Published in final edited form as:

J Acquir Immune Defic Syndr. 2010 October 1; 55(2): 170–175. doi:10.1097/QAI.0b013e3181e36420.

Women Experience Higher Rates of Adverse Events During HCV Therapy in HIV Infection: A Meta-Analysis

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Abstract

Background—In HIV/HCV coinfection, adverse events (AE) during HCV therapy account for 12–39% of treatment discontinuations. It is unknown whether sex influences complications.

Methods—Meta-analysis to study the effect of sex and other predictors of AEs in 3 randomized trials, ACTG 5071, APRICOT, and ANRS-HCO2-RIBAVIC of Interferon (IFN) and Pegylated IFN (PEG), both with and without Ribavirin, in HIV/HCV coinfection. Primary endpoints were AEs requiring treatment discontinuation (AETD) or first dose modification (AEDM). Multi-covariate stratified logistic regression was used to study predictors and assess interactions with sex.

Results—21% of 1376 subjects were women; 61% had undetectable HIV RNA; 14% were antiretroviral therapy (ARV) naïve at entry; median CD4 was 485 cells/mm³. 17% had an AETD and 50% AEDM; women had more AETD than men, (24% vs. 16% p=0.003) and AEDM (61% vs. 48% p<0.0001). AETD and AEDM occurred earlier in women; but the types of AETD and AEDM were similar between sexes. 74% of AETDs and 49% of AEDMs involved constitutional AEs; 18% of AETDs depression; and 26% of AEDM neutropenia. We identified interactions with sex and BMI (p=0.04, continuous) and NNRTI (p=0.03); more AETDs were seen in men with lower BMI (p=0.01) and in women on NNRTIs (p=0.009). More AEDMs were seen with PEG (OR=2.07); older age (OR=1.48 per 10yrs); decreasing BMI (OR=1.04 per kg/m²); HCV genotype 1,4 (OR=1.31); Ishak 5,6 (OR=1.42); decreasing Hgb (OR=1.23 per g/dL); and decreasing ANC (1.04 per 500 cells/mm³). Interactions between sex and ARV-naïve status (p=0.001) and AZT (p=0.001) were identified: there were more AEDMs in ARV naïve women (p=0.06) and ARV experienced men (p=0.001); and higher AEDMs in women with AZT (p=0.0002).

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Presented at Conference of Retroviruses and Opportunistic Infections (CROI), Montreal February 9–11 2009

Conflicts of Interest: DB, TU, and FT report no conflicts of interest. JA has served on the data safety monitoring board (DSMB) of Tibotec. FC was a consultant for Roche, Glaxo-Smith Kline, Sanofi-Aventis, Novartis, received grants from Roche, Glaxo-Smith Kline, Sanofi-Aventis and had travel expenses paid by Roche, Glaxo-Smith Kline, Sanofi-Aventis, Novartis, and Schering-Plough. RTC has received research support from Roche. JSC has received research grants from Schering Plough, Merck, and Tibotec and has been on the Advisory Boards for BMS and Merck (2008). MP has been a consultant for Roche, Merck, and Pharmasset.

Conclusions—Although there was no difference in type of AE, AETD and AEDM were more frequent and occurred earlier in women. In women, ARV regimen may be an important predictor of AETDs during HCV therapy and should be explored as a predictor of AEs in HIV/HCV coinfection trials.

Keywords

HIV; hepatitis C virus; sex differences; toxicity; drug therapy

Introduction

HIV and HCV coinfection is common, with reported prevalences of 16-33% in HIV-infected individuals in the US(1,2). Liver-related mortality is the leading cause of death among HIV-infected persons in the U.S. in the HAART era(3). When compared to HCV monoinfection, hepatitis C therapy is less effective in HIV and HCV coinfecting individuals due, in part, to high rates of treatment discontinuation (4-6). In HCV infection without HIV, the percentage of discontinuations secondary to adverse events or laboratory abnormalities ranged from 7-21% (7-9) while in HIV coinfection, treatment discontinuations occurred in 12-39% (4-6). Understanding the role of factors such as sex and its relationship with the development of adverse drug reactions will be critical to improving treatment outcomes in HIV and HCV coinfection.

In HCV monoinfection, women are more likely to experience anemia with interferon and ribavirin therapy (10) and may be more likely to develop depression (11-13). In HIV infection, studies with nucleoside analogue therapy suggested that women were more likely to require dose modifications, to develop severe symptoms, and to experience adverse events related to didanosine (14,15). There is little known, however, about the sex differences in adverse events during HCV therapy in HIV/HCV coinfection. Additionally, the relationship between female sex, adverse events during therapy, and other factors potentially related to adverse events such as body mass index (BMI) and antiretroviral (ARV) regimen have not been well described in HIV and HCV coinfection.

The aim of our study was to investigate whether female sex was associated with an increased incidence and/or more rapid onset of adverse events requiring treatment modification or discontinuation. In addition, we examined whether factors such as antiretroviral regimen and BMI were important in predicting adverse events in women and men.

Methods

We performed a meta-analysis of the AIDS Clinical Trials Group (ACTG) A5071, AIDS Pegasys Ribavirin International Coinfection Trial (APRICOT), and Agence Nationale de Recherches sur le SIDA (ANRS) HCO2-RIBAVIC HCV treatment studies in HIV/HCV coinfection, conducted by different clinical trials networks between 2000 and 2003. Subject level data was obtained for each study. Only subjects who initiated HCV treatment were included in the analysis. Detailed inclusion criteria, study design, and criteria for treatment discontinuation and dose modifications are described in detail elsewhere (4-6). In A5071, subjects were randomized to receive 180 µg of peginterferon alfa-2a weekly for 48 weeks and dose-escalated ribavirin or 6 million IU of interferon alfa-2a three times weekly for 12 weeks followed by 3 million IU three times weekly for 36 weeks with dose-escalated ribavirin (5). Ribavirin was administered as 600 mg per day for 4 weeks, 800 mg per day for 4 weeks, and then 1000 mg per day for the remainder of the study. In APRICOT, subjects were randomized to peginterferon alfa-2a (180 µg per week) plus ribavirin (800 mg per day), peginterferon alfa-2a plus placebo, or interferon alfa-2a (3 million IU three times a week) plus ribavirin (800

mg per day) (6). In RIBAVIC, subjects were randomized to 1.5 µg/kg peginterferon alfa-2b once a week or subcutaneous injections of 3 million units of interferon alfa-2b 3 times a week for 48 weeks. All subjects also received 800 mg of ribavirin daily (4). Laboratory toxicities, signs and symptoms and clinical events, excluding death, were considered adverse events (AEs). The primary endpoints were AEs requiring treatment discontinuation (AETD) or first dose modification (AEDM). The primary endpoints were decided a priori and were selected because identification of factors responsible for treatment discontinuations and drug dose modifications may lead to implications for patient selection and management prior to and during therapy. Since the present analyses used data on subject level, the overall results are weighted by study, giving the greatest weight to APRICOT (62% of the N=1376 subjects) followed by ANRSHCO2-RIBAVIC (28%) and A5071 (10%).

Statistical Analysis

Breslow-Day tests were used to ensure that it was appropriate to combine estimates from the three studies. Cochran-Mantel-Haenszel tests stratified by study were used to test statistical significance of differences in categorical variables between two groups. Stratified Wilcoxon rank-sum tests were used to test the statistical significance of differences between two groups in continuous variables. Predictors of AETD and AEDM were examined using simple logistic regression models, stratified by study. In addition to sex, predictors considered in analysis were: HCV treatment (pegylated interferon-containing vs. not); race (White vs. non-White); age (continuous); BMI (continuous); HCV genotype (1, 4 vs. other); baseline Ishak fibrosis score (1 – 4 vs. higher); baseline HCV RNA (<800,000 vs. ≥800,000 IU/mL); baseline HIV-1 RNA (detectable vs. undetectable per definition of each study); baseline CD4 cell count (<500 vs. ≥500 cells/mm³); ARV naive at baseline; stavudine (D4T) use at baseline; zidovudine (AZT) use at baseline; ARV regimen at baseline (nucleoside reverse transcriptase inhibitors (NRTI) only; containing non-nucleoside reverse transcriptase inhibitor(s) (NNRTI) but no protease inhibitor (PI); containing any PI); baseline absolute neutrophil count (ANC, continuous); baseline platelets (continuous); baseline hemoglobin (continuous); baseline alanine aminotransferase (ALT, continuous); and baseline aspartate aminotransferase (AST, continuous). Variables and their interactions with sex that were significant at 0.2 significance level in simple stratified logistic regression were considered in multi-covariate logistic regression models, stratified by study.

Kaplan-Meier estimates were used to summarize time-to-event results. Log-rank tests stratified by study were used to compare times to event between men and women. Stratified Cox proportional hazards model were used to provide an estimate for the magnitude of sex effect. Because AETD and AEDM are competing risks, times to AETD and AEDM were also analyzed using the competing risks methods (16) (treating death, non-response, LFU and other known reason (primarily administrative) for treatment discontinuation as competing risks. The results were very similar to the results from Kaplan-Meier and Cox proportional hazards models, and the conclusions on the effect of sex were the same in both analyses. Therefore, the results of standard Kaplan-Meier analysis along with Cox proportional hazards model are provided for simpler interpretation.

Results were considered statistically significant if $p < 0.05$ (two-sided).

Results

One thousand three hundred seventy-six subjects were included in the analysis, 288 (21%) of whom were women; 133 (10%), 860 (62%), and 383 (28%) subjects were from A5071, APRICOT and ANRSHCO2-RIBAVIC, respectively. Subjects from A5071 were more likely to be non-white (52%), older (median age 45 years), overweight or obese (57%) and have HCV

genotype 1 or 4 (80%) than the subjects from APRICOT (21%, 39 years, 39% and 68%) or from ANRSHCO2-RIBAVIC (5%, 39 years, 18% and 61%).

Overall, 67% of subjects were infected with HCV genotype 1 or 4 and 83% had Ishak fibrosis score ≤ 4 (Table 1). Treatment regimens included pegylated interferon and ribavirin in 40%, interferon and ribavirin in 39% and pegylated interferon alone in 21%; 40% of men and 40% of women received pegylated interferon and ribavirin therapy. Seventeen percent of women and 13% of men were ARV naïve ($p=0.16$); 48% of women and 42% of men were on D4T-containing regimens ($p=0.11$); 18% of women and 11% of men were on NRTI-only regimens ($p=0.004$); 29% of women and 34% of men were on AZT-containing regimens ($p=0.15$); and 26% of women and 28% of men were on NNRTI-containing regimens ($p=0.47$).

Fifty-three percent of women vs. 67% of men completed study treatment as specified by the respective study protocol; 24% vs. 16% discontinued treatment early due to toxicities, 11% vs. 9% due to non-response, 9% vs. 6% due to other known reasons; 1 woman of 288 vs. 1 man of 1088 died and 3% of both women and men were lost to follow-up ($p=0.002$, stratified by study) (not shown in Table 1).

Adverse Events Requiring Treatment Discontinuation (AETD)

Women were more likely to experience an AETD than men, 24% vs. 16% ($p=0.003$). Primary etiologies of AETD among the 238 who experienced an AETD included constitutional or other symptoms in 176 (74%) and depression in 44 (18%). Discontinuation due to hematologic abnormalities was not common; anemia, thrombocytopenia, and neutropenia were involved in 5%, 5%, and 3% of the treatment discontinuations, respectively, and there was no difference observed by sex. In a post-hoc analysis that examined detailed etiologies of AETD among the 176 subjects with constitutional or other symptoms, 68 (39%) included fever, fatigue, weight loss, or gastrointestinal symptoms; 42 (24%) neurologic or psychiatric side effects, and 15 (9%) elevations in hepatic transaminases or lactic acid. The type of AETD was similar between the two sexes.

Predictors of AETD—In simple stratified analysis, female sex ($OR=1.63$) was a predictor of AETD. In addition, older age and lower baseline hemoglobin were statistically significant and lower baseline BMI was a marginally significant risk factor of AETD (Table 2). There was no evidence of association between AETD and the other factors listed in *Methods - Statistical Analysis*. In multi-covariate analysis, age ($p<0.0001$) and interactions between sex and BMI ($p=0.04$) and between sex and NNRTI ($p=0.03$) were statistically significant (Table 2). Men with higher BMIs were less likely to experience AETD than men with lower BMIs ($OR=0.94$). This association was not observed in women. Women on NNRTI-containing regimens were more likely to have an AETD than ARV naïve women or women on other ARV regimens ($OR=2.23$) whereas in men, no association between NNRTI-containing regimen and AETD was observed. Of the 69 women with an AETD, depression was responsible for 16/69 (23%) of AETDs; women on NNRTI therapy were more likely to experience depression, 8/25 (32%), than those who were on other ARV or not on ARV, 8/44 (18%); ($p=0.02$).

AEDM (Adverse Events Requiring Treatment Modification)

Women were more likely to experience an AEDM than men, 61% vs. 48% ($p<0.0001$). Neutropenia and anemia were the primary hematologic etiologies of AEDM, involved in 26% and 17% of the AEDMs, respectively, and 49% of AEDMs involved constitutional AEs, but the type of AEDM was similar in men and women. An analysis that examined only subjects who received pegylated interferon and ribavirin, the standard of care regimen, demonstrated similar results (not shown).

Predictors of AEDM—In simple stratified analysis, female sex was a predictor of AEDM (OR=1.72). In addition, pegylated interferon containing regimen, non-White race, older age, lower baseline BMI, HCV genotype 1 or 4, Ishak fibrosis score 5 or 6, CD4 cell count <500, ARV experienced, AZT use, and lower baseline ANC, Hgb, and ALT were statistically significant predictors of AEDM (Table 3). The other factors listed in the *Methods - Statistical Analysis* were not statistically significantly associated with AEDM. In multi-covariate analysis, receipt of pegylated interferon therapy (OR=2.07, $p<0.0001$), increasing age (OR=1.48 per 10yrs), decreasing BMI (OR=1.04 per kg/m^2), HCV genotype 1,4 (OR=1.31), Ishak 5,6 (OR=1.42), decreasing ANC (OR=1.04 per 500 cells/ mm^3), and decreasing Hgb (OR=1.23 per g/dL) remained statistically significant (Table 3).

We also identified interactions between sex and ARV naïve status ($p=0.001$) and between sex and AZT use ($p=0.001$). Interestingly, ARV naïve women were more likely to experience AEDMs than ARV experienced women (OR= 1.96, $p=0.06$) but ARV naïve men were less likely to experience AEDMs (OR=0.51, $p=0.001$). In women, more AEDMs were seen with AZT compared to non-AZT regimens or no ARV (OR 3.56, $p=0.0002$); but this association was not seen in men ($p=0.59$). In a subgroup analysis examining etiologies of dose modifications in 175 women with AEDM, women on AZT-containing therapy were more likely to experience neutropenia and anemia; 20/67 (30%) vs. 21/108 (19%); ($p=0.12$) and 23/67 (34%) vs. 13/108 (12%); ($p=0.0004$), respectively.

Time to AETD and AEDM

See Figure 1. Women discontinued therapy and required dose modification earlier than men. The Cox proportional hazards ratio for time to AETD was 1.54 (95% CI: 1.16-2.04) for women compared to men ($p=0.003$) while the Cox proportional hazards ratio for time to AEDM was 1.43 (95% CI: 1.20-1.70) for women compared to men ($p<0.0001$). The median time to AE requiring first dose modification was 24 weeks in women and 48 weeks in men. There was also a trend towards more rapid platelet decline in women; the median time to the lowest platelet level was 15.6 (12.1-18.1) vs. 18.1 (16.1-18.9) weeks ($p=0.05$).

Discussion

In a meta-analysis of three large HIV/HCV coinfection trials, women were more likely to experience an AETD or AEDM during HCV therapy in HIV infection. However, the observed types of adverse events were similar between sexes. Additionally, AETD and AEDM occurred earlier in women. When exploring the effect modification by sex, women on regimens containing an NNRTI without a PI experienced more adverse events requiring treatment discontinuation and women on AZT-containing regimens experienced more adverse events requiring interferon or ribavirin dose modification.

This is the first study to demonstrate that HIV-infected women on hepatitis C therapy experience more adverse events requiring treatment discontinuation. Although similar sex effects on treatment discontinuation have not been reported in HIV-uninfected HCV-positive women receiving interferon and ribavirin therapy (7-9), hepatitis C mono-infection trials have demonstrated that women experience some adverse events (depression and anemia) more commonly than men (10,11). The relatively lower proportion of women enrolled in the landmark registration trials (7-9) may have precluded analysis of sex effects and discontinuation rates.

When examining the HIV literature, our findings of higher treatment discontinuations in women are similar to some (17,18) but not all (14,19,20) studies in HIV infection. In the CASCADE collaboration, women were more likely to discontinue ARV therapy (HR = 1.61, 95% CI: 1.15–2.27) (17) while in the ICONA study group, women were twice as likely to

discontinue treatment secondary to toxicity (18). Conversely, three other studies did not find higher overall rates of treatment discontinuations among women (14,19,20).

A sex effect on ARV modifications has also been noted in HIV studies; Currier and colleagues demonstrated that women were 1.25 times more likely to modify didanosine dosage (14). In HIV infection, women are also more likely to experience adverse events while on therapy with descriptions of increased rates of rash and hepatitis with nevirapine (21) and lactic acidosis with nucleoside analogues (22). The reasons for heightened rates of adverse events in women are poorly understood. Differences in body weight and composition, renal clearance, cellular kinase activity, and P glycoprotein activity may all play a role.

Our finding that women on NNRTI regimens were more likely to discontinue HCV therapy than men is in agreement with other studies examining ARV regimen discontinuation in HIV infection. Women were more likely to discontinue efavirenz-based regimens with 38.8% (95% CI: 28.8% to 48.7%) stopping EFV by 48 weeks of treatment compared with 28.3% of men (95% CI: 23.4% to 33.2%) (23). In our analysis, among women with AETD, women receiving NNRTI-based regimens had more depression. This finding, along with the findings that women are more likely to have elevated plasma efavirenz concentrations (24), are more likely to have mood disorders (25); and may be more likely to experience depression while on interferon therapy (11) raise the possibility that neuropsychiatric side effects from interferon and efavirenz based regimens may be accentuated in women. These findings should be interpreted with caution in this study, however, as we did not have data on type of NNRTI regimen, and the number of women on NNRTI regimens who discontinued was small.

The finding that women were more likely to have AEDMs with AZT-containing regimens, and a subgroup analysis demonstrating that the majority of AEDM on AZT-containing regimens were hematologic are not unexpected. Women are at an increased risk of developing anemia during ribavirin therapy (10) and our study suggests that AZT may also play a role in hematologic toxicities in women receiving ribavirin. In hepatitis C mono-infection trials, Sulkowski and colleagues found that the incidence of reaching a Hgb<10 g/dL was fourfold higher in women (10) while an analysis of interferon alpha-2a trials also found that women were more likely to have anemia (26). One study demonstrated higher levels of AZT in women (27), suggesting a possible mechanism for the additive toxicity of ribavirin and AZT. Anderson and colleagues found that women had significantly higher intracellular concentrations of AZT with a female to male ratio of 2.3. Interestingly, we did not find a statistically significant sex difference in the rates of anemia leading to treatment discontinuation; the respective rates were small among both men and women, suggesting that these adverse events were well managed in this clinical trial setting.

We also found that older age was independently associated with the incidence of adverse events requiring treatment discontinuation and dose modification. This is supported by Sulkowski and colleagues (10) who also found that older age was associated with hemoglobin decrease in hepatitis C mono-infection studies. The authors speculated that older age may impact hematopoietic reserves in bone marrow, leading to more bone marrow suppression than in younger subjects (10).

One limitation of our analysis was the heterogeneity of treatment protocols. In ACTG 5071, ribavirin was dose-escalated from 600 mg to 800 mg, and subjects who experienced severe adverse events stopped therapy. This dose escalation, however, would only have masked severe adverse events. Additionally, the three protocols included varying regimens of interferon and ribavirin, with 40% of individuals receiving combination therapy with pegylated interferon and ribavirin. Subgroup analyses on this group with combination therapy, however, demonstrated similar results to that of all regimens. Another limitation of the study included

the extensive use of ARVs (zidovudine and stavudine) that are less common in clinical practice today. Newer, more tolerable ARV regimens such as the nucleos(t)ide transcriptase inhibitor combinations (i.e. tenofovir/emtricitabine and abacavir/lamivudine), boosted atazanavir, and raltegravir may lead to a reduced rate of adverse reactions attributable to concomitant ARV and HCV therapy. Analyses of these newer regimens with hepatitis C therapy, and their interactions with sex, are needed. We also acknowledge the presence of competing risks such as loss to follow-up, death, non-response, and unknown reasons for discontinuation. Therefore, time to adverse event requiring treatment discontinuation and time to first dose modification, respectively, were also analyzed in the competing risks setting, treating death, non-response, LFU and other known reason for treatment discontinuation as competing risks. The results were very similar to the results from Kaplan-Meier and Cox proportional hazards model, and the conclusions on the effect of sex were the same in both analyses. Competing risks may have also reduced the observed adverse events and, if drop-out secondary to competing risks was associated with covariates, then confounding may have been introduced. Finally, the overall numbers of women experiencing AETDs and AEDMs were low at 69 and 175, respectively, leading us to interpret the interactions and subgroup analyses, including comparisons of types of adverse events between men and women, with caution.

In conclusion, women are more likely to experience adverse events leading to hepatitis C treatment dose modification and discontinuation in the setting of HIV/HCV coinfection. Women on NNRTI regimens were more likely to discontinue therapy and women on AZT-containing regimens were more likely to require dose modifications, suggesting an important sex-mediated role of ARV regimen on the impact of adverse events during hepatitis C therapy. ARV regimen may be an important predictor of treatment discontinuation and modification in women and should be further explored as predictors of adverse events in HIV/HCV coinfection trials.

Acknowledgments

Financial Support. National Institutes of Health 5K12HD01400 and K23 AI066983A (salary support DB), DK078772 (salary support RC), K24 AI 56933 (salary support JSC). ACTG 5071 was supported by General Clinical Research Center grants (RR00046, RR00096, and RR00044) and a Center for AIDS Research grant (P30-AI27763D) from the National Institute of Allergy and Infectious Diseases and by grants (AI068634, AI25868, AI27661, AI27670, AI27675, AI46370, AI25897, AI50410, AI046376, and AI27659) from the ACTG. The APRICOT study was supported by Roche, Basel, Switzerland. The RIBAVIC study was supported by a grant from the Agence Nationale de Recherches sur le SIDA, a publicly funded agency involved in clinical research on HIV and HCV and the study drugs were provided by Schering-Plough.

Sources of support: National Institutes of Health 5K12HD01400 and K23 AI066983A (salary support DB), DK078772 (salary support RC), K24 AI 56933 (salary support JSC). ACTG 5071 was supported by General Clinical Research Center grants (RR00046, RR00096, and RR00044) and a Center for AIDS Research grant (P30-AI27763D) from the National Institute of Allergy and Infectious Diseases and by grants (AI068634, AI25868, AI27661, AI27670, AI27675, AI46370, AI25897, AI50410, AI046376, and AI27659) from the ACTG. The APRICOT study was supported by Roche, Basel, Switzerland. The RIBAVIC study was supported by a grant from the Agence Nationale de Recherches sur le SIDA, a publicly funded agency involved in clinical research on HIV and HCV and the study drugs were provided by Schering-Plough.

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Figure 1.

A, Sex effect on the Time to AE requiring treatment discontinuation. B, Sex effect on the Time to AE requiring first study treatment dose modification.

Table 1

Baseline Characteristics

	Sex			
	Total (N=1376)	Male (N=1088)	Female (N=288)	p-value
<u>Race</u>				
White	1107 (81%)	871 (80%)	236 (82%)	0.5267(a)
Black (African Origin)	144 (10%)	113 (10%)	31 (11%)	
Hispanic	102 (7%)	83 (8%)	19 (7%)	
Other	2 (2%)	20 (2%)	2 (1%)	
Unknown *	1 (0%)	1 (0%)	0 (0%)	
<u>Age, median (Q1–Q3)</u>				
	40 (36–44)	40 (36–45)	38 (34–43)	0.0005(b)
<u>BMI, median (Q1–Q3)</u>				
	24 (21–26)	24 (22–26)	22 (20–25)	<0.0001(b)
<u>HCV Regimen</u>				
PEG + RBV	549 (40%)	433 (40%)	116 (40%)	0.8364(a)
Interferon + RBV	541 (39%)	421 (39%)	120 (42%)	
PEG alone	286 (21%)	234 (22%)	52 (18%)	
<u>HCV Genotype</u>				
1, 4	918 (67%)	726 (67%)	192 (67%)	0.7152(a)
2, 3	449 (33%)	356 (33%)	93 (32%)	
Other/Unknown *	9 (1%)	6 (1%)	3 (1%)	
<u>Ishak Fibrosis Score</u>				
1 – 4	1138 (83%)	887 (82%)	251 (87%)	0.2018(a)
5, 6	186 (14%)	152 (14%)	34 (12%)	
Unknown *	52 (4%)	49 (5%)	3 (1%)	
<u>HIV RNA</u>				
Undetectable	834 (61%)	680 (63%)	154 (53%)	0.0047(a)
Detectable	526 (38%)	397 (36%)	129 (45%)	
Unknown *	16 (1%)	11 (1%)	5 (2%)	
<u>CD4, median (Q1–Q3)</u>				
	485 (349–666)	473 (342–653)	530 (381–719)	0.0006(b)
<u>ARV status</u>				
ARV naïve	194 (14%)	145 (13%)	49 (17%)	0.1553(a)
D4T	595 (43%)	458 (42%)	137 (48%)	0.1142(a)
AZT	456 (33%)	372 (34%)	84 (29%)	0.1541(a)
NRTI only	173 (13%)	121 (11%)	52 (18%)	0.0039(a)
NNRTI and no PI	385 (28%)	310 (28%)	75 (26%)	0.4678(a)
PI	603 (44%)	496 (46%)	107 (37%)	0.0151(a)

(a) P-values are from Cochran-Mantel-Haenszel tests, stratified by study.

(b) P-values are from Wilcoxon rank-sum tests, stratified by study.

* Unknowns were omitted from p-value calculations.

Table 2
Predictors of AE Requiring Withdrawal from Study Treatment

Predictor (reference/unit)	Simple stratified analysis *	
	OR (95% CI)	P-value
Sex (Male)	1.63 (1.19 – 2.24)	0.0026
Age (per 10 years)	1.60 (1.31 – 1.96)	<0.0001
BMI (per kg/m ²)	0.97 (0.93 – 1.01)	0.0870
NNRTI (Yes)**	1.20 (0.88 – 1.63)	0.2480
HGB (per g/dL)	0.90 (0.81 – 0.99)	0.0303
Multi-covariate analysis ***		
Predictor (reference/unit)	OR (95% CI)	P-value
<i>Main effects</i>		
Age (per 10 years)	1.70 (1.38 – 2.09)	<0.0001
<i>Interactions</i>		
BMI × Sex ****:		0.0392
BMI (per kg/m ²) in Men	0.94 (0.89 – 0.99)	0.0149
BMI (per kg/m ²) in Women	1.02 (0.96 – 1.08)	0.5799
NNRTI × Sex ****:		0.0309
NNRTI (No) in Men	1.03 (0.71 – 1.49)	0.8864
NNRTI (No) in Women	2.23 (1.22 – 4.07)	0.0087

* Estimates and p-values are from simple logistic regression stratified by study.

** NNRTI interaction with sex had $p < 0.2$ in the simple stratified analysis and was entered in the multi-covariate modeling.

*** Estimates and p-values are from multi-covariate logistic regression stratified by study.

**** Interaction models included both main factors. P-value is for the interaction term.

Table 3
Predictors of AE Requiring Treatment Modification

Predictor (reference/unit)	Simple stratified analysis*	
	OR (95% CI)	P-value
Sex (Male)	1.72 (1.32 – 2.24)	0.0001
HCV RX (non-PEG)	1.97 (1.58 – 2.46)	<0.0001
Race (White)	1.55 (1.17 – 2.07)	0.0026
Age (per 10 years)	1.48 (1.26 – 1.73)	<0.0001
BMI (per kg/m ²)	0.96 (0.93 – 0.99)	0.0058
HCV Genotype (not 1 or 4)	1.28 (1.02 – 1.60)	0.0344
Ishak fibrosis score (1-4)	1.71 (1.25 – 2.35)	0.0009
CD4 (≥500)	1.40 (1.13 – 1.73)	0.0021
ARV naïve (No)	0.61 (0.44 – 0.83)	0.0015
AZT (No)	1.55 (1.23 – 1.94)	0.0002
ANC (per 500 cells/mm ²)	0.93 (0.89 – 0.96)	0.0001
HGB (per g/dL)	0.83 (0.82 – 0.83)	<0.0001
ALT×ULN (per 1 unit)	0.94 (0.89 – 1.00)	0.0392
Predictor (reference/unit)	Multi-covariate analysis**	
	OR (95% CI)	P-value
<i>Main effects</i>		
HCV RX (non-PEG)	2.07 (1.63 – 2.62)	<0.0001
Age (per 10 years)	1.48 (1.25 – 1.76)	<0.0001
BMI (per kg/m ²)	0.96 (0.94 – 0.99)	0.0202
HCV Genotype (not 1 or 4)	1.31 (1.02 – 1.67)	0.0318
Ishak fibr sc (1-4)	1.42 (1.05 – 1.93)	0.0236
ANC (per 500 cells/mm ³)	0.96 (0.92 – 1.00)	0.0496
HGB (per g/dL)	0.81 (0.74 – 0.89)	<0.0001
<i>Interactions</i>		
ARV naïve × Sex***:		0.0011
ARV naïve (No) in Men	0.51 (0.34 - 0.77)	0.0012
ARV naïve (No) in Women	1.96 (0.97 - 3.99)	0.0619
AZT use × Sex***:		0.0010
AZT use (No) in Men	1.08 (0.81 - 1.44)	0.5927
AZT use (No) in Women	3.56 (1.84 - 6.87)	0.0002

* Estimates and p-values are from simple logistic regression stratified by study.

** Estimates and p-values are from multi-covariate logistic regression stratified by study.

*** Interaction models included both main factors. P-value is for the interaction term.