

# EFFICACY OF PEGYLATED INTERFERON PLUS RIBAVIRIN TREATMENT IN HIV/HEPATITIS C VIRUS-COINFECTED PATIENTS RECEIVING ABACAVIR PLUS LAMIVUDINE OR TENOFOVIR PLUS EITHER LAMIVUDINE OR EMTRICITABINE AS NUCLEOSIDE ANALOGUE BACKBONE

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## ABSTRACT

**BACKGROUND:** Recent studies have provided data suggesting that the administration of abacavir (ABC) along with pegylated interferon (PEG-IFN) and ribavirin (RBV) is associated with lower rates of response to HCV therapy. However, in most of these studies, ABC was combined with zidovudine in a substantial proportion of patients, which could have been a confounder.

**OBJECTIVE:** The aim of this study was to compare the efficacy of PEG-IFN plus RBV combination among HIV/HCV-coinfected patients taking a nucleos(t)ide reverse transcriptase inhibitor (N(t)RTI) backbone consisting of ABC plus lamivudine (3TC) with that observed in subjects who receive tenofovir (TDF) plus 3TC or emtricitabine (FTC).

**PATIENTS AND METHODS:** Two hundred and fifty-six patients starting first-line PEG-IFN and RBV while under a three-drug antiretroviral regimen including one protease inhibitor (PI) or one non-nucleoside reverse transcriptase inhibitor (NNRTI) and ABC plus 3TC or TDF plus 3TC or FTC as N(t)RTI backbone were included in this retrospective multicenter study. Sustained virologic response (SVR) rates in both groups were compared, along with other associated factors.

**RESULTS:** In an intention-to-treat analysis, 20 out of 70 (29%) individuals receiving ABC and 83 out of 186 (45%) who were treated with TDF showed SVR (p=0.02). N(t)RTI backbone containing TDF was an independent predictor of SVR in the multivariate analysis [adjusted odds ratio (95% CI) 2.6 (1.05-6.9); p=0.03]. HCV genotype 2 or 3, baseline LDL cholesterol levels  $\geq 100$  mg/dL, lower baseline plasma HCV-RNA load and undetectable baseline HIV viral load also predicted SVR. The association between ABC use and lower SVR rate was mainly seen in patients with plasma HCV-RNA load higher than 600,000 IU/mL, HCV genotype 1 or 4 and in who received lower dose of RBV. More in detail, among individuals treated with daily dose of RBV  $<13.2$  mg/kg, 3 (20%) of those under ABC vs. 22 (52%) under TDF reached SVR (p=0.03), whereas the rates were 31% and 38% (p=0.4), respectively, in those receiving RBV dose  $\geq 13.2$  mg/kg.

**CONCLUSIONS:** HIV/HCV-coinfected patients who receive ABC plus 3TC respond worse to PEG-IFN plus RBV than those who are given TDF plus 3TC or FTC as N(t)RTI backbone. Differences between these N(t)RTI combinations are chiefly observed in subjects receiving lower RBV doses and in patients who need higher dosage of this drug. These findings suggest a negative interaction between RBV and ABC.

## BACKGROUND

Recent studies have provided data suggesting that abacavir (ABC) use along with pegylated interferon (PEG-IFN) and ribavirin (RBV) therapy is associated with lower rates of response to HCV therapy.

However, in most of the former studies, ABC was given along with zidovudine in a substantial proportion of individuals. As the latter antiretroviral may enhance the hematological toxicity of RBV, it could have been a confounder in these studies.

In addition, the most commonly used nucleos(t)ide reverse transcriptase inhibitor (N(t)RTI) backbones in developed countries currently are ABC plus lamivudine (3TC) and tenofovir (TDF) plus emtricitabine (FTC). Because of these reasons, it is critical to clarify if the combination of ABC plus 3TC as N(t)RTI backbone is associated with lower sustained virologic response (SVR) rates to PEG-IFN and RBV treatment.

## OBJECTIVE

To compare the efficacy of PEG-IFN plus RBV combination among HIV/HCV-coinfected patients taking a N(t)RTI backbone consisting of ABC plus 3TC with that observed in subjects who receive TDF plus 3TC or FTC.

## PATIENTS AND METHODS

### Patients

HIV/HCV-coinfected patients previously naïve for therapy against HCV infection (age  $\geq 16$  years) with detectable serum HCV-RNA level followed in fifteen hospitals in Spain.

### Study design

This was a retrospective multicenter study of the patients attending in the participating centers who were treated with PEG-IFN plus RBV and a three-drug antiretroviral regimen including one protease inhibitor (PI) or one non-nucleoside reverse transcriptase inhibitor (NNRTI) along with ABC plus 3TC or TDF plus 3TC or FTC as N(t)RTI backbone during HCV therapy. The study period lasted from October 2001 to January 2006.

### Treatment regimens

All individuals were treated with the combination of subcutaneous PEG-IFN alpha-2a (180  $\mu$ g/week) or alpha-2b (1.5  $\mu$ g/kg/week) plus oral RBV (600-1500 mg/day). The length of the therapy was 48 weeks in all HCV genotype 1 or 4 carriers. Subjects harboring HCV genotype 2 or 3 received HCV therapy during 24 or 48 weeks, according to the decision of the caring physician. Temporary discontinuations and stepwise reductions in PEG-IFN and RBV dosage, and the use of growth factors were done according to the decision of the physician who was in charge of the patient.

### Assessment of efficacy

The main outcome variable was SVR, defined as undetectable serum HCV-RNA 24 weeks after completion of PEG-IFN plus RBV treatment.

### Statistical analysis

Two sensitivity analyses were carried out for estimating the efficacy: The first one was done according the principle of intention to treat, considering all missing values as failures. The second one was per-protocol analysis.

Univariate and multiple logistic regression analysis were performed to identify factors predictive of SVR, including the type of N(t)RTI backbone administered during the course of HCV therapy.

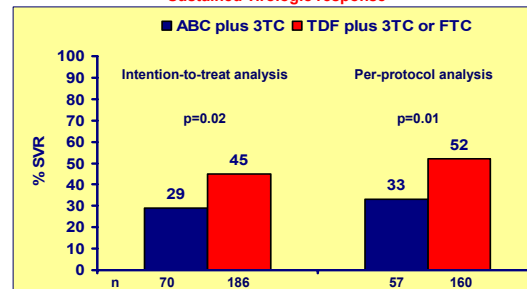
## RESULTS

### Characteristics of the study population

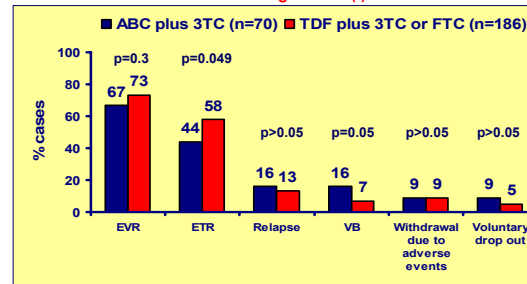
Parameter	TDF-3TC/FTC group n=186	ABC-3TC group n=70	p
Age (years)*	42 (38-45)	41 (39-44)	0.6
Male gender, n (%)	149 (80)	50 (71)	0.2
Baseline body weight (kg)*	69 (61-76)	68 (60-76)	0.5
Baseline LDL-cholesterol (mg/dL)*	91 (66-112)	89 (65-115)	0.7
Baseline HCV-RNA load (log <sub>10</sub> IU/mL)*	5.8 (5.4-6.5)	6 (5.6-6.7)	0.02
HCV genotype 1-4, n (%)	121 (65)	52 (74)	0.2
Advanced liver fibrosis (F3-F4), n (%)†	56 (46)	28 (49)	0.7
Use of PEG-IFN alpha-2a, n (%)	170 (91)	64 (91)	0.9
RBV dose/weight (mg/Kg/day)*‡	14.7 (13.1-16.1)	14.7 (13.3-16.3)	0.8
Baseline CD4 cell counts/mm <sup>3</sup>	479 (351-699)	458 (301-600)	0.3
Baseline undetectable HIV viral load, n (%)	159 (85)	63 (90)	0.4
PEG-IFN dose reduction, n (%)	22 (12)	7 (10)	0.8
RBV dose reduction, n (%)	19 (10)	8 (11)	0.8
Compliance with HCV therapy $\geq 80\%$ , n (%)	180 (96)	64 (92)	0.1
Use of growth factors, n (%)	13 (9)	6 (12)	0.6
PIs as third drug in ART combination, n (%)	79 (43)	36 (51)	0.2

\* Median (Q1-Q3); † Liver biopsy was available in 123 individuals in the TDF group and in 57 subjects in the ABC group. ‡ Available in 167 patients in the TDF group and in 69 individuals in the ABC group.

### Sustained virologic response

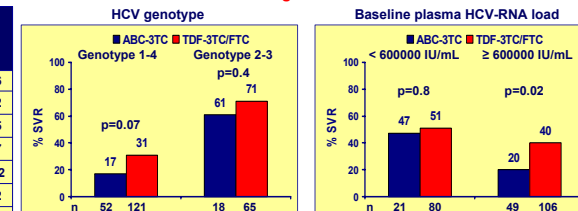


### Other outcomes according to the N(t)RTI backbone

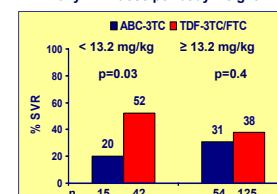


EVR: Early virologic response. ETR: End of treatment response. VB: Viral breakthrough.

### SVR according to different variables



### Daily RBV dose per body-weight



### Factors associated with sustained virologic response

Parameter	SVR no. (%)	p univariate	Adjusted Odds Ratio (AOR) (95% CI)	p multivariate
HCV genotype 1-4	46 (27)			
2-3	57 (69)	< 0.001	8.9 (4-20)	< 0.001
HCV-RNA (log <sub>10</sub> IU/mL)*			1.85† (1.1-3.1)	0.016
Type of PEG-IFN				
Alfa-2a	94 (40)			
Alfa-2b	9 (41)	0.9	-	-
Exposure to HCV therapy				
< 80%	3 (25)			
$\geq 80\%$	100 (41)	0.3	-	-
CD4 cell count/mm <sup>3</sup>				
$\geq 200$	99 (40)			
< 200	4 (44)	0.8	-	-
LDL-cholesterol (mg/dL)				
$\geq 100$	34 (56)			
< 100	35 (31)	0.003	3.06 (1.4-6.7)	0.004
Daily dose of RBV (mg/kg)				
< 13.2	25 (44)			
$\geq 13.2$	65 (36)	0.3	-	-
Undetectable plasma HIV-RNA				
Yes	96 (43)			
No	7 (21)	0.02	3.5 (1.01-12.5)	0.03
N(t)RTIs backbone				
ABC plus 3TC	20 (29)			
TDF plus 3TC or FTC	83 (45)	0.02	2.6 (1.05-6.9)	0.03
Third drug in ART combination				
PIs	40 (35)			
NNRTIs	63 (45)	0.1	-	-

\* Median (Q1-Q3) HCV-RNA levels in patients with and without SVR were 5.8 log IU/mL (5.2-6.1) and 6 log IU/mL (5.6-6.7), respectively (p=0.02). † Increase in AOR per one log HCV-RNA decrease.

## CONCLUSIONS

- HIV/HCV-coinfected patients who receive a three-drug regimen including one PI or one NNRTI and ABC plus 3TC respond worse to PEG-IFN plus RBV treatment than those who take TDF plus 3TC or FTC as N(t)RTI backbone.
- The negative impact of ABC on SVR is particularly remarkable among individuals receiving lower RBV doses per body-weight and in patients who need to be treated with higher doses of RBV, as carriers of elevated baseline HCV-RNA levels and of HCV genotype 1 or 4.
- These data suggest a negative interaction between RBV and ABC.

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