

# The progression of liver fibrosis in prison inmates co-infected by HIV and HCV who started on boosted protease inhibitor therapy

P Saiz de la Hoya Zamácola, C Alía Alía, A Marco,  
A López Burgos, J de Juan Ramírez, A Herrero Matías,  
J Portilla Sogorb

Healthcare Services. Fontcalet Prison, Alicante

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## ABSTRACT:

**Objectives:** To analyse the progression of liver fibrosis as measured by elastography and biochemical testing in prison inmates co-infected by HIV and HCV who started on ritonavir-boosted protease inhibitor (PI) therapy.

**Methods:** A prospective, observational and multi-centre study. The progression of liver fibrosis as measured by transient elastography (FibroScan) and biochemical testing was monitored for 48 weeks in a Spanish prison population co-infected with HIV and HCV.

**Results:** Of the 94 patients included, 54 (57.4%) were followed-up for 48 weeks. At week 48, no significant changes were seen in the grade of fibrosis measured using FibroScan (8.1 kPa vs. 8.3 kPa;  $p=0.20$ ) or the Forns index (5.6 vs. 5.1;  $p=0.50$ ), although significant changes were detected using the APRI (0.7 vs. 0.6;  $p=0.05$ ) and the FIB-4 indexes ( $p=0.02$ ). When measurement was done compared to baseline fibrosis, it was seen that therapy reduced the percentage of patients with fibrosis  $\geq 3$  but  $< 4$  (50% vs. 15%;  $p=0.001$ ), but no change was seen in those found to have grade 4 fibrosis at baseline (20.4% vs. 20.4%).

**Conclusion:** The inmates co-infected with HIV and HCV who were started on antiretroviral therapy with the boosted protease inhibitor (PI) showed staterilizationbilisation of the liver fibrosis as measured with FibroScan after one year of follow-up. Overall, the therapy improved fibrosis when measured using the APRI or FIB-4 indexes, but not when using the Forns index or elastography.

**Key words:** HIV; HCV Antibodies; Highly Active Antiretroviral Therapy; Protease inhibitors; Prisons; Liver cirrhosis; Elasticity Imaging Techniques; Liver Function Tests.

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## INTRODUCTION

Mortality due to liver disease is the primary cause of death in patients infected by HIV (human immunodeficiency virus) in Spain,<sup>1</sup> with the degree of immunodeficiency, patient age and coinfection with the hepatitis B virus (HBV) and hepatitis C virus (HCV) being the primary associated causes. The consumption of alcohol must be added to these factors, as it can greatly complicate the evolution of the disease in this type of patient.<sup>2-3</sup>

HCV and HIV share the same routes of infection, and coinfection with HIV and HCV is therefore very common in intravenous drug users (IDU), who often enter prison. It is estimated that the current prevalence of HIV infection in prison inmates in Spain is 10.8%.<sup>4</sup> Of the patients infected with HIV, 85% are also infected with HCV,<sup>4</sup> while 40.5% of those infected with HCV are co-infected with HIV.<sup>5</sup>

The rate of HIV-HCV coinfection among inmates is 9.5%, which would mean that more than 6000 inmates are currently co-infected with the two viru-

ses.<sup>4-7</sup> The prevalence of both viruses in the inmate population is 15 to 18 times greater than in the general population.<sup>8</sup>

The progression of liver damage caused by the infection is determined by the grade of the fibrosis. Until recently, the appearance of fibrosis and its grade of progression could be known only by using a liver punch biopsy, a test with limitations regarding availability, cost and safety, and which although it is a diagnostic test that usually involves few complications, is not risk free. The appearance of transient elastography (FibroScan), a test which is less specific, but more easily available, safer and less expensive, has permitted repeated assessment of the progression of fibrosis in both monoinfected<sup>9</sup> and coinfecting<sup>10</sup> patients. When biochemical methods of estimation (APRI, Forns, etc.), the usefulness of which has been validated in prisons,<sup>11</sup> are added to transient elastography, diagnostic tools are obtained that do not use invasive procedures and permit determination of the progression of liver fibrosis with greater patient comfort.<sup>12</sup>

Many factors are thought to be predictors of the progression of fibrosis, among these are the use of certain families of antiretroviral drugs,<sup>13-19</sup> although the degree of their true involvement has not been determined with absolute certainty. Our study was designed with the objective of aiding in clarifying this question by identifying the progression of liver fibrosis in patients co-infected with HIV and HCV who were started on antiretroviral treatment with ritonavir-boosted protease inhibitors as well as two nucleoside analogue (NA) inhibitors.

## MATERIAL AND METHODS

The FIBROHCEP Study (*FIBROsis Hepática en Centros Penitenciarios* [liver fibrosis in penitentiaries]) is a prospective, observational and multicentre study conducted in 16 Spanish prisons in 2008 and 2009. The progression of liver fibrosis was studied in inmates co-infected with HIV and HCV who began antiretroviral therapy with a ritonavir-boosted PI and two nucleoside analogues. The follow-up period lasted for 48 weeks.

Patients were included who met the following inclusion criteria: a) age 18 or over; B) HIV infection; C) positive HCV RNA test; D) foreseen prison stay of two or more years; e) start of treatment with PI+ritonavir and two nucleoside analogue reverse-transcriptase inhibitors (NRTIs); f) no requirement for treatment of hepatitis C foreseen during the ob-

servation period; and g) performance of baseline transient elastography ( $\pm$  3 months from start of therapy) and at 48 weeks.

The following were considered exclusion criteria: 1) pregnancy; 2) the existence of other possible causes of hepatitis; 3) presence of ascites, portal hypertension, hepatic encephalopathy, spontaneous bacterial peritonitis or hepatocellular carcinoma; 4) evidence of consumption of alcohol, drugs or hepatotoxic medicines at the time of the study; 5) inability, in the judgment of the investigator, to comply with the requirements of the study.

The primary objective of our study was to analyse the progression of liver fibrosis using non-invasive testing (transient elastography) for a period of 48 weeks in patients who had begun antiretroviral therapy with a combination (ritonavir-boosted PI and two NAs) selected by the treating physician. In addition to transient elastography, the biochemical APRI, Forns, and FIB-4 tests were also used to calculate the progression of fibrosis.

Internationally recognised cut-off points<sup>10,20-23</sup> were used to assess fibrosis (FibroScan  $>12$  or APRI  $>2$  for grade 4 fibrosis, and FibroScan  $>9$ , Forns  $>6.9$ , APRI  $>1.5$  or FIB-4  $>3.25$  for grade 3/4 fibrosis).

The immunological and virological efficacy of the selected regimen were also evaluated using the CD4<sup>+</sup> lymphocyte count (cells/mm<sup>3</sup>) and the plasma HIV viral load (copies/ml) respectively.

The study was approved by the Ethics Committee of the Hospital General Universitario de Alicante. Participants received an information sheet which explained the study and the corresponding informed consent form.

Statistical analysis was performed using the SPSS statistical program, version 10.0. Parametric quantitative variables were described using the mean and standard deviation (SD), while for nonparametric quantitative variables, the median and 25/75 percentiles were used. The comparative study was performed using the baseline data and those collected at 48 weeks, but excluding those individuals for whom data was lacking for a comparison of any of the variables analysed.

To determine if differences existed and, given that the same patients were being assessed at different times, a pre-post study was conducted. For that purpose, once the normality or non-normality of distribution of variables had been demonstrated using the Kolmogorov-Smirnov test, the data were studied using the comparison of means test for two dependent samples (parametric test) or the Wilcoxon test (nonparametric test). Qualitative variables were com-

pared using Pearson's chi-square test. For qualitative or ordinal variables, the linear-by-linear association chi-square test was used. The level of statistical significance in hypothesis testing was  $p \leq 0.05$ .

## RESULTS

A total of 94 patients were included, of whom 89 (94.7%) were male, with a mean age ( $\pm$ SD) of 39.2 years ( $\pm$  4.2 years). Of the total, 96.8% had a history of intravenous drug use; 80 (85.1%) reported no alcohol consumption in the previous year, and of the remainder, only 4 (4.4%) reported consuming 10 or more units of alcohol per month; while 2 patients presented with other causes of liver disease (lupus and HBV); and 5 (5.4%) had previously-diagnosed cirrhosis.

Other patient characteristics related to the HIV and HCV infections can be seen in Table 1.

The protease inhibitors used were lopinavir/ritonavir in 89 (94.7%) patients, fosamprenavir/ritonavir in 4 (4.3%) and atazanavir/ritonavir in 1 (1.1%). The NRTIs used were Truvada<sup>®</sup>, (TDF+FTC) in 64.9%, Kivexa<sup>®</sup> (3TC+ABC) in 24.5%, Combivir<sup>®</sup> (AZT+3TC) in 6.4% and others, which were not co-formulations, in 4.3%.

Concomitant treatment with methadone was being administered to 35.5% of patients. Psychiatric drug therapy was being administered to 66%, while 13.8% were receiving co-trimoxazole.

At the baseline visit, the median (25/75 percentiles) of the results for FibroScan<sup>®</sup> in the 94 patients included was 7.8 kPa (6.2/10.8), while for the biochemical tests they were 0.7 (0.4/1.4) for APRI; 5.5 (4.1/7.1) for Forns; and 1.3 (0.9/2.49) for FIB-4.

The following results were obtained in the baseline biochemistry tests for fibrosis:

• APRI <0,5	Grade F0/F1;	35 patients (37,6%)
• APRI >1,5	Grade F3/F4;	21 patients (22,6%)
• APRI >2	Grade F4	12 patients (12,9%)
• FORNS <4,2	Grade 0/F1;	27 patients (29,4%)
• FORNS >6,9	Grade F3/F4	25 patients (27,2%)
• FIB4 <1,45	Grade F0/F1;	46 patients (54,1%)
• FIB4 >3,25	Grade F3/F4	13 patients (15,3%)

Analysing the biochemistry methods and the FibroScan together, it can be determined that 45 patients (48.4%) had grade 3/4 fibrosis at baseline and 19 patients (20.4%), grade 4.

Table 2 shows the overall results for the FibroScan and the biochemistry tests in assessing the fibrosis.

By analysing the biochemical methods and FibroScan jointly and using predetermined cut-off points<sup>10,19-22</sup> for assessment, it was possible to determine that of the 94 patients included, 45 patients (48.4%) had fibrosis grade 3/4 (FibroScan >9, Forns >6.9, APRI >1.5 or FIB-4 >3.25) and that 19 patients (20.4%) had fibrosis grade 4 (FibroScan >12 or APRI >2).

At 48 weeks, 54 (57.4%) of the 94 patients initially included in the study remained. A change of the PI used was necessary in 5 patients due to intolerance or adverse events.

Changes in anthropometric and laboratory values occurring in these patients between baseline and week 48 of follow-up are shown in Table 3.

Regarding overall changes in the grade of fibrosis (Table 4), the median of the results using FibroScan was 8.1 kPa at baseline and 8.3 kPa at week 48, without statistically significant differences ( $p=0.20$ ). Using biochemical methods, the median fibrosis varied with APRI from 0.7 to 0.6 ( $p=0.05$ ) and for FIB-4 from 1.5 to 1.4 ( $p=0.02$ ); however, no statistically significant differences were found when calculated using Forns index (from 5.6 to 5.1;  $p=0.5$ ).

However, when progression was measured separately based on the grade of baseline fibrosis it was observed that the therapy had reduced the percentage of patients with fibrosis 3/4 (50% vs. 15%;  $p=0.001$ ), but that no change had been demonstrated in patients with grade 4 fibrosis at baseline (20.4% vs. 20.4%) (Table 5).

A mean increase of 119 CD4<sup>+</sup> lymphocytes/mm<sup>3</sup> ( $p<0.0001$ ) was also seen, as well as a reduction in the median viral load of HIV, which fell from 16,700 copies/ml to 0 copies/ml.

## DISCUSSION

Our study did not find overall differences between the results of elastography conducted at the baseline visit and at one year of antiretroviral therapy with PI/ritonavir (the primary objective), although the loss of patients (40 in 1 year) and the decision not to continue the study for that reason, may have influenced the inability to define such differences. However, we did observe significant reductions in the fibrosis indexes measured by biochemical procedures such as APRI and FIB-4, even though these changes were not observed using Forns index. It should be noted, however, that when measurement was done compared to baseline fibrosis, it was seen that therapy reduced the percentage of patients with fibrosis 3/4

Table 1. Study Population Characteristics (n=94).

	Mean	±SD
Mean age	39.2	4.2
Weight (Kg) (n=93)	69.5	11.2
Height cm (n=90)	172.6	8
Years infected with HIV	15	6.3
Baseline CD4 (start of study)	282	164
Years of treatment since 1st antiretroviral treatment (n=86)	7	4.8
Years infected with HCV (n=90)	20	5
	Median	25/75 percentile
Baseline HIV viral load in cop/ml (start of study)	17600	311/81234
Baseline HCV viral load, in IU/ml (start of study) (n=74)	1930000	464500/10501344
	n.	%
Male gender	89	94.7
IDU	80	85.1
Alcohol consumption >10 units of alcohol units/month (prior to inclusion)	4	4.4
Cirrhosis	5	5.4
Diagnosed with AIDS (n=79)	17	21.5
CD4 nadir <200	50	63.3
Antiretroviral therapy (ART) prior to study	31	33

SD: Standard Desviation. HIV: Human immunodeficiency virus. HCV: Hepatitis C virus. IDU: Injecting drug users.

Table 2. Baseline results of the Fibrosis assessment tests.

	Mean	SD	Median	Percentiles 25/75
FibroScan (n=75)	12.1	12.2	7.8	6.2/10.8
APRI (n=93)	1.2	1.4	0.7	0.4/1.4
FORNS (n=92)	5.7	2.1	5.5	4.1/7.1
FIB4 (n=85)	2.3	2.6	1.3	0.9/2.4

The shaded results indicate the test that best defined the variable whether or not it had parametric distribution.

(50% vs. 15%;  $p=0.001$ ), although no change was seen in those found to have grade  $\geq 4$  fibrosis at baseline (20.4% vs. 20.4%). These results are similar to those found in other studies in non-inmate, co-infected populations.<sup>14-17</sup>

Coinfection by HIV and HCV worsens the histological course of hepatitis and increases the risk of progression of cirrhosis. The viral load of HCV (RNA/IU) affects this situation, with progression worsening when the quantity of circulating vi-

Table 3: Patient characteristics (n=54) at baseline visit and 48 weeks with comparison of variables

Variables:	Mean Baseline Visit (95% CI)	Mean Visit (week 48) (95% CI)	Difference Means (95% CI)	Significance (p)
Weight (kg)	70.2 (67.1 to 72.9)	72.3 (68.3 to 74.3)	2.1 (-0.3 to 4.4)	0.088
BMI (kg/m <sup>2</sup> )	23.3 (22.4 to 23.9)	24.1 (22.8 to 24.5)	0.8 (-0.1 to 1.7)	0.086
Waist circumference (cm)	85.9 (83.5 to 88.6)	86.6 (83.4 to 89.6)	0.7 (-0.8 to 2.2)	0.374
CD4 (cells/mcl)	269.3 (223.3 to 313.9)	388.3 (329.1 to 434.5)	118.9 (73.4 to 164.4)	<0.0001
Quick Index	88.9 (72.5 to 93.0)	91.5 (84.6 to 96.9)	2.6 (-2.0 to 7.1)	0.241
GGT	116.3 (88.9 to 341.9)	84.2 (20.0 to 176.5)	-32.1 (-57.2 to -7.0)	0.013
Albumin	4.2 (1.7 to 7.3)	4.4 (3.5 to 4.7)	0.2 (-0.3 to 0.7)	0.375
Glucose	91.0 (81.2 to 97.8)	92.6 (85.8 to 95.7)	1.6 (-6.7 to 9.9)	0.703
HDL cholesterol	34.5 (20.7 to 39.3)	39.6 (25.2 to 52.8)	5.1 (-0.05 to 10.2)	0.052
Total cholesterol	162.4 (120.8 to 222.2)	183.9 (138.3 to 207.2)	21.5 (6.9 to 36.0)	0.005
LDL cholesterol	91.8 (46.9 to 151.5)	93.6 (82.1 to 111.4)	1.8 (-7.8 to 11.4)	0.702

BMI: Body mass index. GGT: Gama glutamil transpeptidase. HDL: High Density lipoproteins. LDL: Low Density Lipoproteins.

Analytical variables	Median Baseline Visit (P <sub>25</sub> , P <sub>75</sub> )	Median Visit (week.48) (P <sub>25</sub> , P <sub>75</sub> )	Significance (Wilcoxon Test)
HIV viral load	16,700 (232.5 and 65,040.5)	0 (0 and 29.8)	<0.0001
HCV viral load	3,000,000 (453,000.0 and 13,133,420.5)	690,849.5 (331,165.0 and 3,466,880.5)	0.005
AFP	2.9 (1.6 and 4.7)	4.2 (1.4 and 5.5)	0.556
AST	53.0 (29.0 and 93.0)	41.0 (33.0 and 55.0)	0.712
ALT	58.0 (43.0 and 128.0)	51.0 (34.0 and 59.0)	0.515
Total bilirubin	0.6 (0.5 and 0.7)	0.7 (0.5 and 0.8)	0.054
Alkaline phosphatases	75.0 (74.0 and 135.0)	98.0 (72.0 and 132.0)	0.580
Triglycerides	122.0 (106.0 and 195.0)	152.0 (113.0 and 207.0)	<0.0001

AFP: Alpha-fetoprotein. ALT: Alanine aminotransferase. AST: Aspartate aminotransferase.

Table 4: Comparison of results of FibroScan® and biochemistry tests at the baseline week and week 48. (n=54)

Variable:	Median Baseline Visit (P <sub>25</sub> , P <sub>75</sub> )	Median Visit (week.48) (P <sub>25</sub> , P <sub>75</sub> )	Significance (Wilcoxon Test) (p)
FibroScan	7.8 (6.2 and 10.8)	8.3 (6.2 and 16.2)	0.203
APRI Index	0.7 (0.4 and 1.4)	0.6 (0.3 and 0.9)	0.056
FIB-4 Index	1.3 (0.9 and 2.4)	1.4 (0.9 and 2.0)	<b>0.022</b>
Forns Index	5.5 (4.1 to 7.1)	5.1 (4.6 to 5.6)	<b>0.5</b> (0.07 to 0.9)

Table 5: Comparison of fibrosis at baseline visit and week 48 measured by biochemistry testing and elastography (n=54)

Fibrosis grade	Baseline visit % (n) (95 CI)	Visit, week 48 % (n) (95 CI)	P
<b>Patients Grade ≥3*</b>	Grade 3: 50 (27) Others: 27 (50) (36.1-63.9)	Grade 3: 27.8 (15) Others: 62.2 (39) (16.5-41.6)	0.001
<b>Patients Grade 4**</b>	Grade 4: 20.4 (11) Others 79.6 (43) (10.6-33.5)	Grade 4: 20.4 (11) Others: 79.6 (43) (10.6-33.5)	NS

\* Patients are considered to be in grade 3 when FibroScan >9, Forns >6.9, APRI >1.5 or FIB-4 >3.25, according to internationally-recognised cut-off criteria<sup>10,20-23</sup>

\*\*Patients are considered to be in grade 4 when FibroScan >12 or APRI >2, according to internationally-recognised cut-off criteria<sup>10,20-23</sup>

ral RNA is higher. It has been suggested that when highly active antiretroviral therapy (HAART) is started, HCV RNA levels fall due to an improved immune response. However, this hypothesis is controversial given that some studies have not necessarily found reductions in the hepatitis C plasma viral load to be associated with the initiation of HAART. Any such changes observed could be due to other factors, such as natural fluctuation of viral RNA over time, the severity of hepatic dysfunction, varied levels of HIV viraemia, treatment compliance or alcohol consumption.<sup>24-28</sup> In our study, a significant reduction was observed in viral load levels of HCV (Table 3) one year after the start of HAART. These data seem consistent with those reported in other studies which examine the impact of PIs in co-infected HIV-HCV patients treated with these drugs for six months. In one of these studies, it was noted that HCV RNA

was 3 to 4 times lower than in patients who had not received treatment.<sup>24</sup> Another study carried out with 112 co-infected patients treated for 24 months with ritonavir-boosted PIs found that 29% showed significant increases in HCV plasma viral load, while 22% showed a reduction and in 60% no changes of importance were observed.<sup>25</sup> It is likely that antiretroviral therapy behaves, at least in some cases, as a protective factor against the progression of liver fibrosis.<sup>26</sup> It is for this reason that treated patients experience reduced mortality in general as well as due to liver-related causes,<sup>27</sup> along with reduced progression of cirrhosis and a lesser degree of hepatotoxicity.<sup>26-28</sup>

It is important to note the high percentage of indefinable results found (those not indicative of a particular grade of fibrosis) when using either liver elastography or biochemical testing. These results suggest that these methods, although valid, could be

improved, above all for the intermediate grades of liver fibrosis.

In terms of laboratory results, our study showed an insignificant reduction in ALT and AST, but significant reductions in GGT. This data could be related to administration of HAART, but it is more likely that it might be due to the period of abstinence from alcohol that being in prison would be expected to involve. Other changes, such as increases in triglycerides and plasma cholesterol, are presumably associated with the use of PIs, which are drugs capable of altering the lipid profile.<sup>29-30</sup> In addition, as would be expected, the patients showed immunological and virological improvement during the 48 weeks that HAART was instituted. It should be remembered in any case that our study was not designed for the purpose of demonstrating the efficacy of the treatment, and that the sample studied is extraordinarily heterogeneous and not comparable to others. Therefore, the data obtained are only indicative in this respect, as they are subject to significant biases.

One important limitation of this study is the high percentage of patients lost to follow-up (42.6%). The loss is due to the fact that in Spain prison stays tend to be brief, especially in prisons that include persons incarcerated for preventative detention — as were some of those who participated in our study — and due also to the frequency of inmate transfers between prisons, which makes follow-up of patients difficult. In one study conducted in a prison with these characteristics, it was observed that only 31.5% of the patients being studied remained in that prison 24 weeks later.<sup>31</sup>

In sum, in our study, at the 48-week point, treatment with PIs (primarily lopinavir) reduced the percentage of patients with fibrosis 3/4, while no change was detected in patients with fibrosis grade 4. Overall, the therapy improved fibrosis when measured using the APRI Index or FIB-4, but not when using the Forns index or elastography. Nonetheless, the little time available for follow-up may have limited observations relevant to the grade of fibrosis. It would therefore be advisable to design studies with larger samples and longer follow-up periods to confirm or modify the conclusions presented.

## CORRESPONDENCIA

Pablo Saiz de la Hoya Zamácola  
Servicios Médicos  
C. P. Fontcalet  
Polígono de la Vallonga, s/n  
03113 Alicante (Alicante)  
pablosz@coma.es

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