Criteria Grid
Best Practices and Interventions for the Diagnosis and Treatment of Hepatitis C

Best Practice/Intervention:	Bhattacharya D. et al. (2010) Women experience higher rates of adverse events during hepatitis C virus therapy in HIV infection: a meta-analysis. Journal of Acquired Immune Deficiency Syndromes: JAIDS, 55(2):170-175.
Date of Review:	February 8, 2015
Reviewer(s):	Christine Hu

Part A

Category:	**Basic Science** ☐ **Clinical Science** ☐ **Public Health/Epidemiology** ☐ **Social Science** ☐ **Programmatic Review** ☒
Best Practice/Intervention:	**Focus:** **Hepatitis C** ☐ **Hepatitis C/HIV** ☒ **Other:** _____ **Level:** **Group** ☒ **Individual** ☐ **Other:** _____ **Target Population:** **Patients who are in the AIDS Clinical Trials Group (ACTG) A5071, AIDS Pegasys Ribavirin International Coinfection Trial (APRICOT), or Agence Nationale de Recherches sur le SIDA (ANRS) HCO2- RIBAVIC HCV treatment studies with HIV/HCV coinfection and initiated HCV treatment** **Setting: Health care setting/Clinic** ☒ **Home** ☐ **Other:** _____ **Country of Origin:** **United States** **Language:** **English** ☒ **French** ☐ **Other:** _____

Part B

	YES	NO	N/A	COMMENTS
Is the best practice/intervention a meta-analysis or primary research?	☒	☐	☐	meta-analysis; the study aim to investigate whether HIV/HCV co-infected women with HCV treatments experience increase incidence and/or more rapid onset of adverse events leading to treatment modification/discontinuation, as well as whether ARV regiment and BMI were important in predicting adverse events in both women and men

The best practice/intervention has utilized an evidence-based approach to assess:				
Efficacy	☒	☐	☐	Primary endpoints: adverse events requiring treatment discontinuation or first dose modification
Effectiveness	☐	☒	☐	All 3 studies analyzed are clinical trials
The best practice/intervention has been evaluated in more than one patient setting to assess:				
Efficacy	☒	☐	☐	1376 subjects included in the analysis; 288 (21%) were women
Effectiveness	☐	☒	☐	

	YES	NO	N/A	COMMENTS
The best practice/intervention has been operationalized at a multi-country level:	☐	☒	☐	
There is evidence of capacity building to engage individuals to accept treatment/diagnosis	☐	☒	☐	
There is evidence of outreach models and case studies to improve access and availability	☐	☒	☐	
Do the methodology/results described allow the reviewer(s) to assess the generalizability of the results?	☒	☐	☐	Methodology described clearly.
Are the best practices/methodology/results described applicable in developed countries?	☒	☐	☐	
Are the best practices/methodology/results described applicable in developing countries?	☒	☐	☐	A similar meta-analysis could be done with same 3 randomized trials (ACTG 5071, APRICOT, and ANRSHCO2-RIBAVIC) used
Evidence of manpower requirements is indicated in the best practice/intervention	☐	☒	☐	
Juried journal reports of this treatment, intervention, or diagnostic test have occurred	☒	☐	☐	*Journal of Acquired Immune Deficiency Syndrome*
International guideline or protocol has been established	☐	☒	☐	
The best practice/intervention is easily accessed/available electronically	☒	☐	☐	Downloaded electronically at www.jaids.com

Is there evidence of a cost effective analysis? If so, what does the evidence say? ***Please go to Comments section***	☐	☒	☐	
How is the best practice/intervention funded? ***Please got to Comments section***	☐	☐	☐	The authors of the study receive salary support from National Institute of Health
Other relevant information: _____	☐	☐	☐	- Women who are HIV/HCV coinfected were significantly more likely to experience adverse events requiring treatment discontinuation (AETD) and adverse event requiring treatment modification (AEDM) than men during HCV therapy - Women on ART regiment (NNRTI regiments or efavirenz-based regimens) were more likely to discontinue HCV therapy than men - Women were more likely to have AEDMs with AZT-containing ART regiments - Old age was independently associated with AETD and dose modification occurrences Limitations: - Heterogeneity of treatment protocols with varying regimens of interferon and ribavirin in the 3 trial studies - Extensive use of AZT and stavudine antiretrovirals that are less common in the present clinical practice - Overall numbers of women experiencing AETDs and AEDMs were low, leading to interpretation of the interactions and subgroup analyses between men and women

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

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Background: In HIV/ hepatitis C virus (HCV) coinfection, adverse events (AEs) 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 ANRSHCO2-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: Twenty-one percent of 1376 subjects were women; 61% had undetectable HIV RNA; 14% were antiretroviral (ARV) therapy naive at entry; median CD4 was 485 cells per cubicmillimeter. Seventeen percent 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. Seventy-four percent of AETDs and 49% of AEDMs involved constitutional AEs; 18% of AETD depression; and 26% of AEDM neutropenia. We identified interactions with sex and body mass index (BMI) ($P = 0.04$, continuous) and nonnucleoside reverse transcriptase inhibitor ($P = 0.03$); more AETDs were seen in men with lower BMI ($P = 0.01$) and in women on nonnucleoside reverse transcriptase inhibitors ($P = 0.009$). More AEDMs were seen with PEG [odds ratio (OR) = 2.07]; older age (OR = 1.48 per 10 years); decreasing BMI (OR = 1.04 per kg/m^2); HCV genotype 1, 4 (OR = 1.31); Ishak 5, 6 (OR = 1.42); decreasing Hgb (OR = 1.23 per g/dL); and decreasing absolute neutrophil count (1.04 per 500 cells/mm^3). Interactions between sex and ARV-naive status ($P = 0.001$) and zidovudine ($P = 0.001$) were identified: There were more AEDMs in ARV-naive women ($P = 0.06$) and ARV-experienced men ($P = 0.001$) and higher AEDMs in women with zidovudine ($P = 0.0002$).

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.

Key Words: HIV, hepatitis C virus, sex differences, toxicity, drug therapy

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Conflicts of interest: D.B., T.U., and F.T. report no conflicts of interest. J.A. has served on the data safety monitoring board (DSMB) of Tibotec. F.C. 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. R.T.C. has received research support from Roche. J.S.C. has received research grants from Schering Plough, Merck, and Tibotec and has been on the Advisory Boards for BMS and Merck (2008). M.P. has been a consultant for Roche, Merck, and Pharmasset.

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INTRODUCTION

HIV and hepatitis C virus (HCV) coinfection is common, with reported prevalences of 16%–33% in HIV-infected individuals in the United States.[1,2] Liver-related mortality is the leading cause of death among HIV-infected persons in the United States in the highly active antiretroviral therapy era.[3] When compared with HCV monoinfection, hepatitis C therapy is less effective in HIV- and HCV-coinfected 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 (AEs) or laboratory abnormalities ranged from 7% to 21%,[7–9] whereas 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 AEs related to didanosine.[14,15] There is little known, however, about the sex differences in AEs during HCV therapy in HIV/HCV coinfection. Additionally, the relationship between female sex, AEs during therapy, and other factors potentially related to AEs 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 AEs requiring treatment modification or discontinuation. In addition, we examined whether factors such as ARV regimen and BMI were important in predicting AEs 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 trial networks between 2000 and 2003. Subject-level data were 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 3 times weekly for 12 weeks followed by 3 million IU 3 times weekly for 36 weeks with dose-escalated ribavirin.[5] Ribavirin was administered as 600 milligrams per day for 4 weeks, 800 milligrams per day for 4 weeks, and then 1000 milligrams per day for the remainder of the study. In APRICOT, subjects were randomized to peginterferon alfa-2a (180 μg/wk) plus ribavirin (800 mg/d), peginterferon alfa-2a plus placebo, or interferon alfa-2a (3 million IU 3 times a week) plus ribavirin (800 mg/d).[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 AEs. The primary endpoints were adverse events 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 before and during therapy. Because 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 3 studies. Cochran–Mantel–Haenszel tests stratified by study were used to test statistical significance of differences in categorical variables between 2 groups. Stratified Wilcoxon rank-sum tests were used to test the statistical significance of differences between 2 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. $\geq$800,000 IU/mL); baseline HIV-1 RNA (detectable vs. undetectable per definition of each study); baseline CD4 cell count ($<$500 vs. $\geq$500 cells/mm^3); ARV naive at baseline; stavudine use at baseline; zidovudine (AZT) use at baseline; ARV regimen at baseline, nucleoside reverse transcriptase inhibitors only; containing nonnucleoside reverse transcriptase inhibitors (NNRTI) but no protease inhibitor (PI); containing any PI; baseline absolute neutrophil count (ANC, continuous); baseline platelets (continuous); baseline hemoglobin (continuous); baseline alanine aminotransferase (continuous); and baseline aspartate aminotransferase (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 risk methods[16] (treating death, nonresponse, loss to follow-up (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 $P < 0.05$ (2 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

TABLE 1. Baseline Characteristics

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

*P values are from Cochran–Mantel–Haenszel tests, stratified by study.
†Unknowns were omitted from P value calculations.
‡P values are from Wilcoxon rank-sum tests, stratified by study.
D4T, stavudine; NRTI, nucleoside reverse transcriptase inhibitor.

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 naive ($P = 0.16$); 48% of women and 42% of men were on D4T-containing regimens ($P = 0.11$); 18% of women and 11% of men were on nucleoside reverse transcriptase inhibitor–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 nonresponse, 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

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 2 sexes.

Predictors of AETD

In simple stratified analysis, female sex [odds ratio (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 multicovariate 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-naive 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 of 69 AETDs (23%); women on NNRTI therapy were more likely to experience depression, 8 of 25 (32%) than those who were on other ARV or not on ARV 8 of 44 (18%); ($P = 0.02$).

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

TABLE 2. Predictors of AE Requiring Withdrawal from Study Treatment

Predictor (Reference/Unit)	Simple Stratified Analysis* OR (95% CI)	*P*
Sex (male)	1.63 (1.19 to 2.24)	0.0026
Age (per 10 y)	1.60 (1.31 to 1.96)	<0.0001
BMI (per kg/m^2)	0.97 (0.93 to 1.01)	0.0870
NNRTI (yes)†	1.20 (0.88 to 1.63)	0.2480
HGB (per g/dL)	0.90 (0.81 to 0.99)	0.0303
Multicovariate analysis‡		
Main effects		
Age (per 10 y)	1.70 (1.38 to 2.09)	<0.0001
Interactions		
BMI × sex§		0.0392
BMI (per kg/m^2) in men	0.94 (0.89 to 0.99)	0.0149
BMI (per kg/m^2) in women	1.02 (0.96 to 1.08)	0.5799
NNRTI × sex‡		0.0309
NNRTI (no) in men	1.03 (0.71 to 1.49)	0.8864
NNRTI (no) in women	2.23 (1.22 to 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 multicovariate modeling.
‡Estimates and *P* values are from multicovariate 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*
Sex (male)	1.72 (1.32 to 2.24)	0.0001
HCV RX (non-PEG)	1.97 (1.58 to 2.46)	<0.0001
Race (white)	1.55 (1.17 to 2.07)	0.0026
Age (per 10 y)	1. 48 (1.26 to 1.73)	<0.0001
BMI (per kg/m^2)	0.96 (0.93 to 0.99)	0.0058
HCV genotype (not 1 or 4)	1.28 (1.02 to 1.60)	0.0344
Ishak fibrosis score (1–4)	1.71 (1.25 to 2.35)	0.0009
CD4 (≥500)	1.40 (1.13 to 1.73)	0.0021
ARV naive (no)	0.61 (0.44 to 0.83)	0.0015
AZT (no)	1.55 (1.23 to 1.94)	0.0002
ANC (per 500 cells/mm^2)	0.93 (0.89 to 0.96)	0.0001
HGB (per g/dL)	0.83 (0.82 to 0.83)	<0.0001
ALT × ULN (per 1 unit)	0.94 (0.89 to 1.00)	0.0392
Multicovariate analysis†		
Main effects		
HCV RX (non-PEG)	2.07 (1.63 to 2.62)	<0.0001
Age (per 10 y)	1.48 (1.25 to 1.76)	<0.0001
BMI (per kg/m^2)	0.96 (0.94 to 0.99)	0.0202
HCV genotype (not 1 or 4)	1.31 (1.02 to 1.67)	0.0318
Ishak fibrosis score (1–4)	1.42 (1.05 to 1.93)	0.0236
ANC (per 500 cells/mm^3)	0.96 (0.92 to 1.00)	0.0496
HGB (per g/dL)	0.81 (0.74 to 0.89)	<0.0001
Interactions		
ARV naive × sex‡		0.0011
ARV naive (no) in men	0.51 (0.34 to 0.77)	0.0012
ARV naive (no) in women	1.96 (0.97 to 3.99)	0.0619
AZT use × sex‡		0.0010
AZT use (no) in men	1.08 (0.81 to 1.44)	0.5927
AZT use (no) in women	3.56 (1.84 to 6.87)	0.0002

*Estimates and *P* values are from simple logistic regression stratified by study.
†Estimates and *P* values are from multicovariate logistic regression stratified by study.
‡Interaction models included both main factors. *P* value is for the interaction term.

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 alanine aminotransferase 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 multicovariate analysis, receipt of pegylated interferon therapy (OR = 2.07, $P < 0.0001$), increasing age (OR = 1.48 per 10 years), 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-naive status ($P = 0.001$) and between sex and AZT use ($P = 0.001$). Interestingly, ARV-naive women were more likely to experience AEDMs than ARV-experienced women (OR = 1.96, $P = 0.06$), but ARV-naive men were less likely to experience AEDMs (OR = 0.51, $P = 0.001$). In women, more AEDMs were seen with AZT compared with 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 of 67 (30%) vs. 21 of 108 (19%) ($P = 0.12$) and 23 of 67 (34%) vs. 13 of 108 (12%) ($P = 0.0004$), respectively.

Time to AETD and AEDM

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 to 2.04) for women compared with men ($P = 0.003$), whereas the Cox proportional hazards ratio for time to AEDM was 1.43 (95% CI: 1.20 to 1.70) for women compared with men ($P < 0.0001$) (Fig. 1). The median time to AEDM was 24 weeks in women and 48 weeks in men. There was also a trend toward 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 3 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 AEs 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 AETD and women on AZT-containing regimens experienced more AEs requiring interferon or ribavirin dose modification.

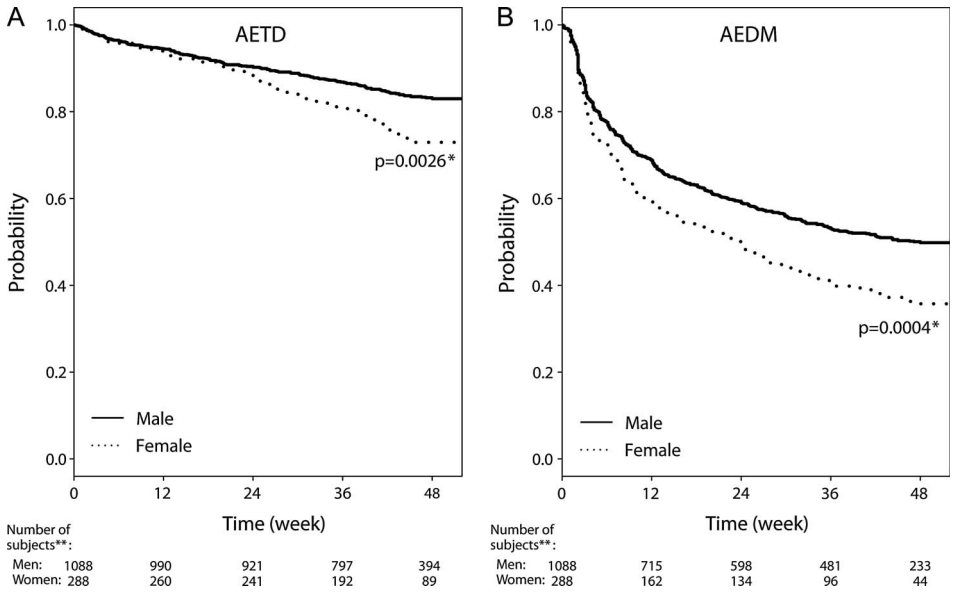

FIGURE 1. A, Sex effect on the Time to AE requiring treatment discontinuation. B, Sex effect on the Time to AE requiring first study treatment dose modification.

This is the first study to demonstrate that HIV-infected women on hepatitis C therapy experience more AETDs. Although similar sex effects on treatment discontinuation were not reported in large trials of HIV-uninfected HCV-infected women receiving interferon and ribavirin therapy,[7–9] other hepatitis C monoinfection analyses have demonstrated that women experience some AEs (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 to 2.27),[17] whereas in the ICONA study group, women were twice as likely to discontinue treatment secondary to toxicity.[18] Conversely, 3 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 et al[14] demonstrated that women were 1.25 times more likely to modify didanosine dosage. In HIV infection, women are also more likely to experience AEs 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 AEs 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 (EFV)-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 EFV 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 EFV-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 monoinfection trials, Sulkowski et al[10] found that the incidence of reaching a Hgb <10 g/dL was 4-fold higher in women, whereas 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 et al 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 AEs were well managed in this clinical trial setting.

We also found that older age was independently associated with the incidence of AETD and dose modification. This is supported by Sulkowski et al[10] who also found that older age was associated with hemoglobin decrease in hepatitis C monoinfection 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 to 800 mg, and subjects who experienced severe AEs stopped therapy. This dose escalation, however, would only have masked severe AEs. Additionally, the 3 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 (AZT and stavudine) that are less common in clinical practice today. Newer more tolerable ARV regimens such as the nucleses(t)ide transcriptase inhibitor combinations (ie, 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 LFU, death, nonresponse, and unknown reasons for discontinuation. Therefore, time to AETD and time to first dose modification, respectively, were also analyzed in the competing risks setting, treating death, nonresponse, 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 AEs and, if dropout 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 AEs between men and women, with caution.

In conclusion, women are more likely to experience AEs, 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 AEs 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 AEs in HIV/HCV coinfection trials.

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