed.

## DISCUSSION

HCV treatment in the setting of HIV infection remains a difficult and challenging management issue. The combination of faster rates of hepatic fibrosis combined with lower rates of response to standard of care therapy, when compared to HCV monoinfection, underscores the need to explore variations of management paradigms to reduce disease impact in this population. The SLAM-C study focused on the role of maintenance therapy to modulate fibrotic progression, but also included elements that permitted exploratory examination of the role of weight-based ribavirin, the effect of race on interferon-based therapy response and for responders, the tolerability and effect of prolonged treatment regimens.

The concept of maintenance therapy for HCV arose in the 1990s from several distinct lines of reasoning and evidence. First, analysis of cohort data suggested an altered natural history for patients who had undergone interferon-based therapy but failed to achieve SVR. Reports suggested that both hepatic fibrosis and the risk of hepatocellular carcinoma (HCC) were reduced.10¯12 This concept was supported in examination of data from randomized clinical trials. Shiffman et al. selected and randomized subjects with significant (>50% decline from baseline) histologic response to continue to maintenance therapy. Notably, the group reported that a one log drop in HCV viral load was associated with decreased hepatic fibrosis in a treatment group. 13 These observations were congruent with a growing body of data from the HIV field that demonstrated that degree of viral suppression was closely linked to clinical outcomes.14 Finally, the absence of a therapeutic intervention for HCV that was effective and tolerable in the majority of treated patients led to a growing interest in defining the role of interferon maintenance therapy for HCV in non-responder patients.15 This interest culminated in the development of several large multicenter trials for HCV

including HALT-C, EPIC and COPILOT. Similarly, the NIH-funded AIDS Clinical Trials Group (ACTG) supported the development and implementation of the SLAM-C maintenance therapy trial in HCV/HIV coinfected patients.

In the last year, it has become clear that interferon maintenance therapy in HCV monoinfection may not represent a viable modality for management of HCV non-responder patients. The HALT-C trial randomized 1050 subjects with advanced fibrosis to receive either half-dose pegylated interferon alfa 2a or no therapy for 3.5 years. There was no difference between groups in any primary outcome (death, HCC, hepatic decompensation or increased fibrosis score by ≥ 2 points in those with bridging fibrosis).16 Though our sample was considerably smaller than that analyzed in HALT-C, the projected rates of progression were significantly greater, permitting the smaller sample size that was utilized in our design. Data regarding long-term outcomes of patients in EPIC-3 and COPILOT remain unpublished, though interim results of COPILOT were presented previously, and these did suggest that certain clinical outcomes may be modulated by maintenance therapy.17 Another randomized trial found a numerical, but not statistically meaningful advantage to prolonged therapy of cirrhotic patients when clinical outcomes were the endpoint of interest. 18 Though the sample size was small in SLAM-C compared to HALT-C, the study population and the intervention design were selected to reflect previously reported differences between mono- and coinfection. However, a recent meta-analysis pooled 17 reports of fibrosis progression, and reported a lower rate of fibrotic progression than our study was powered to evaluate (0.11–0.12 Metavir units/year).19 These data were not available at the time SLAM-C was designed however. Extrapolating the metanalysis findings to our study, we would have expected at least a 0.11 worsening in the Metavir score, but in fact there was no worsening of fibrosis in the control arm. The reason for failure to see progression in the control arm is unclear, but several hypotheses may be considered. It is possible that the initial twelve weeks of therapy halted progression long enough to prevent fibrotic progression during the subsequent 72 weeks. Additionally, it is possible that the high rate of HIV viral suppression was associated with decreased rates of fibrotic progression compared to early reports derived from untreated/inadequately treated HIV populations. In our study, 74% of subjects had undetectable HIV RNA. In contrast, Benhamou *et al*. reported that while 67.2% of subjects were receiving anti-HIV therapy, few were on HAART (10.9%). The median CD4 count was 305 cell/mm$^3$ In addition, heavy alcohol use was an important cofactor in fibrosis progression in prior literature, but active alcohol abusers were excluded from the SLAM-C study.2 Subsequent analysis of this cohort suggested that both protease inhibitor use and undetectable HIV viremia were associated with decreased fibrotic progression, though viral undetectability fell out of a multivariate model.20 However, Brau et al. has reported slower fibrosis progression in coinfected patients with HAART-associated HIV suppression.21 This is further supported by a recent paper which used transient elastography to suggest that fibrosis rates in HCV/HIV coinfected subjects was now similar that seen in HCV monoinfection.22 Finally, we suspect that there has been a significant evolution in antiretroviral therapy which is reflected in decreased rates of drug-associated hepatoxicity. For example, SLAM-C discouraged use of didanosine during HCV treatment, an agent which was associated with significant hepatotoxicity in prior clinical trials and few patients used this agent. 23. Subsequently this guidance has been reflected in the product insert which indicates that co-administration of ribavirin and didanosine is not recommended. (from product insert, Genentech dated June 2010).

This study has several limitations. The underlying assumptions regarding rates of fibrotic progression may have overestimated the actual rates that occur in subjects using current and less hepatotoxic antiretroviral regimens. Another limitation of this study is our inability to characterize the effects of initial histologic response (during the first 12 weeks of therapy)

on subsequent response during the maintenance phase due to the lack of access to the slides for centralized review of pretreatment biopsies. Since the study did not permit enrollment of patients with very high HIV viral load (>50,000 copies/ml) and very low CD4 (<200 cells/$mm^3$) any conclusions drawn may not be generalized to these subpopulations. Finally, the proportion of woman enrolled did not permit detailed sub-analysis of gender associations with histologic response.

This clinical trial did provide valuable information regarding treatment response to pegylated interferon with weight-based ribavirin. Prior studies of treatment of HCV in the setting of HIV utilized either fixed dosing with 800 mg daily of ribavirin (APRICOT, RIBAVIC) or a unique dose-escalation regimen (600–1000 mg/day) in ACTG 5071.[24–26] The dose approved by the U.S. FDA is 800 mg/day for use in coinfected patients. The SLAM-C study utilized weight based dosing of ribavirin in the entry Step 1 of the protocol. However, this study was performed in a highly comparable population to that utilized in ACTG 5071.[25] The EVR rate in SLAM-C was 56% which is somewhat higher than a historic comparison of 47% (95% CI: 34–60%) in the PEG/Ribavirin arm of ACTG A5071 (personal communication from RTC). In fact, EVR rate was so high that early planned interim analysis required resizing of the sample population from Step 1, since there was a concern that a lack of non-responders would jeopardize Step 2 enrollment. Similarly, the PRESCO trial also utilized weight-based ribavirin also reported higher response rates than previously noted in coinfection trials which they attributed to the increased ribavirin dosing.[27] However, data from both trials are uncontrolled, and should be used with caution when selecting the ribavirin dose in HCV/HIV coinfected patients. A controlled trial of ribavirin dosing in coinfected patients is in progress which may provide additional insights to this issue (NCT00353418).

SLAM-C does provide a unique window into racial disparities in treatment response in coinfected patients. Prior large multicenter trials in HCV/HIV coinfection enrolled relatively few minority subjects, while this study is much more reflective of the U.S. population of HCV/HIV coinfected patients. In SLAM-C more than 50% of subjects were not Caucasian, permitting a unique comparison of the effect of race on the biological response to pegylated interferon/ribavirin on viral decline. EVR was significantly less common in African-Americans and Hispanic subjects, consistent with reports in HCV monoinfected patients.[28–30] Some experts had previously suggested that the overall decrement in interferon-based treatment response in those with HIV would blur the race effects, but our data clearly shows that race remains a significant factor in treatment outcome. However, the confounding role of potential response confounders (e.g. BMI, gender) do not permit detailed attribution of the race effect size. The proportional differences between EVR and cEVR that are illustrated in Figure 2 are also worth noting. These data support that concept of decreased rates of viral decline in minority populations. In 2009, several reports describing the relationship between IL-28b polymorphisms, viral clearance and treatment outcome and race were published.[31, 32] These studies clearly demonstrate that viral clearance is associated with specific polymorphism near and within the coding domain for the IL-28b gene, and explain a significant portion of observed racial disparities. The SLAM-C cohort has not undergone analysis of the distribution of these polymorphisms, but such studies are planned.

In summary, the SLAM-C trial failed to find evidence of hepatic fibrosis progression among an untreated control group followed for 72 weeks after a short course of pegylated interferon/ribavirin therapy. Further investigation of the mechanism(s) associated with a halt in fibrotic progression are warranted. Finally, race appears to be an important factor in response to interferon-based therapy in HCV/HIV coinfected subjects. The association of this finding with IL28b polymorphisms is under active investigation.

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**Figure 1.**
Study Schema
* denotes direct entry of nonresponders from comparable non-study treatments, or roll-back of nonresponders from Step 1

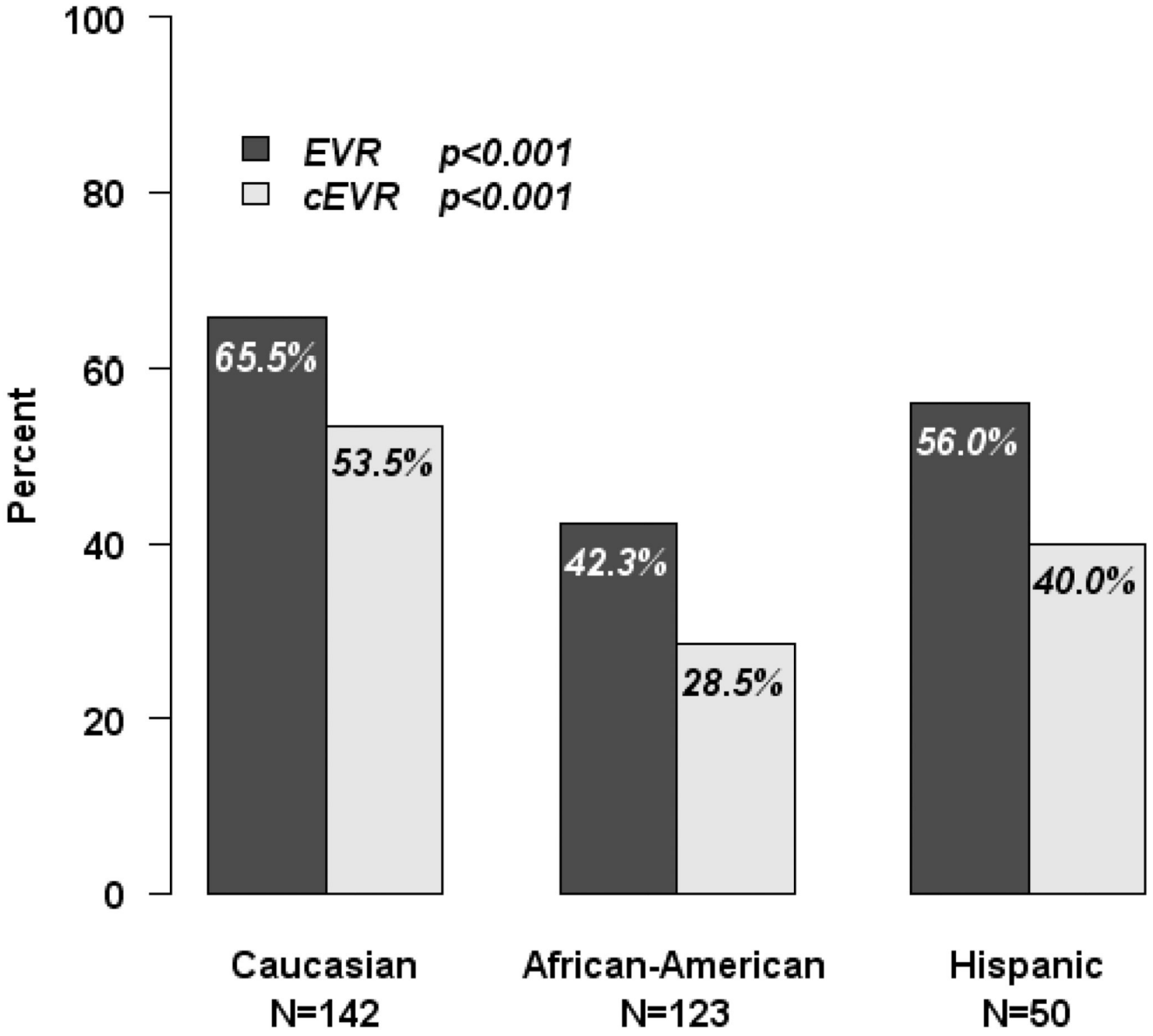


**Figure 2.**
Early viral response rates (%) by race. EVR represents either 2 log drop in HCV viral load from baseline at 12 weeks of treatment or viral undetectable at 12 weeks. cEVR refers to subjects who were HCV undetectable (<600 IU/ml HCV RNA). p values by Fisher's exact test.

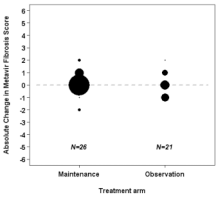


**Figure 3.**

Bubble-plot of absolute change in Metavir fibrosis score for subjects in Step 2, randomized to receive either pegylated interferon alfa for 72 weeks or observation as untreated controls. Paired biopsies compared in blinded manner by single pathologist. Composite change in fibrosis score shown. Bubble size is proportionate to number of subjects.

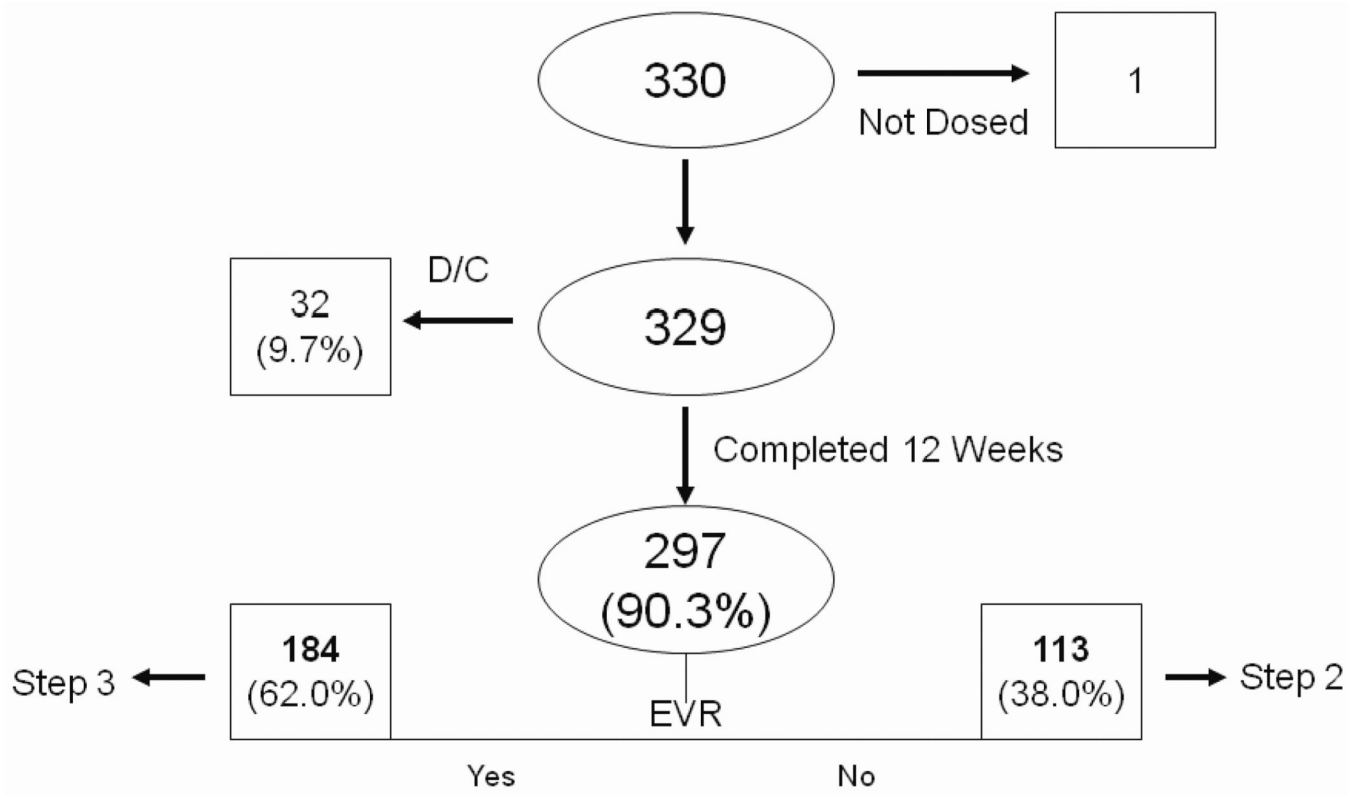


**Figure 4.**
Subject outcomes during course of clinical trial accounting for all randomized subjects. Step 2 entry total does not include direct admission/rollback subjects (n=5) or 1 misclassified subject as described in text.

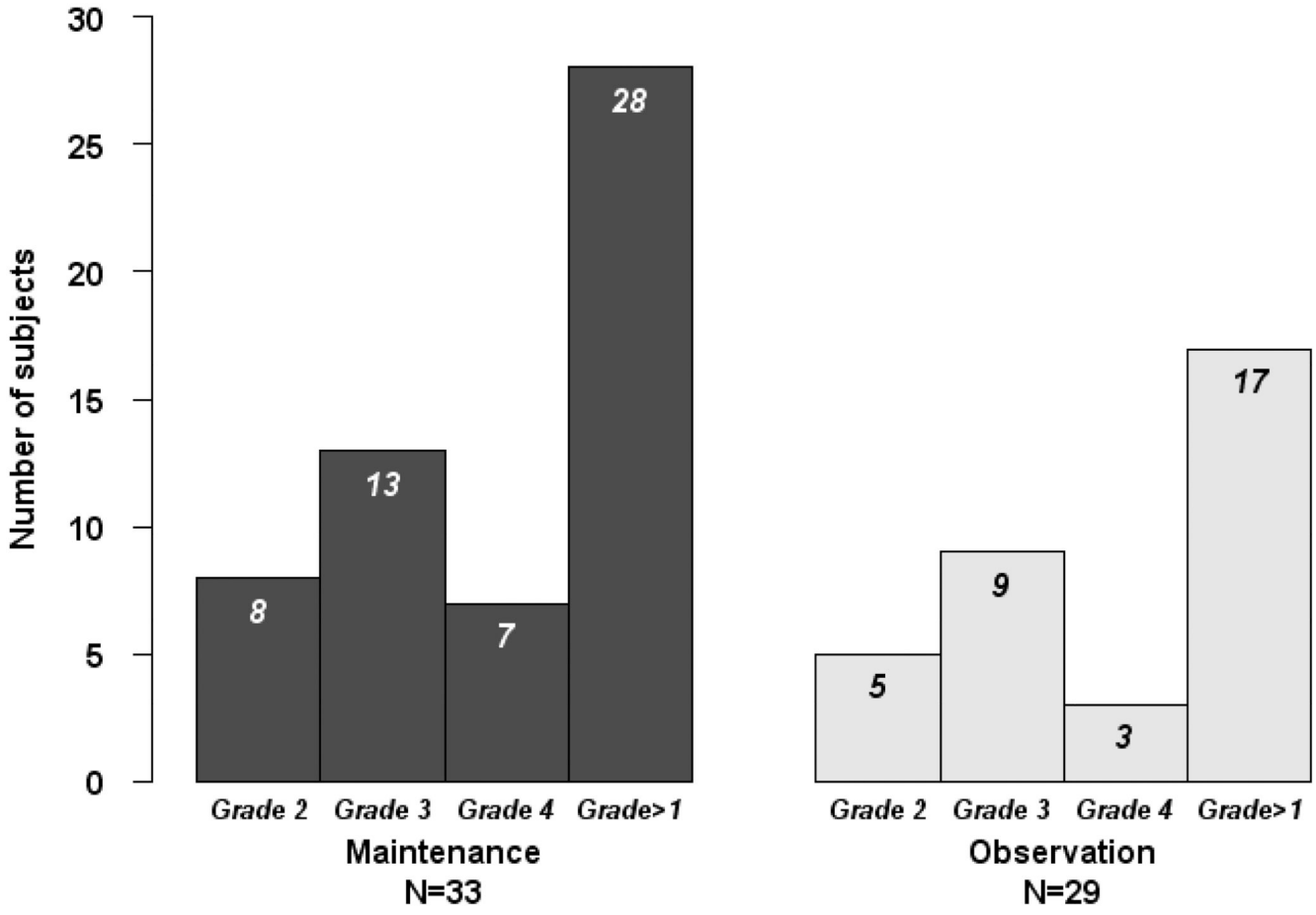


**Figure 5.**
Toxicity grades during Step 2. Total numbers of patients with all toxicities greater than Grade 1 during course of pegylated interferon maintenance vs. observation control arm.

**Table 1**

Characteristics of Subjects at Baseline

| | |
|---|---|
| N | 329 |
| Gender- Male | 274 (83%) |
| Race | |
| White Non-Hispanic | 142 (43%) |
| Black Non-Hispanic | 123 (37%) |
| Hispanic | 50 (15%) |
| Asian, Pacific Islander | 3 (1%) |
| American Indian, Alaskan Native | 4 (1%) |
| More than one race | 6 (2%) |
| Unknown | 1 (0%) |
| Age- Median (years) | 48 |
| BMI-Median | 26 |
| HIV-1 RNA- Undetectable | 245 (74%) |
| CD4- Median Cells/$mm^3$ | 498 |
| HCV Viral Load- Median IU/ml | $3.98 \times 10^6$ |
| HCV Genotype | |
| 1,4 | 283 (86%) |
| 2,3 | 43 (13%) |
| Unknown | 3 (1%) |
| Cirrhosis | 43 (13%) |
| Interferon-treatment Naïve | 223 (68%) |

**Table 2**

Univariate analysis of factors associated with EVR

| | ODDS RATIO | 95% CI | p-value* |
|---|---|---|---|
| White vs. Other | 1.98 | (1.26 – 3.11) | 0.0029 |
| Male vs. Female | 1.98 | (1.10 – 3.57) | 0.0224 |
| Genotype 2,3 vs 1,4 | 9.55 | (3.32 – 27.42) | <0.0001 |
| Non-cirrhotic vs Cirrhotic | 2.15 | (1.11 – 4.13) | 0.0223 |
| ANC≥2500 vs. <2500 | 2.44 | (1.56 – 3.82) | 0.0001 |
| Hgb≥13 vs. <13 | 2.51 | (1.37 – 4.59) | 0.0027 |
| BMI <30 vs. ≥30 | 1.22 | (0.73 – 2.06) | 0.4503 |
| IFN Naïve vs. Experienced | 1.20 | (0.76–1.91) | 0.4396 |

*Estimates and p-values are from simple logistic regressions.