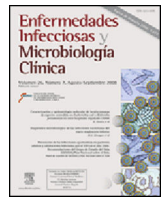




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Original article

Hepatic safety of maraviroc in HIV-1-infected patients with hepatitis C and/or B co-infection. The Maraviroc Cohort Spanish Group



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ABSTRACT

Introduction: Limited data is available regarding the hepatic safety of maraviroc in patients co-infected with HIV and HCV and/or HBV. Our objective was to compare the hepatic safety profile and fibrosis progression in HIV-mono-infected patients and co-infected with HCV and/or HBV treated with maraviroc. **Methods:** Retrospective multicentre cohort study of HIV-infected patients receiving treatment with a maraviroc-containing regimen in 27 hospitals in Spain.

Results: A total of 667 patients were analyzed, of whom 313 were co-infected with HCV ($n = 282$), HBV ($n = 14$), or both ($n = 17$). Maraviroc main indications were salvage therapy (52%) and drug toxicity (20%). Grade 3–4 hypertransaminasaemia (AST/ALT >5 times ULN) per 100 patient-years of maraviroc exposure, was 5.84 (95% CI, 4.04–8.16) and 1.23 (95% CI, 0.56–2.33) in co-infected and HIV-mono-infected patients, respectively (incidence rate ratio, 4.77; 95% CI, 2.35–10.5). However, the degree of aminotransferase abnormalities remained stable throughout the study in both groups, and no significant between-group differences were seen in the cumulative proportion of patients showing an increase in AST/ALT levels greater than 3.5 times baseline levels. No between-group differences were seen in liver fibrosis over time. With a maraviroc median exposure of 20 months (IQR, 12–41), two patients (0.3%) discontinued maraviroc because of grade 4 hepatitis, and other 2 died due to complications associated to end-stage-liver disease.

Conclusions: Maraviroc-containing regimens showed a low incidence of hepatitis in a large Spanish cohort of HIV-infected patients, including more than 300 patients co-infected with HCV and/or HBV. Co-infection did not influence the maximum liver enzyme level or the fibrosis progression throughout the study.

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Seguridad hepática de maraviroc en pacientes coinfectados con VIH y hepatitis C y/o B. Grupo español de la cohorte de Maraviroc

RESUMEN

Introducción: La seguridad hepática del maraviroc en pacientes coinfectados por VIH y VHC y/o VHB es poco conocida. Nuestro objetivo es comparar el riesgo de hepatitis y la progresión de la fibrosis hepática en pacientes mono infectados por VIH y coinfectados por VHC y/o VHB, tratados con maraviroc.

Palabras clave:

Maraviroc

VIH

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VHC
VHB
Coinfección
Hepatitis
Fibrosis hepática

Métodos: Estudio de cohortes, retrospectivo, en pacientes infectados por VIH, tratados con maraviroc en 27 hospitales españoles.

Resultados: Analizamos 667 pacientes, 313 coinfectados por VHC (n = 282), VHB (n = 14) o ambos (n = 17). El rescate (52%), y la toxicidad farmacológica (20%) fueron las principales indicaciones de tratamiento con maraviroc. La incidencia de hipertransaminasemia de grado 3–4 (AST o ALT >5 veces el LSN), por 100 paciente-años de exposición a maraviroc, fue 5,84 (IC 95%, 4,04–8,16) y 1,23 (IC 95%, 0,56–2,33) en coinfectados y mono infectados por VIH, respectivamente (razón de tasas, 4,77; IC95%, 2,35–10,5). No se observaron diferencias en la proporción acumulada de pacientes con elevación de AST o ALT mayor de 3,5 veces respecto al valor basal, ni en la progresión de la fibrosis hepática entre ambos grupos. Tras una mediana de tratamiento de 20 meses (AIC, 12–41), dos pacientes (0,3%) discontinuaron el maraviroc por hepatitis de grado 4, y dos pacientes fallecieron por enfermedad hepática.

Conclusiones: En una cohorte española de pacientes infectados por VIH que incluye más de 300 pacientes coinfectados por VHC y/o VHB, maraviroc mostró una baja incidencia de hepatitis. La coinfección no afectó al grado de elevación de las transaminasas ni a la progresión de la fibrosis hepática.

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Introduction

Approximately 1–8% of HIV-infected patients develop severe hepatitis, mostly grade 3 or 4 elevations in aminotransferases, during the first year of antiretroviral therapy (ART).¹ Coinfection with either hepatitis B (HBV) or hepatitis C (HCV) has been frequently reported as a major risk factor for liver toxicity after initiation of ART.¹

Although the incidence of severe liver toxicity is lower with currently recommended regimens, and the majority of cases involve asymptomatic liver enzyme elevations^{2–5} some cases of severe liver disease have been still reported³ and ART-related hepatotoxicity is a concern in the management of HIV-infected subjects, mainly in those coinfecting with HCV and/or HBV.

Initial concerns were raised in regard with the hepatic safety of CCR5 antagonists, following the description of severe cases of hepatotoxicity with aplaviroc.⁶ Maraviroc (MRV), the first and only CCR5 antagonist approved so far for ART, has shown a favorable safety profile both in patients enrolled in clinical trials and in the expanded access program.⁷ However, very limited data is available regarding the hepatic safety of maraviroc in patients co-infected with HCV and/or HBV,⁸ and the package insert for maraviroc includes some specific warnings in regard with the potential risk of hepatotoxicity.⁹

On the other hand, development of progressive liver disease is one of the principal comorbidities in HIV infected patients coinfecting with HCV and/or HBV, and complications associated to end-stage liver disease remain a major cause of morbidity and mortality among coinfecting patients.¹⁰ In chronic hepatitis, the CCR5/RANTES pathway appears to be involved in the inflammatory response, a critical step in the promotion of hepatic fibrosis, metabolic liver disease and the development of hepatocellular carcinoma.¹¹

Preclinical data, obtained from different animal models of liver injury, have shown that blocking the CCR5 activation pathway could play a protective role on liver fibrosis progression^{12,13} hepatocellular carcinoma development,^{14,15} and in protecting against the development of non-alcoholic fatty liver disease (NAFLD).¹⁶

The primary outcome of this substudy was to compare the liver safety profile of maraviroc-containing ART in a large heterogeneous cohort of patients coinfecting or not with HBV and/or HCV, in real-life conditions. As a secondary outcome we studied the impact of maraviroc treatment on liver fibrosis progression by analyzing changes in FIB-4 index over time.

Methods

Study design and follow-up

Demographic and clinical data from all maraviroc-treated subjects in 27 centers across Spain were retrospectively collected in an observational multicenter cohort study. Complete study design and data on efficacy and overall safety have been reported elsewhere.¹⁷ Briefly, all HIV-1 infected adults receiving a first dose of maraviroc and with at least one follow-up visit were recruited. Data obtained from every 3–6 months scheduled visits until the last follow-up control were entered into a web database, from October 2012 to May 2013 at each center, and transferred to a central database for data monitoring and analysis. Follow-up data included clinical adverse events, laboratory parameters, progression of HIV disease (occurrence of an AIDS-defining event or death), discontinuation of maraviroc and reasons for discontinuing maraviroc.

HBV infection was defined as testing positive for hepatitis B surface antigen and HCV infection as testing positive for HCV antibodies.

Statistics

Adverse events were graded in accordance with the National Institutes of Health Division of AIDS scale.¹⁸ Elevations in AST and ALT, were graded as grade 1 (AST or ALT 1.25–2.5× the upper limit of normality, ULN); grade 2 (AST or ALT 2.6–5× ULN); grade 3 (AST or ALT 5.1–10× ULN); grade 4 (AST or ALT >10× ULN). As almost half of patients were coinfecting with HCV/HBV and amongst them, 50% had elevated AST/ALT levels at baseline, we performed a sensitivity analysis defining grade 3–4 hypertransaminasemia as the increase of liver enzymes more than 3.5 times over baseline values.

The proportion of patients with grade 3–4 hypertransaminasemia was calculated as the number of events divided by the number of patients exposed to MRV in each group, and the incidence rate as the number of events divided by years of exposure to maraviroc × 100. Incidence rates in HCV/HBV co-infected and HIV mono-infected patients were compared using the incidence rate ratio and its corresponding 95% CI. The survival probability of being free of grade ≥3 hypertransaminasemia was estimated by Kaplan–Meier method, and we used the log-rank test for comparison of hepatitis free survival curves of HIV-mono infected and coinfecting patients.

Table 1
Demographic and clinical baseline characteristics.

	HCV and/or HBV coinfectdN = 313	No coinfectdN = 354	p-Value
Sex, male	236 (75.4)	255 (72)	0.325
Age	45 (42–49)	45 (38–52)	1.0
Risk Group	293/313	317/354	<0.001
IDU	236 (80.5)	32 (10.1)	
MSM	16 (5.5)	145 (45.7)	
Heterosexual	35 (11.9)	124 (39.1)	
Hemoderivates transfusion	4 (1.4)	4 (1.3)	
Other	2 (0.7)	12 (3.8)	
CD4+ cells/mm ³	297 (165–482)	357 (202–602)	0.001
HIV RNA <50 copies/mL	117 (38)	130 (37)	0.861
ALT, IU/L	39 (25–76)	27 (19–39.5)	0.001
AST, IU/L	40 (28–68)	25 (20–34)	<0.001
Maraviroc indication			
Salvage therapy	163 (52.1)	183 (51.7)	0.266
Drug toxicity	71 (22.7)	64 (18.1)	
Immune discordance	29 (9.3)	31 (8.8)	
Simplification	21 (6.7)	27 (7.6)	
Clinical trial	14 (4.5)	19 (5.4)	
Treatment intensification	7 (2.2)	10 (2.8)	
First-line therapy	3 (1.0)	15 (4.2)	
Other	5 (1.6)	5 (1.4)	
Maraviroc dose, mg/day			
150	64 (20.4)	44 (12.4)	0.012
300	177 (56.5)	199 (56.2)	
600	62 (19.8)	97 (27.4)	
1200	10 (3.2)	14 (4.0)	
Median time on maraviroc, months	19 (12–41)	20.5 (11–42)	0.783

Results are expressed as number (%) or median (interquartile range). IDU, injection drug users; MSM, men who have sex with men.

Cox proportional hazards models (univariate and multivariate) were fitted to investigate those factors associated with grade ≥ 3 hypertransaminasemia, including gender, age, HCV and/or HBV coinfection, CD4+ lymphocytes; detectable plasma HIV RNA; maraviroc dose, time of maraviroc exposure and liver fibrosis at baseline as covariates.

Both in HIV-monoinfected and coinfectd patients included in the study, liver fibrosis was estimated by FIB-4 index, calculated as: age $\times$ AST/platelet count ($\times 10^9/L$) $\times$ (ALT)^{1/2}.¹⁹ FIB-4 index trend along the study period was evaluated using a generalized linear mixed effect model: FIB-4 index as the outcome variable (using data from baseline, months 6, 12, 16 and 24) and time of follow up in years as a main covariate.

All tests were two-sided and *p* values of <0.05 were considered statistically significant. Categorical variables are expressed as number (percentage) and continuous variables as median (interquartile range, IQR).

The Wilcoxon's rank-sum test was used for comparisons between two continuous variables, and Chi-squared tests to compare two categorical variables. For statistical analysis we used SPSS software package (version 20, IBM Corp, Armonk, NY).

The study was approved by the Institutional Review Boards and the Ethic Committees at all investigative centers. All data remained anonymous.

Results

Patient characteristics

Baseline characteristics of 667 patients analyzed are summarized in Table 1. Of them, 313 (46.9%) were co-infected either with HCV (*n* = 282; 42.2%) or HBV (*n* = 14; 2.1%) or both HBV and HCV (*n* = 17; 2.5%). Median age was 45 years; 74% were men; main route of infection was IDU (80.5%) in coinfectd and sexual intercourse (84.8%) in HIV-monoinfected patients. Salvage therapy was the

indication for the maraviroc-containing regimen in more than half of patients in both groups. Maraviroc dose ranged from 150 mg once daily to 600 mg/twice daily, without differences between groups (Table 1).

Liver toxicity

At baseline, aminotransferase levels were higher in coinfectd vs. monoinfected patients, and 50% of coinfectd vs. 20% of HIV-monoinfected patients had abnormal ASL/ALT levels (Table 2). The proportion of patients showing aminotransferase elevations and the degree of aminotransferase abnormalities remained stable throughout the study in both coinfectd and monoinfected patients (Table 2).

After a median exposure to maraviroc of 20 months (IQR, 12–41), 10.9% of coinfectd (*n* = 39) and 2.5% (*n* = 9) HIV-monoinfected patients showed grade ≥ 3 hypertransaminasemia (*p* < 0.001). Corresponding figures for AST/ALT increase over 3.5-times baseline levels were 9.6% (*n* = 30) and 5.4 (*n* = 19), respectively (*p* = 0.012) (Table 3).

Grade 3–4 hepatitis free survival during the first 24 months of follow-up, was significantly higher in HIV mono-infected patients, using the former definition (Fig. 1a), whereas no significant differences were seen in hepatitis free survival using the increase in AST/ALT levels greater than 3.5 times over baseline levels (Fig. 1b) as grade 3–4 hypertransaminasemia definition.

In an analysis adjusted by maraviroc exposure, the risk of AST/ALT increase over 5 times the ULN, per 100 patient-years, was 5.84 (95% CI, 4.04–8.16) and 1.23 (95% CI, 1.23 (0.56–2.33)) in coinfectd and HIV-monoinfected patients, respectively (incidence rate ratio, 4.77; 95% CI, 2.35–10.05; *p* < 0.001) (Table 3). On the other hand, the risk of AST/ALT increase greater than 3.5-times baseline levels was slightly higher in coinfectd patients (incidence rate ratio: 1.94; 95% CI, 1.09–3.50; *p* = 0.012) (Table 3).

Table 2
Distribution of transaminase levels throughout the study.^a

Timepoint	AST/ALT levels	HCV and/or HBV coinfectd	No coinfectd	p value
Baseline	Normal	141 (50.5)	250 (80.1)	<0.001
	Grade 1	79 (28.3)	39 (12.5)	
	Grade 2	45 (16.1)	20 (6.4)	
	Grade 3	13 (4.7)	1 (0.3)	
	Grade 4	1 (0.4)	3 (0.6)	
Week 12	Normal	128 (50.2)	237 (81.4)	<0.001
	Grade 1	83 (32.5)	39 (13.4)	
	Grade 2	34 (13.3)	13 (4.5)	
	Grade 3	9 (3.5)	2 (0.7)	
	Grade 4	1 (0.4)	0 (0)	
Week 24	Normal	112 (49.1)	208 (80.9)	<0.001
	Grade 1	69 (30.3)	32 (12.5)	
	Grade 2	35 (15.4)	14 (5.4)	
	Grade 3	12 (5.3)	2 (0.8)	
	Grade 4	0 (0)	1 (0.4)	
Week 48	Normal	104 (47.5)	205 (82)	<0.001
	Grade 1	63 (28.8)	34 (13.6)	
	Grade 2	44 (20.1)	8 (3.2)	
	Grade 3	7 (3.2)	2 (0.8)	
	Grade 4	1 (0.5)	1 (0.4)	
Week 96	Normal	69 (50.4)	139 (82.7)	<0.001
	Grade 1	41 (29.9)	23 (13.7)	
	Grade 2	22 (16.1)	4 (2.4)	
	Grade 3	4 (2.9)	2 (1.2)	
	Grade 4	1 (0.7)	0 (0)	
Linear trend over time		p=0.9656	p=0.9213	

Grade 1 (AST or ALT 1.25–2.5 × ULN); grade 2 (AST or ALT 2.6–5 × ULN); grade 3 (AST or ALT 5.1–10 × ULN); grade 4 (AST or ALT >10 × ULN).

^a ALT values were missing at different time points: baseline n=95, 14.2%; week 12, n=141, 21.1%; week 24, n=205, 30.7%; week 48, n=226, 33.9%; week 96, n=375, 56.2%. Corresponding figures for AST values were: baseline n=88, 13.2%; week 12, n=137, 20.5%; week 24, n=197, 29.5%; week 48, n=221, 33.1%; week 96, n=371, 55.6%.

Using a Cox-regression analysis, the adjusted risk of severe hypertransaminasemia (defined as AST/ALT increase over 5-fold the ULN) was 4.53-fold higher among coinfectd patients (Table 4). No dose-effect was observed between maraviroc exposure and the risk of grade 3–4 hepatitis. In other model, considering grade 3–4 hepatitis as AST/ALT increase higher than 3.5-times baseline values, no variable, neither HCV and/or HBV-coinfection, was associated with severe hypertransaminasemia (Table 4).

Table 3
Incidence of grade 3–4 hepatitis along maraviroc treatment.

	HCV and/or HBV coinfectd N= 313	No coinfectd N= 354
<i>Any AST/ALT increase > 5-fold ULN</i>		
Events, n (%)	34 (10.9)	9 (2.5)
Maraviroc exposure, patient-years	582.1	734.6
Incidence per 100 patient-years of maraviroc exposure (95% CI)	5.84 (4.04–8.16)	1.23 (0.56–2.33)
Incidence rate ratio, coinfectd vs. no coinfectd	4.77 (95% CI, 2.35–10.5) (p < 0.001)	
<i>Any AST/ALT increase > 3.5-fold baseline levels</i>		
Events, n (%)	30 (9.6%)	19 (5.4%)
Total exposure, patient-years	588.8	722.8
Incidence per 100 patient-years of maraviroc exposure (95% CI)	5.10 (3.44–7.27)	2.63 (1.58–4.11)
Incidence rate ratio, coinfectd vs. no coinfectd	1.94 (1.09–3.50) (p = 0.012)	

ULN, upper limit of normality.

During follow-up, 2 patients (0.3%) discontinued maraviroc because of grade 4 hepatitis and other 2 died due to complications associated to end-stage-liver disease (hepatocarcinoma and hepatic failure, each one).

Outcome of liver fibrosis

Among coinfectd patients, 71 (26.3%) out of 270 patients with available data at baseline, had an advanced liver fibrosis (FIB-4 >3.25).

Using a linear mixed effect model, a non statistically significant decrease was seen in the FIB-4 index: –0.011 every 12 weeks of treatment with maraviroc (95% CI, –0.034 to 0.012; p=0.341). No interaction was detected between FIB-4 index trend and HCV-coinfection. This data suggests no between-group (HIV-monoinfectd vs. HCV and/or HBV-coinfectd) differences in liver fibrosis over time.

Discussion

In the present study, including more than 300 patients coinfectd with HCV and/or HBV, only 2 patients (0.3%) discontinued maraviroc because of severe hepatitis. In regard with the impact of HCV or HBV coinfection on the risk of hepatitis, the incidence of grade 3–4 hypertransaminasemia, was 5-fold higher in coinfectd patients. Notwithstanding, the relative risk in coinfectd patients was inferior to 2-fold in the analysis adjusted by baseline levels, when defining grade 3–4 as ASLT/ALT elevation over 3.5-times baseline levels, and no between-group differences were seen in the cumulative proportion of patients showing ASLT/ALT elevation over 3.5-times baseline levels up to 48 weeks of treatment with maraviroc. Indeed, in our study, coinfection with HCV and/or HBV did not influence the overall grade 3–4 liver enzyme levels during the study and was not independently associated with

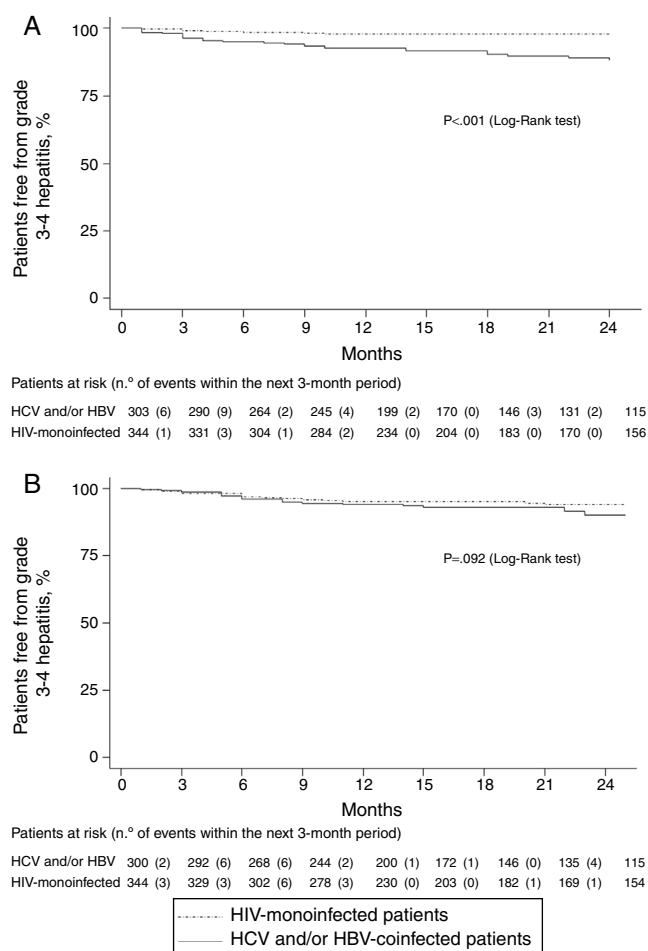


Fig. 1. Cumulative incidence of grade 3–4 hepatitis, defined either as any ALT or AST increase higher than 5-fold upper normal levels (A) or as any ALT or AST increase over 3.5-fold the baseline levels (B).

an increased risk of AST/ALT elevation, in the analysis adjusted by baseline levels.

Despite initial concerns regarding the potential hepatic safety of CCR5 antagonists⁶ analysis of the data up to 48 weeks of treatment with maraviroc in 938 treatment-experienced patients with R5 virus in the MOTIVATE studies did not show a significant difference in grade 3–4 hepatitis between maraviroc and placebo.²⁰ Indeed, in a pooled safety analysis up to 96 weeks of treatment, the exposure-adjusted incidence for grade 3–4 ALT abnormalities, a reliable marker of drug-induced hepatic injury, was lower in the

patients treated with maraviroc once daily, 3.9 per 100 patient-years, or maraviroc twice daily, 2.6 per 100 patient-years, than among patients in the placebo group, 6.5 per 100 patient-years.²¹ In addition, no significant safety concerns were seen in an extended follow-up analysis of patients enrolled the MOTIVATE trials, over more than 5 years,²² or in the expanded access program.⁸

However, scarce information was available regarding the hepatic safety of maraviroc in HCV and/or HBV coinfecting patients, considered to be at higher risk for ART-associated hepatotoxicity.

In a double-blind, placebo-controlled, multicentre study, 137 HIV-1-infected subjects, co-infected with HCV and/or HBV, were randomized to maraviroc twice daily ($n = 70$) or placebo ($n = 67$) in combination with a suppressive regimen. In this study, the risk of maraviroc-associated hepatotoxicity was similar to placebo: one subject in each group was reported to have grade 3–4 hepatotoxicity through 48 weeks, the primary safety end-point.²³

Liver biopsies were not performed in our study to confirm liver toxicity. Consequently, if elevations in liver enzymes can be attributed to a drug-induced liver damage or a fluctuation of transaminases levels observed during the natural course of chronic HCV infection²⁴ cannot be elucidated.

Furthermore, in keeping with previous data the risk of hepatitis was not associated with the dosing of maraviroc.⁷

In patients with chronic hepatitis, signaling through CCR5 pathway appears to be an important step in the inflammatory response and in the progression of liver fibrosis.¹¹ Preclinical data suggests that maraviroc, by blocking the CCR5 co-receptor could play a protective role in preventing the progression of liver fibrosis and cancer development.^{12–15} In our study, liver fibrosis, as evaluated by the FIB-4, a non invasive test that accurately predicts hepatic fibrosis, remained stable over a median follow-time of 20 months, and no differences were seen between monoinfected and coinfecting patients. However, we do not have a comparator arm not treated with maraviroc, which could have shown a progression along these 20 months, therefore establishing a difference. Nevertheless, in a study comparing the liver safety of maraviroc with placebo in patients coinfecting with placebo, no significant difference in liver fibrosis progression was observed at treatment week 48 in patients receiving maraviroc as compared to those receiving placebo,²³ although final 148-week data have not been reported yet.

In addition, preclinical data suggest that maraviroc might protect against the development of non-alcoholic fatty liver disease, a condition relatively common in HCV/HIV coinfecting patients, associated with an increased risk of having advanced fibrosis²⁵ However, the impact of maraviroc on hepatic steatosis was not evaluated in our study.

Our study has the limitations of its retrospective design. No biochemical data was available up to the third month of treatment and ALT values were missing in 14–56% of patients throughout the

Table 4
Variables associated with severe hepatitis using Cox proportional hazards models.

Variable	Risk of AST/ALT increase 5-fold over ULN		Risk of AST/ALT increase 3.5-fold over baseline levels	
	Crude analysis HR (95% CI)	Adjusted analysis HR (95% CI)	Crude analysis HR (95% CI)	Adjusted analysis HR (95% CI)
HCV and/or HBV coinfection	4.54 (2.19–9.63)	4.53 (2.15–9.54)	1.71 (0.94–3.10)	No variable was independently associated with AST/ALT increase 3.5-fold over baseline levels
Age, per year	0.97 (0.94–1.02)		0.99 (0.95–1.02)	
Sex, man	1.26 (0.60–2.66)		1.77 (0.82–3.83)	
CD4+ >200 cells/mm ³	0.96 (0.50–1.87)		0.95 (0.49–1.81)	
HIV RNA >50 copies/mL	1.21 (0.59–2.47)		0.67 (0.26–1.75)	
Maraviroc dose, mg/day				
150	Reference	Reference	Reference	
300	0.31 (0.13–0.73)	0.34 (0.15–0.76)	0.67 (0.26–1.75)	
600	0.83 (0.35–1.96)	0.88 (0.38–2.04)	1.66 (0.64–4.34)	
1200	1.61 (0.43–6.00)	1.85 (0.50–6.78)	1.39 (0.28–7.07)	

MRV, maraviroc; ULN, upper limit of normality.

study, which could underestimate the incidence of severe hypertransaminasemia. Also, HCV infection was defined as HCV antibody positivity without assessment of HCV RNA. As 20–30% of patients classified as coinfecting with HCV could have spontaneously cleared HCV RNA, this approach could potentially underestimate the risk of hepatitis among HCV-coinfecting patients. Moreover, anti-HCV treatment was not recorded but treatment uptake was inferior to 30% in the period when the study was conducted. Finally, consumption of alcohol or other potentially hepatotoxic drugs was not registered during the study. Conversely, the main strength being that is the largest multicenter cohort reported so far evaluating the safety of maraviroc in routine clinical practice in 27 independent centers, including more than 300 patients coinfecting with HCV and/or HBV.

In summary, this study demonstrates the long-term safety and tolerability of maraviroc in a large Spanish cohort of patients, with a high prevalence of HCV and/or HBV coinfection. Coinfection with HCV and/or HBV did not influence the maximum liver enzyme level throughout the study, and was not associated with AST/ALT increase over 3.5-times baseline levels. Liver fibrosis, as evaluated by FIB-4 remained stable after a median time treatment with maraviroc of 20 months.

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Conflict of interest

The authors declare no conflicts of interest.

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References

- Nunez M. Hepatotoxicity of antiretrovirals: incidence, mechanisms and management. *J. Hepatol.* 2006;44 1 (Suppl.):S132–9.
- Clotet B, Feinberg J, van Lunzen J, et al. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naïve adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. *Lancet.* 2014;383:2222–31.
- Raffi F, Rachlis A, Stellbrink HJ, et al. Once-daily dolutegravir versus raltegravir in antiretroviral-naïve adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study. *Lancet.* 2013;381:735–43.
- Walmsley SL, Antela A, Clumeck N, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. *N. Engl. J. Med.* 2013;369:1807–18.
- Wohl DA, Cohen C, Gallant JE, et al. A randomized, double-blind comparison of single-tablet regimen elvitegravir/cobicistat/emtricitabine/tenofovir DF versus single-tablet regimen efavirenz/emtricitabine/tenofovir DF for initial treatment of HIV-1 infection: analysis of week 144 results. *J. Acquir. Immune Defic. Syndr.* 2014;65:e118–20.
- Currier J, Lazzarin A, Sloan L, et al. Antiviral activity and safety of apaliviroc with lamivudine/zidovudine in HIV-infected, therapy-naïve patients: the ASCENT (CCR102881) study. *Antiviral Ther.* 2008;13:297–306.
- Ayoub A, Alston S, Goodrich J, et al. Hepatic safety and tolerability in the maraviroc clinical development program. *Aids.* 2010;24:2743–50.
- Lazzarin A, Reyes J, Molina JM, et al. The maraviroc expanded access program – safety and efficacy data from an open-label study. *HIV Clin. Trials.* 2015;16:10–21.
- http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000811/WC500022190.pdf
- Hernando V, Perez-Cachafeiro S, Lewden C, et al. All-cause and liver-related mortality in HIV positive subjects compared to the general population: differences by HCV co-infection. *J. Hepatol.* 2012;57:743–51.
- Marra F, Tacke F. Roles for chemokines in liver disease. *Gastroenterology.* 2014;147:577–94, e571.
- Seki E, De Minicis S, Gwak GY, et al. CCR1 and CCR5 promote hepatic fibrosis in mice. *J. Clin. Invest.* 2009;119:1858–70.
- Berres ML, Koenen RR, Rueland A, et al. Antagonism of the chemokine Ccl5 ameliorates experimental liver fibrosis in mice. *J. Clin. Invest.* 2010;120:4129–40.
- Barashi N, Weiss ID, Wald O, et al. Inflammation-induced hepatocellular carcinoma is dependent on CCR5 in mice. *Hepatology.* 2013;58:1021–30.
- Ochoa-Callejero L, Perez-Martinez L, Rubio-Mediavilla S, Oteo JA, Martinez A, Blanco JR. Maraviroc, a CCR5 antagonist, prevents development of hepatocellular carcinoma in a mouse model. *PLOS ONE.* 2013;8:e53992.
- Perez-Martinez L, Perez-Matute P, Aguilera-Lizarraga J, et al. Maraviroc, a CCR5 antagonist, ameliorates the development of hepatic steatosis in a mouse model of non-alcoholic fatty liver disease (NAFLD). *J. Antimicrob. Chemother.* 2014;69:1903–10.
- Llibre JM, Rivero A, Rojas JF, et al. Safety, efficacy and indications of prescription of maraviroc in clinical practice: factors associated with clinical outcomes. *Antiviral Res.* 2015;120:79–84.
- DAIDS table for grading the severity of adult and pediatric adverse events. Available at: <http://rsc.tech-res.com/safetyandpharmacovigilance/gradingtables.aspx> (accessed September 21).
- Sterling RK, Lissen E, Clumeck N, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology.* 2006;43:1317–25.
- Gulick RM, Lalezari J, Goodrich J, et al. Maraviroc for previously treated patients with R5 HIV-1 infection. *N. Engl. J. Med.* 2008;359:1429–41.
- Hardy WD, Gulick RM, Mayer H, et al. Two-year safety and virologic efficacy of maraviroc in treatment-experienced patients with CCR5-tropic HIV-1 infection: 96-week combined analysis of MOTIVATE 1 and 2. *J. Acquir. Immune Defic. Syndr.* 2010;55:558–64.
- Gulick RM, Fatkenheuer G, Burnside R, et al. Five-year safety evaluation of maraviroc in HIV-1-infected treatment-experienced patients. *J. Acquir. Immune Defic. Syndr.* 2014;65:78–81.
- Rockstroh JK, Soriano V, Plonski F, et al. Hepatic safety in subjects with HIV-1 and hepatitis C and/or B virus: a randomized, double-blind study of maraviroc versus placebo in combination with antiretroviral agents. *HIV Clin. Trials.* 2015;16:72–80.
- Cicconi P, Cozzi-Lepri A, Phillips A, et al. Is the increased risk of liver enzyme elevation in patients co-infected with HIV and hepatitis virus greater in those taking antiretroviral therapy? *Aids.* 2007;21:599–606.
- Sterling RK, Contos MJ, Smith PG, et al. Steatohepatitis: risk factors and impact on disease severity in human immunodeficiency virus/hepatitis C virus coinfection. *Hepatology.* 2008;47:1118–27.