

# Aspartate-to-platelet ratio index evaluation in a cohort of HIV/HCV infected patients treated with raltegravir

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**ABSTRACT:** Several serologic markers of liver fibrosis have been developed in last years. Among them, Aspartate-to-Platelet Ratio Index (APRI) has demonstrated good correlation with liver biopsy in advanced stages of fibrosis and has been used in monitoring the fibrosis evolution in HIV/HCV co-infected individuals, in correlation with different cART regimens. Nevertheless, data on APRI score in patients treated with INSTI are still lacking. In the context of the SCOLTA project HIV/HCV co-infected patients who started raltegravir (RAL), the first-in class INSTI, have been prospectively followed-up for 24 months. Globally, 124 patients (71.0% males) started RAL with PI (n=95, 76.6%) or with NRTI (n= 29, 23.4%). At the end of follow-up 94 patients were observed: 73 in treatment with PI and 21 with NRTI. The difference between APRI values at 24 months and baseline was 0.0 (IQR -0.4-0.2) in PI group (+ 0.0%) and -0.2 (IQR -1.1-0.1) in NRTI group (-14.3%). Although our work considers a limited number of patients and a short follow-up, RAL use in HIV/HCV individuals has not been linked to worsening of APRI in any group of patients, suggesting that RAL can be safely used in HIV/HCV co-infected patients.

— **Keywords:** Raltegravir, HCV/HIV coinfection, Hepatic fibrosis, APRI, FIB4, Safety, Non-invasive markers.

## INTRODUCTION

People living with HIV and HCV coinfection are estimated to be 2.3 million in the world<sup>1</sup> and they constitute a large proportion of all people infected by the HIV virus. The current follow-up of this population requires the assessment of their grade of fibrosis, that is generally evaluated by liver biopsies (gold standard) or imaging methods such as transient elastography or acoustic radiation force

impulse imaging<sup>2</sup>. Neither the biopsy nor the imaging methods are rapidly available in all centres and repeatable in all visits, due to their costs, waiting lists, and, in the case of biopsy, invasiveness. At the same time, the indirect biomarkers of liver fibrosis are becoming reliable and increasingly used. They are scores based on plasma blood examinations, such as Aspartate-to-Platelet Ratio Index (APRI) and The Fibrosis 4 score (Fib4)<sup>3</sup>. Even not validated in all settings, they can give information on

**Table 1.** Comparison between values of APRI and Fib4 at each plasma blood examination, according to number and percentages of patients achieving HIV viral load < 200 copies/ml.

	NRTI + RAL			PI + RAL		
	T0	T12	T24	T0	T12	T24
Number of patients	29	23	21	95	86	73
APRI (median, IQR)	1.4 (0.6-2.5)	0.9 (0.3-1.9)	0.8 (0.4-1.9)	0.7 (0.5-1.5)	0.7 (0.4-1.4)	0.7 (0.4-1.4)
FIB 4 (median, IQR)	2.42 (1.61-4.31)	1.64 (1.13-4.60)	2.08 (1.09-4.35)	1.99 (1.22-3.14)	1.76 (1.01-3.57)	1.85 (1.15-3.06)
Number of patients with HIV RNA > 200 copies/ml (%)	5 (17.2%)	3 (13.0%)	3 (13.0%)	49 (51.5%)	11 (12.8%)	8 (10.9%)

**Abbreviations:** APRI: Aspartate-to-Platelet Ratio Index; Fib 4: Fibrosis 4 score; IQR: Interquartile range; T0: baseline evaluation; T12: after 12 months of follow-up; T24: end of follow-up (24 months).

the grade of liver fibrosis and are largely used in clinical practice, as they are rapidly available and not expensive. Moreover, they correlate to biopsy results in advanced stages of fibrosis, with an area under the receiver operating characteristic curve (AUROC) of 0.91 for FIB4 and 0.89 for APRI in patients with cirrhosis (F4) and of 0.77 and 0.76 for FIB4 and APRI in patients with significant fibrosis ( $\geq$  F2)<sup>4</sup>. Several studies<sup>5,6</sup> are now evaluating their variation along the time, their correlation with hepatic outcome and hepatic tolerance of therapies. The impact of the integrase strand transfer inhibitors (INSTI) class on liver fibrosis is still unknown, even if they are now the preferred third agents in patients initiating cART<sup>7</sup> and, among them, raltegravir (RAL) had been the first INSTI largely used in all settings (naïve, experienced)<sup>8</sup>. The objective of the present report is to give information about the hepatic impact of RAL in a cohort of HIV/HCV co-infected individuals.

**PATIENTS AND METHODS**

In the context of the SCOLTA project (Surveillance Cohort Long-Term Toxicity Antiretrovirals)<sup>9</sup> we prospectively followed-up HIV/HCV co-infected patients who started a RAL-containing treatment in 25 infectious diseases centres in Italy. Data were collected in 2007-2013<sup>10</sup>. We selected patients aged  $\geq$ 18 years with detectable HCV-RNA at RAL initiation. APRI score has been calculated as [aspartate-aminotransferase (AST)/upper limit of normal AST] x 100 / platelet count<sup>3</sup>. Fib4 score has been calculated as [age (years) x AST /platelet count x alanine-aminotransferase (ALT)<sup>1/2</sup>]<sup>3</sup>. Epidemiological characteristics and APRI scores were evaluated for all patients at baseline, three and six months since RAL initiation and then every six months, for 24 months of total follow-up. APRI values have been expressed as median (interquartile range, IQR) and compared between people taking RAL associated to protease inhibitors (PI) and to nucleosidic backbones (NRTI).

**RESULTS**

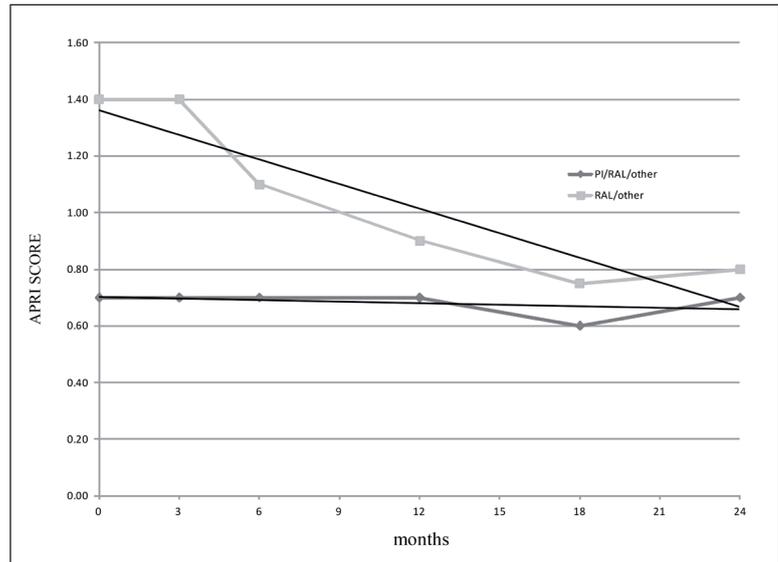
Overall, 124 patients (71.0% males) started RAL in combination with PI (n=95, 76.6%) or with a NRTI backbone

(n=29, 23.4%). The patients in the PI group also received non-nucleoside reverse transcriptase inhibitors (NNRTI) in 11 cases, maraviroc in 8, and NRTI in 38: of them, 16 tenofovir/emtricitabine, (TDF/FTC), 4 abacavir/lamivudine (ABC/3TC) and 18 other combinations. Instead, in the NRTI group the backbone was not associated to other classes of antiretroviral agents and it was TDF/FTC in 26 patients, ABC/3TC in 1 and 3TC/zidovudine in 2. APRI has been calculated at baseline, three and six months since RAL initiation and then every six months, up to 24 months of follow-up. At baseline, 66 patients (53.2%) had a HIV-RNA > 200 copies/ml (n= 49, 51.5% in the PI group and n=5, 17.2%, in NRTI group). Median values of APRI were lower in PI group (0.7, IQR, 0.5-1.5) than in NRTI group (1.4, IQR 0.6-2.5) at baseline evaluation, while APRI was 0.8 (IQR, 0.5-1.6) in the global population. Ninety-four patients concluded the follow-up, 73 in treatment with PI and 21 with NRTI. Of them, 11 (11.7%) patients still had detectable HIV-RNA (viral load > 200 copies/ml), 8 (10.9%) patients taking PI and 3 (14.3%) tacking NRTI. The difference between APRI values at 24 months and baseline APRI was 0.0 (IQR -0.4-0.2) in PI group (+ 0.0%) and -0.2 (IQR -1.1-0.1) in NRTI group (-14.3%). The same analysis was performed using the last observation carried forward: the result did not differ. A comparison between values of APRI and Fib4 at each plasma blood examination is reported in table 1. According to the last observed APRI score, most patients (53.2%) did not change fibrosis stage, whereas 30.1% showed an improvement and 16.7% a worsening. The corresponding figures were 50.0%, 39.3% and 10.7% for NRTI group and 54.4%, 27.2% and 18.5% for PI group. Accounting for baseline stage, final stage was similar between treatment groups. Figure 1 shows the medians over time by regimen group.

**DISCUSSION**

In the present work we evaluated the liver tolerability of RAL-based regimens in terms of variation of APRI score. In the natural history of HIV/HCV coinfection, a worsening of the grade of fibrosis and of APRI score can be expected, as recently demonstrated in course of antiretroviral therapy by Brunet and colleagues<sup>6</sup>. In their

**Figure 1.** Median APRI over time (0, 3, 6, 12, 18, 24 month follow-up), by regimen.



research, the authors correlated APRI variations with antiretroviral therapy in a group of HIV/HCV co-infected patients. They concluded that APRI increased during 5 years of observation, either in people using PI and NNRTI, especially when the associated backbone was ABC/3TC. In particular, APRI score increased by 11% in the PI group and by 7% in the NNRTI group. On the contrary, in our sample APRI score was not worsened during the 24-months follow-up, but, a slight improvement (-14%) was observed on median APRI values, in patients on RAL associated with a NRTI backbone. Even if it did not imply the transition to a lower class of fibrosis, according to APRI values interpretation, to best of our knowledge, for the first time an improvement in APRI values is reported in a study focalized on a co-infected population<sup>11</sup>. As APRI score is heavily influenced by the platelet count, a possible role in score variation may have been played by HIV control. In fact, low platelet count is a common finding in uncontrolled HIV infection. Globally, 51.5% and 17.2% patients in the PI and NRTI group respectively, had uncontrolled HIV infection at the moment of RAL initiation. At the end of the follow-up the number of uncontrolled infections dropped to 10.9% and 14.3% in PI and NRTI groups, probably contributing to the achievement of better values of APRI. Nevertheless, the amelioration of the HIV control has been noticed in both groups, with a greater impact in PI group, while the only NRTI group had lower APRI values at the end of the follow-up. This is in accordance with the previous finding of the hepatic impact of PI use and underlines the tolerability of RAL when used alone with a NRTI backbone<sup>6</sup>. A further point of interest is that many HIV/HCV co-infected patients are currently performing therapies with direct-acting antiviral agents (DAAs) finalized to the eradication of HCV infection. To date, no interaction between RAL and DAAs has been reported and RAL is often used as concomitant HIV therapy also for this reason. According to our data, RAL is improbably correlated to a worsening in APRI values and it might suggest its safe use in this context, in which is very important not to have confounding factors in case of APRI variations.

Although our work considers a limited number of patients and a relatively short follow-up, RAL use in HIV/HCV individuals has not been linked to worsening of APRI in any group of patients. Indeed, a slight improvement in the APRI has been noticed in NRTI group. Largest studies are desirable to better clarify the topic, nevertheless.

## CONCLUSIONS

Our study suggests that RAL can be safely used in HIV/HCV co-infected patients.

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## CONFLICT OF INTEREST:

The Authors declare that they have no conflict of interests

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