OPEN

JAIDS Journal of Acquired Immune Deficiency Syndromes Publish Ahead of Print
DOI: 10.1097/QAI.0000000000001986

Title

The effect of switching to Maraviroc + Darunavir/ritonavir dual therapy in virologically suppressed patients on the progression of liver fibrosis: findings from a randomized study

Running Title: Effect of MVC + DRV/r on liver fibrosis

Authors: B. Rossetti[1,2], R. Gagliardini[3], G. Sterrantino[4], V. Colangeli[5], A. Latini[6], M.Colafigli[6], F. Vignale[7], S. Rusconi[8], A. Di Biagio[9], G. Orofino[10], I. Mezzaroma[11], V. Vullo[12], D. Francisci[13], C. Mastroianni[14], M. Trezzi[15], B. Canovari[16], S. Lamonica[2], A. Ciccullo[2], A. Borghetti[2], A. D'Arminio Monforte[17], S. Di Giambenedetto[2], A. De Luca[1,3] for GUSTA trial study group

[1] Infectious Diseases Unit, Azienda Ospedaliera Universitaria Senese, Siena, Italy,

[2] Clinic of Infectious Diseases, Catholic University of Sacred Heart, Roma, Italy,

[3] Department of Medical Biotechnologies, University of Siena, Italy

[4] Clinic of Infectious Diseases, Azienda Ospedaliera Universitaria Careggi, Firenze, Italy,

[5] Clinic of Infectious Diseases, Azienda Ospedaliera Universitaria S.Orsola Malpighi, Bologna, Italy,

[6] Infectious Dermatology and Allergology IRCCS IFO, Roma, Italy,

[7] Clinic of Infectious Diseases, G. D'Annunzio University, Chieti, Italy,

[8] Infectious and Tropical Diseases Unit, DIBIC L. Sacco Hospital, University of Milano, Italy,

[9] Infectious Diseases Unit, IRCCS S. Martino-IST, Genova, Italy,

[10] Infectious Diseases Unit A, Amedeo di Savoia Hospital, Torino, Italy,

[11] Department of Translational and Precision Medicine, Sapienza University of Rome, Roma, Italy

[12] Department of Public Health and Infectious Diseases, Sapienza University of Rome, Roma, Italy,

[13] Clinic of Infectious Diseases, University of Perugia, Italy,

[14] Infectious Disease Unit, SM Goretti Hospital, Department of Public Health and Infectious Diseases, Sapienza University, Latina, Italy,

[15] Infectious Diseases Unit, Pistoia Hospital, Italy

[16] Infectious Diseases Unit, Pesaro Hospital, Italy

[17] Infectious and Tropical Diseases Institute, Department of Health Sciences, University of Milan, San Paolo Hospital, Milan, Italy

Funding: This work was partially funded by grants from Ministero della Salute, ISS, for Programma Nazionale AIDS project number 40H94. Janssen Europe provided Darunavir tablets for patients in the study arm and supported the pharmacovigilance of the study and ViiV Healthcare Italy supported tropism testing for all patients for conducting the study. ViiV Healthcare Italy also supported plasma antiretroviral drug monitoring for patients in the study arm for conducting the study. No additional external funding was received for this study. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: AB reports non-financial support from Bristol Myers Squibb, personal fees from Gilead Sciences, non-financial support from ViiV Healthcare. ADL reports consulting fees from Gilead Sciences, Abbvie, Janssen, Bristol- Myers Squibb, ViiV Healthcare Italy, Merck Sharp and Dohme, outside the submitted work. BR reports non-financial support from Janssen, ViiV Healthcare Italy, Abbvie, Gilead, and consulting fees from Merck Sharp and Dohme, outside the submitted work. ADM reports grants and consulting fees from Bristol-Myers Squibb, Merck Sharp and Dohme Gilead, consulting fees from ViiV Healthcare Italy, outside the submitted work. CM reports consulting fees and non-financial support from ABBVIE, consulting fees from Merck Sharp and Dohme, Gilead Sciences, ViiV Healthcare Italy, BMS, non-financial support from ASTELLAS, outside the submitted work. FV reports non- financial support from Bristol-Myers Squibb, ViiV Healthcare Italy, Gilead Sciences, consulting fees from Merck Sharp and Dohme, BMS, outside the submitted work. MC reports consulting fees from Gilead Sciences, Janssen-Cilag, Merck Sharp and Dohme, Bristol-Myers Squibb, ViiV Healthcare Italy, outside the submitted work. IM reports grants and consulting fees from ViiV Healthcare Italy. SR reports grants and consulting fees from ViiV Healthcare Italy, Bristol-Myers Squibb, Merck Sharp and Dohme, Gilead Sciences, Janssen, outside the submitted work. SDG reports personal fees from Bristol-Myers Squibb, Janssen Cilag, ViiV Healthcare Italy, Gilead, Merck Sharp and Dohme, outside the submitted work.

All other authors have nothing to disclose.

The data were presented as poster at 9° Italian conference on AIDS and Antiviral Research, Siena, Italy (P67)

The authors report no conflicts of interest related to this work.

Keywords: Simplification Antiretroviral therapy Maraviroc Liver fibrosis Switch Dual therapy

In vitro and animal studies revealed a potential protective role of CCR5-antagonists on reducing liver fibrosis progression and protecting from developing hepatocellular carcinoma. [1] Hepatocytes bear CXCR4 and CCR5, the two main co-receptors for HIV entry into cells, and the blockade of co-receptors on hepatic stellate cells, the major producers of extracellular matrix in the liver, will slow progression of liver fibrosis, especially due to HIV-envelope gp120-mediated fibrogenesis modulation. [2-5] .

The aim of present analysis was to compare the evolution of liver fibrosis over time evaluated by surrogated biomarker assays in HIV-1 infected patients on a virologically successful antiretroviral therapy (stable HIV-1 RNA <50 copies/mL), randomized to switch to maraviroc + darunavir/r (MVC + DRV/r arm) qd or to continue the current maraviroc-free 3-drug ART (3-drug ART arm).

Patients included in the study were enrolled in the GUSTA (GUided Simplification with Tropism Assay) trial, a multicenter, open-label, randomized study (www.clinicaltrials.gov, number NCT01367210), whose main results have been published [6].

Briefly, GUSTA included patients with HIV-1 RNA <50 copies/mL for at least 6 months, R5 tropism and CD4 counts >200 cells/μL for at least 3 months before enrollment; HBV coinfected patients and those with Child-Pugh B/C cirrhosis were excluded.

We retrospectively evaluated Fibrosis-4 (FIB-4) Index and AST to Platelet Ratio Index (APRI) scores, at baseline and after 12, 24, 48 and 96 weeks. The cut-off points of serum marker tests of hepatic fibrosis were: FIB-4 <1.45 (F0-F1), 1.45-3.25 (indeterminate), >3.25 (F3-F4) and APRI <0.5 (F0-F1), >1.5 (F2) and >2 (cirrhosis).

Differences between arms were assessed by χ-square and Student's t-test, longitudinal within group differences by McNemar test. The FIB-4 Index and APRI scores were employed as continuous variables; their predictors at baseline and their change over time were investigated by linear regression.

We included 150 patients, 76 randomized to MVC + DRV/r arm and 74 to 3-drug ART arm. Baseline characteristics were homogeneous between arms except for relative younger age in the MVC + DRV/r arm (median 47 yrs; IQR 40-52) than in the 3-drug ART arm (50 yrs; IQR 44-57) (p=0.08), more frequent African ethnicity in the 3-drug ART arm than in the MVC + DRV/r arm (8% vs. 1%) (p=0.05) and FIB-4 median value higher in the MVC + DRV/r arm (1.15; IQR 0.82-1.32) than in the 3-drug ART arm (0.91; IQR 0.68-1.20) (p=0.01). APRI score was similar between arms: 0.23 (0.18-0.29) in the MVC + DRV/r arm and 0.25 (0.20-0.33) in the 3-drug ART arm (p=0.12).

Overall, 89% (134/150) were males and Caucasians, 41% (61/150) were heterosexuals, (57/150) 38% homosexuals/bisexuals, 7% (10/150) reported history of injected drug use, 11 years of HIV (7-18), 10 years of ART (6-15), CD4 at nadir 222 cells/mmc (132-319) and at baseline 654 cells/mmc (506-905). Eighteen patients presented positive serology for HCV and 8 had a detectable HCV RNA, 4 in each arms.

Sixteen (11%) presented diabetes mellitus: 12% (9/76) in the MVC + DRV/r arm and 9% (7/74) in the 3-drug ART arm (p=0.04). At screening NRTIs were used in 95% (143/150), NNRTIs in 12% (18/150), INSTIs in 18% (17/150), PIs in 69% (103/150) of which boosted PI in 63% (94/150) and DRV/r in 31% (47/150). No differences between arms were observed in terms of dislypidemia (in 100/150, 66%), with total cholesterol 203 mg/dL (IQR 173-230), body mass index (23 kg/m^2, IQR 22-26) and glucose 89 mg/dL (IQR 82-100). Median value of false positive rate (FPR) at geno2pheno was 43 (IQR 24-69) with no differences between groups.

During observation in the 3-drug ART arm (n=74) NRTIs were used in 92%, NNRTIs in 16%, INSTIs in 15%, PIs in 69%, boosted PI in 51% and DRV/r in 43%.

According to the cut-off points of hepatic fibrosis FIB-4 in the MVC + DRV/r arm was <1.45 in 83% (63/76), between 1.45 and 3.25 in 16% (12/76) and >3.25 in 1% (1/76); in the 3-drug ART arm it was <1.45 in 88% (65/74), between 1.45 and 3.25 in 12% (9/74) (no one had FIB-4 >3.25).

Overall, APRI was <0.5 in 91% (137/150) and no one had >1.5 at baseline.

Based on the FIB-4 score, at 48 weeks progression to a higher level was observed in 6% (4/63) in the MVC + DRV/r arm and in 6% (4/65) in 3-drug ART arm; in 3% (4/12) among those in MVC + DRV/r arm and in 3% (3/9) in 3-drug ART arm FIB-4 improved at least one stage, while the other patients did not modify their FIB-4 stratum.

Based on the APRI score, at 48 weeks significant modification of stratum was no observed.

In addition, no significant differences between arms were observed in platelet counts and alanine transaminase changes at 48 weeks from baseline. We observed a more profound decrease of aspartate transaminase levels in the MVC + DRV/r arm (mean change -4.19 IU/L, SD 7.2) vs 3-drug ART arm (mean change +0.58 IU/L, SD 9.9) (p=0.007).

In a multivariable model adjusting for risk factor for HIV acquisition and duration of ART exposure, longer time from HIV diagnosis (per 1 year increase +0.031, 95% CI +0.007; +0.055, p=0.01), lower nadir $CD4^+$ cells count (+100 cells increase, -0.060, 95% CI -0.107; -0.014, p=0.01) and HCV antibody positive status (+0.321, 95% CI +0.000; +0.642, p=0.05) were associated with higher baseline FIB-4 values. No factor independently associated with baseline APRI values was observed. During follow-up, the APRI score decreased more prominently in the MVC + DRV/r arm *vs.* 3-drug ART arm at week 12 (median change -0.77; IQR -1.11; -0.58 *vs.* -0.67; IQR -0.97; -0.46; p=0.02), at week 48 (-0.04; IQR -0.09; +0.02 *vs.* +0.001; IQR -0.037; +0.049; p=0.01) and at week 96 (-0.03; IQR -0.06; +0.01 *vs.* +0.02; IQR -0.01; +0.10; p=0.053).

In a multivariable model, predictors of APRI change at 48 weeks were baseline APRI (-0.391; 95% CI -0.515; -0.266; p<0.001) and MVC + DRV/r arm vs 3-drug ART arm (-0.040; 95% CI -0.006; -0.074; p= 0.021).

FIB-4 also showed a trend towards a more prominent reduction in the MVC + DRV/r arm (-0.02; IQR -0.21; +0.13) *vs.* 3-drug ART arm (+0.02; IQR -0.23; +0.20) (p=0.35) at week 48. Baseline FIB-4 but not study arm predicted FIB-4 modifications during follow up.

In conclusion we observed that switch to MVC + DRV/r in HIV-1 infected, but virologically suppressed patients on 3-drug ART, was associated with a slight but significant improvement of the APRI score over time as compared to continuing 3-drug ART without maraviroc. This maraviroc-containing regimen did not significantly influence the longitudinal change of the FIB-4 score, possibly due to the presence of age as a component of the score, which was increasing over time in the study patients, although a trend towards an improvement was observed. Our observations are in agreement with experiments showing a reduction of hepatic stellate cells activation and fibrosis progression and an improved survival in a murine model of hepatocellular

carcinoma [1] and in vitro observations on the inhibitory effect of maraviroc on the accumulation of fibrillar collagens and extracellular matrix proteins by human hepatic stellate cells [7]. Results from this study are also in line with a previous retrospective non-comparative analysis on 71 HIV/HCV co-infected patients treated with maraviroc, showing a potential beneficial effect on liver fibrosis measured by the APRI score [8]. In a previous prospective, non-controlled pilot study on 24 HIV/HCV co-infected patients starting a maraviroc-based regimen, liver fibrosis was slightly but not significantly reduced, although observation was limited to 6 months [9]. In addition, a recent study suggests that a validated marker of liver fibrosis was reduced in HIV-1 infected patients carrying the variant allele CCR5 delta-32, associated with reduced CCR5 expression, and in patients exposed to cenicriviroc, a CCR5/CCR2 blockade agent [10].

Our study adds to previous evidence and has its strenghts in the randomized comparison, the study arm treated with an homogeneous maraviroc-containing regimen and the prospective follow up of the patients up to 96 weeks. Its main limitation is the lack of information on the liver histological pattern modification rather than indirect biomarkers, as it remains unclear whether their change truly reflects hepatic fibrosis change. The lack of information on patients alcohol consumption and the absence of transient liver elastography measurements also represent limitations to this analysis.

Further studies are warranted to confirm an anti-fibrotic effect of CCR5 antagonist therapy.

Aknowledgment:

- ✓ Patients that shared their data,
- ✓ GUSTA study group,
- ✓ ViiV Healthcare, Verona, supported viral tropism determination and TDM
- ✓ Janssen supported pharmacovigilance and gived darunavir

References

1. Ochoa-Callejero L, Pérez-Martínez L, Rubio-Mediavilla S, et al. Maraviroc, a CCR5 antagonist, prevents development of hepatocellular carcinoma in a mouse model. PLoS One. 2013;8:e53992.

2. Friedman SL. 2008. Preface. Clinics in Liver Disease 12(4):xiii-xiv.

3. Seki E, De Minicis S, Gwak G-Y, et al. CCR1 and CCR5 promote hepatic fibrosis in mice. The Journal of Clinical Investigation. 2009; 119:1858- 1870.

4. 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.

5. Bruno R, Galastri S, Sacchi P, et al. Gp120 modulates the biology of human hepatic stellate cells: a link between HIV infection and liver fibrogenesis. Gut. 2010. 59: 513–520.

6. Rossetti B, Gagliardini R, Meini G, et al. Switch to maraviroc with darunavir/r, both QD, in patients with suppressed HIV-1 was well tolerated but virologically inferior to standard antiretroviral therapy: 48-week results of a randomized trial. PLoS One. 2017;12(11):e0187393.

7. Coppola N, Perna A, Lucariello A, et al. Effects of treatment with Maraviroc a CCR5 inhibitor on a human hepatic stellate cell line. J Cell Physiol. 2018;233(8):6224-6231.

8. Gonzales E, Boix V, Deltoro MG et al. The effects of Maraviroc on liver fibrosis in HIV/HCV co-infected patients. J Int AIDS Soc. 2014;17(4 Suppl 3):19643.

9. Macos J, Viloria MM, Rivero A, et al. Lack of short-term increase in serum mediators of fibrogenesis and in non-invasive markers of liver fibrosis in HIV/hepatitis C virus-coinfected patients starting maraviroc-based antiretroviral therapy. Eur J Clin Microbiol Infect Dis. 2012;31(8):2083-8.

10. Sherman KE, Abdel-Hameed E, Rouster SD, et al. Improvement in hepatic fibrosis biomarkers associated with chemokine receptor inactivation through mutation or therapeutic blockade. Clin Infect Dis. 2018 Sep 20.

Legend

Fig. 1 a APRI score during follow up

Fig. 1 b FIB-4 during follow up

No significant difference between arms at each time-point

Fig. 1 a APRI score during follow up

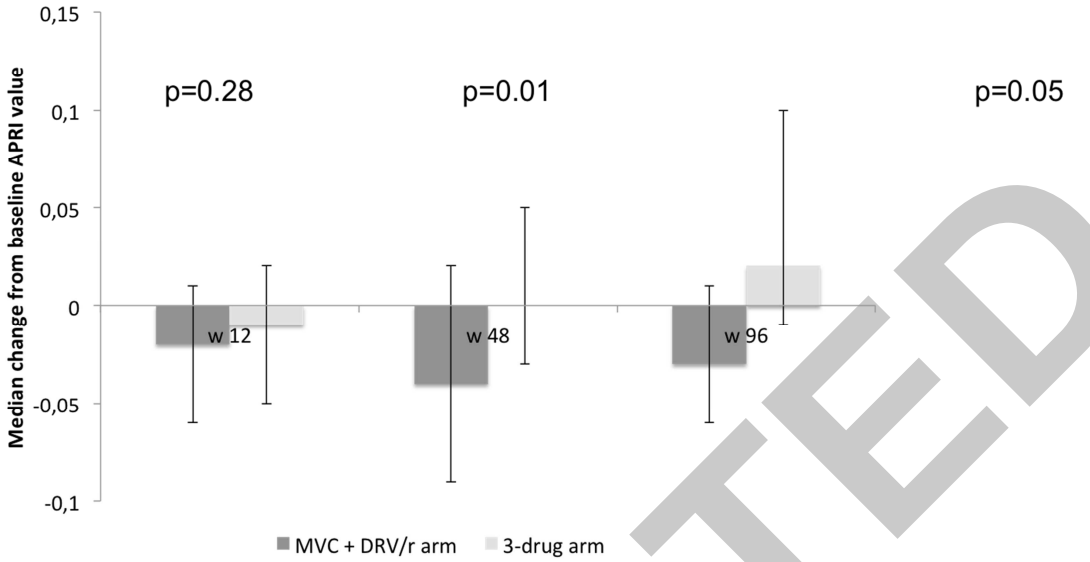
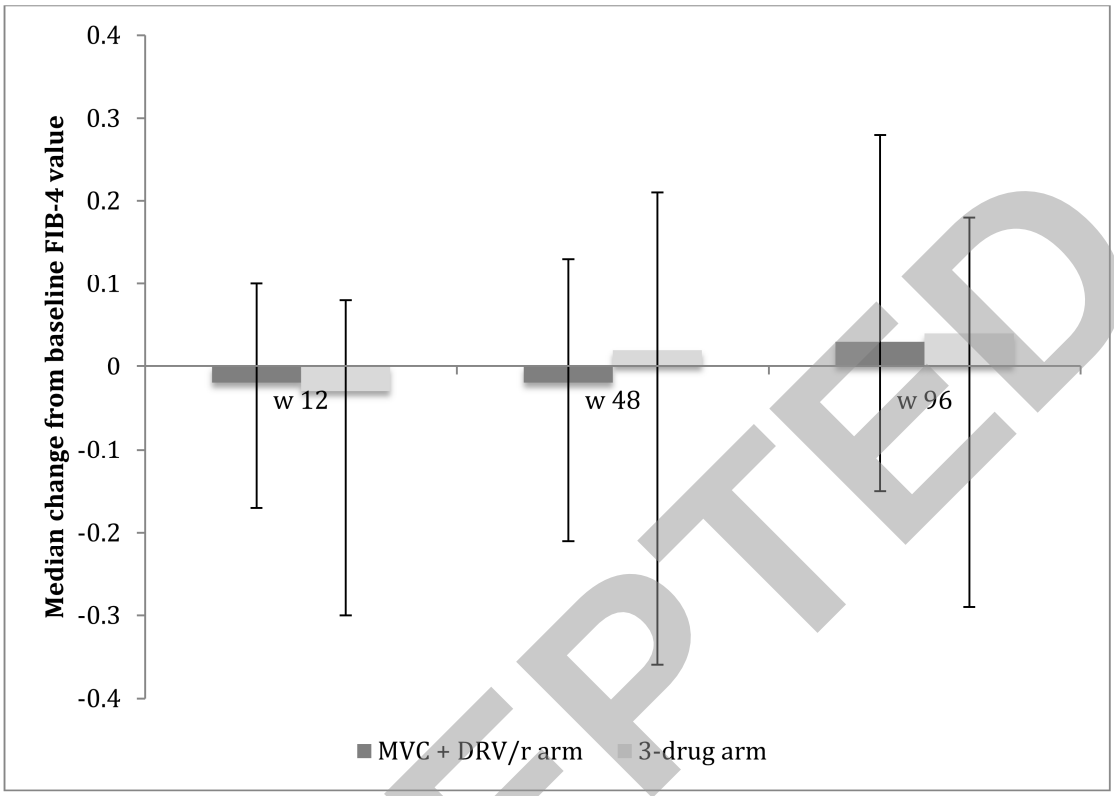


Fig. 1 b FIB-4 during follow up



No significant difference between arms at each time-point