

Real-life Impact OfThe Onset Of Darunavir/Cobicistat On Estimated Glomerular Filtration Rate

M.J.Perez Elias¹, M.M. Gutierrez², M.J.Vivancos¹, A. Ocampo,³ L. Garcia Fraile,⁴ F. Iozano,⁵ M. Montero,⁶ A. Payeras⁷, V. Boix⁸, M.J. Galindo⁹, C. Gonzalez-Domenech¹⁰, J. Sanz¹¹, S. de La Fuente Moral¹², J. Troya¹³, M. Torralba¹⁴, M.A. Sepulveda¹⁵, E. Negredo¹⁶, H. Knobel¹⁷, E. Rivera¹⁸, L. Carbonero¹⁹, B.Alejos²⁰, E. Martinez²¹, Codar Study Group

¹Hospital Ramon y Cajal, Infectious Diseases, Madrid, Spain, ² Hospital Santa Creu y San Pau, Barcelona, Spain, ³Hospital Álvaro Cunqueiro,Vigo, Spain, ⁴Hospital Universitario La Princesa, Madrid, Spain, ⁵Hospital Virgen de Valme, Sevilla, Spain, ⁶Hospital Universitario y politécnico La Fe, Valencia, Spain, ⁷Hospital Sont Llatzer, Mallorca, Spain, ⁸Hospital General Universitario de Alicante,Alicante, Spain, ⁹Hospital Clínico Universitario de Valencia,Valencia, Spain, ¹⁰Hospital Universitario Virgen de la Victoria, Malaga, Spain, ¹¹Hospital Universitario Príncipe de Asturias,Alcalá de Henares, Spain, ¹²Hospital Universitario Puerta de Hierro, Majadahonda, Spain, ¹³Hospital Universitario Infanta Leonor, Madrid, Spain, ¹⁴Hospital Universitario de Guadalajara, Guadalajara, Spain, ¹⁵Complejo Hospitalario de Toledo, Toledo, Spain, ¹⁶Hospital Universitari Germans Trias i Pujol, Barcelona, Spain, ¹⁷Hospital del Mar, Barcelona, Spain, ¹⁸Hospital Universitari Vall d'Hebron, Barcelona, Spain, ¹⁹Hospital Universitario La Paz, Madrid, Spain, Instituto de Salud Carlos III, Madrid, Spain, ²¹Hospital Clinic de Barcelona, Barcelona, Spain

• BACKGROUND

❖ A fixed-dose combination of Daunavir(DRV)/cobicistat (C) 800/150mg was found to be bioequivalent to darunavir plus cobicistat administered as single agents, and yielded comparable DRV exposure to DRV/ritonavir, at steady-state and under fed and fasted conditions in healthy subjects.^{1,2}

❖ A Phase IIIb trial and two controlled trials including DRV/emtricitabina (FTC)/TAF concluded that DRV and C was generally well tolerated, and with a safety profile that was consistent with the one of each agent separately. The combination achieved high rates of virologic suppression over 48 weeks.³⁻⁵

❖ Ritonavir-boosted protease inhibitors such as lopinavir or atazanavir have been associated with a greater decrease in estimated glomerular filtration rate (eGFR) than that of darunavir (DRV)⁶.

❖Cobicistat is known to affect tubular creatinine secretion and hence eGFR⁷.

❖Data on the impact of DRV/c on eGFR, with other concomitant tubular secretion inhibitors , is scarcely known.

• OBJECTIVE

❖ To estimate short and long term eGFR change and factors influencing it, in patients starting different DRV/c with other tubular secretion inhibitors, in clinical practice.

• METHODS

❖ Nation-wide retrospective cohort study of consecutive HIV-infected patients initiating DRV/c, from June/2014 to March/2017.

❖ The eGFR was calculated with CKD-EPI in mL/min/1.73m2, Baseline values and trend over time were described.

❖ At 12, 24 and 48 weeks, eGFR dynamics was explored according to different treatment groups combinations, specially other known inhibitors of active creatinine secretion transporters, Rilpivirine, Dolutegravir or both.

❖ The relationship between eGFR change over time and different HIV patient’s characteristics, socio-demographics, HIV severity, antiretroviral treatment -ARV- categorized as only one drug inhibitor of active creatinine secretion (Cobicistat) vs. two or more (RPV Dolutegravir), and concomitant medication other than ARV was explored through univariate and multivariate analyses.

❖ Ethics approval was obtained and patients signed informed consent.

• RESULTS

❖ 761 patients from 21 Spanish HIV Units initiating DRV/c were included in the overall cohort. Thirty-six (5%) patients were excluded due to the lack of eGFR data.

| Baseline Characteristics | Total (n=761) |
|---|---------------|
| Age, years (±SD) | 49 (10) |
| Men (%) | 568 (75) |
| Caucasian (%) | 694 (91) |
| Years from HIV Dx (±SD) | 16 (9) |
| Nadir CD4/mm³ (±SD) | 228 (183) |
| Prior AIDS (%) | 247 (32) |
| HIV transmission | |
| MSM (%) | 252 (33) |
| IVDU (%) | 237 (31) |
| Heterosex (%) | 210 (28) |
| Other / NA (%) | 62 (8) |
| CD4 >200/mm³ (%) | 671 (88) |
| CD4 cell count (±SD) | 662 (333) |
| <50 copies/mL (%) | 639 (84) |
| Plasma log HIV RNA (±SD) | 1.63 (0.82) |
| Hepatitis C co-infection (antibodies) (%) | 259 (34) |
| Previous ART | |
| No (%) | 12 (2) |
| DRV/rit regimen (%) | 610 (80) |
| No DRV/rit regimen (%) | 139 (18) |
| Reason for starting DRV/c | |
| Naive (%) | 10 (4) |
| Simplification (%) | 618 (81) |
| Toxicity / intolerance (%) | 49 (6) |
| Interactions (%) | 6 (1) |
| Virological failure (%) | 25 (3) |
| Other (%) | 29 (4) |
| Non available (%) | 24 (3) |
| Concomitant regimen | |
| Only DRV/Cobicistat (%) | 623 (82%) |
| DRV/C + Rilpivirine (RPV) (%) | 30 (4%) |
| DRV/C+ Dolutegravir (DTG) (%) | 69 (9%) |
| DRV/C+RPV+DTG (%) | 3 0,4% |
| DRV/c + either RPV or DTG or both | 102 (13.4%) |

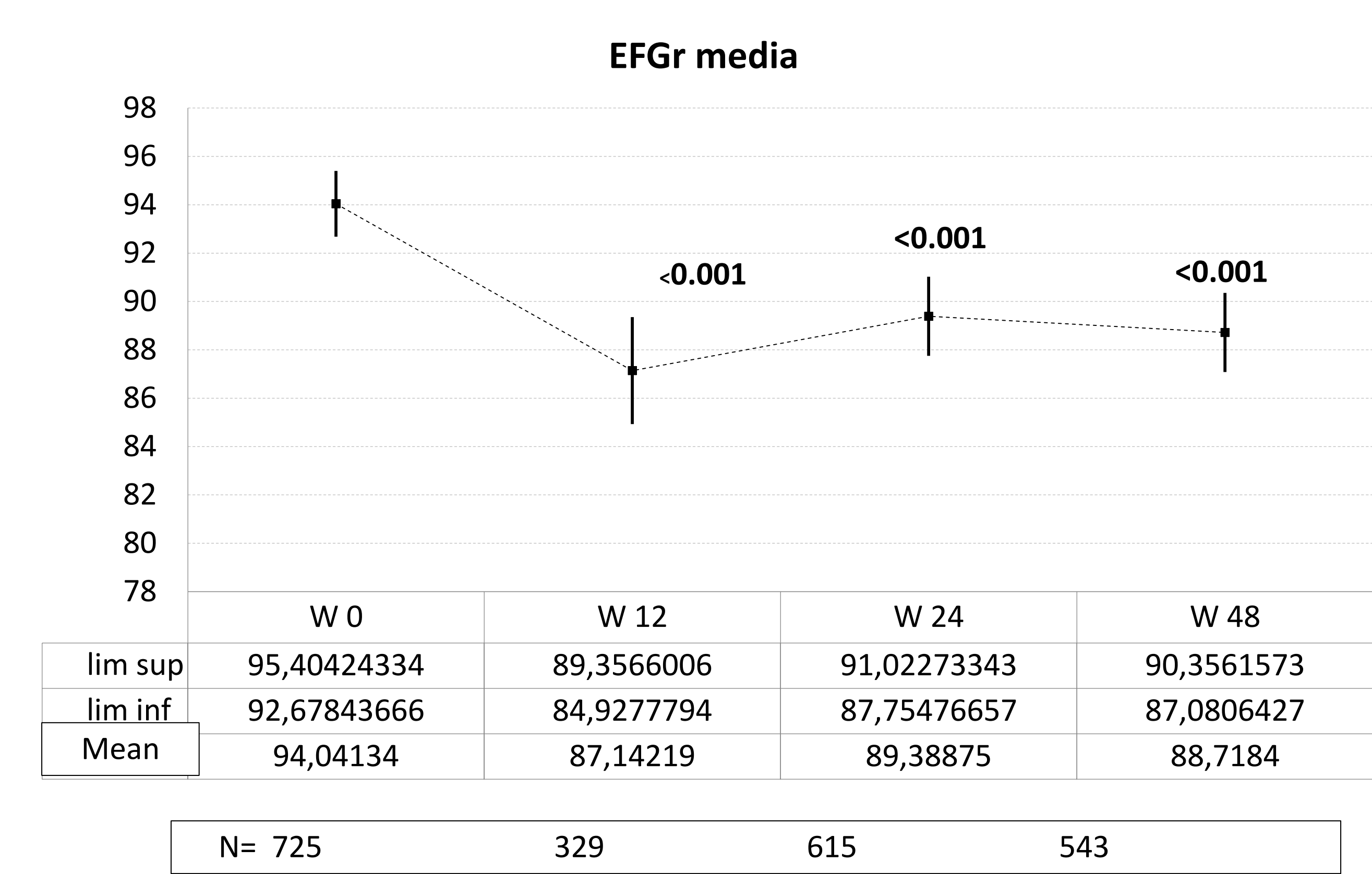
Baseline eFGR and associated Factors

❖ Baseline (mean ±SD) eGFR was **94±19** and **4.83% had eGFR below 60 increasing to 8.47% at 48 week**.

❖ In multivariate analysis, only **age** was independently associated with a higher baseline eGFR Adjusted Mean Difference (AMD) (per year old) -9.3 ± 0.06 CI 95% (-10.5 to -8.29), p <0.001, While **black ethnicity** AMD 8.2 ±4.1 CI 95% (1.5 to 16.2), p =0.046 with lower baseline eGFR.

❖ Only 6/761 (0.8%) switched a DRV/c containing regimen due to renal adverse event.

Change of eFGR after DRV/c initiation



In clinical practice DRV/c Initiation significantly decreases eGFR followed by a plateau , as described in clinical trials.

• CONCLUSIONS

❖ An expected small eGFR decrease is observed after Darunavir /cobicistat is initiated in clinical practice, with a low impact in patient management.

❖At 48 weeks, independent factors influencing eGFR were gender, females experienced lower decrease of eGFR, while concomitant use of Dolutegravir, Rilpivirine or both increases eGFR.

❖The concomitant use of cobicistat plus other known inhibitors of the creatinine active tubular secretion (Dolutegravir, Rilpivirine or both) produced and additive effect in the eGFR decrease at 12, 24 and 48 weeks.

Factors influencing Change of eFGR after DRV/c initiation

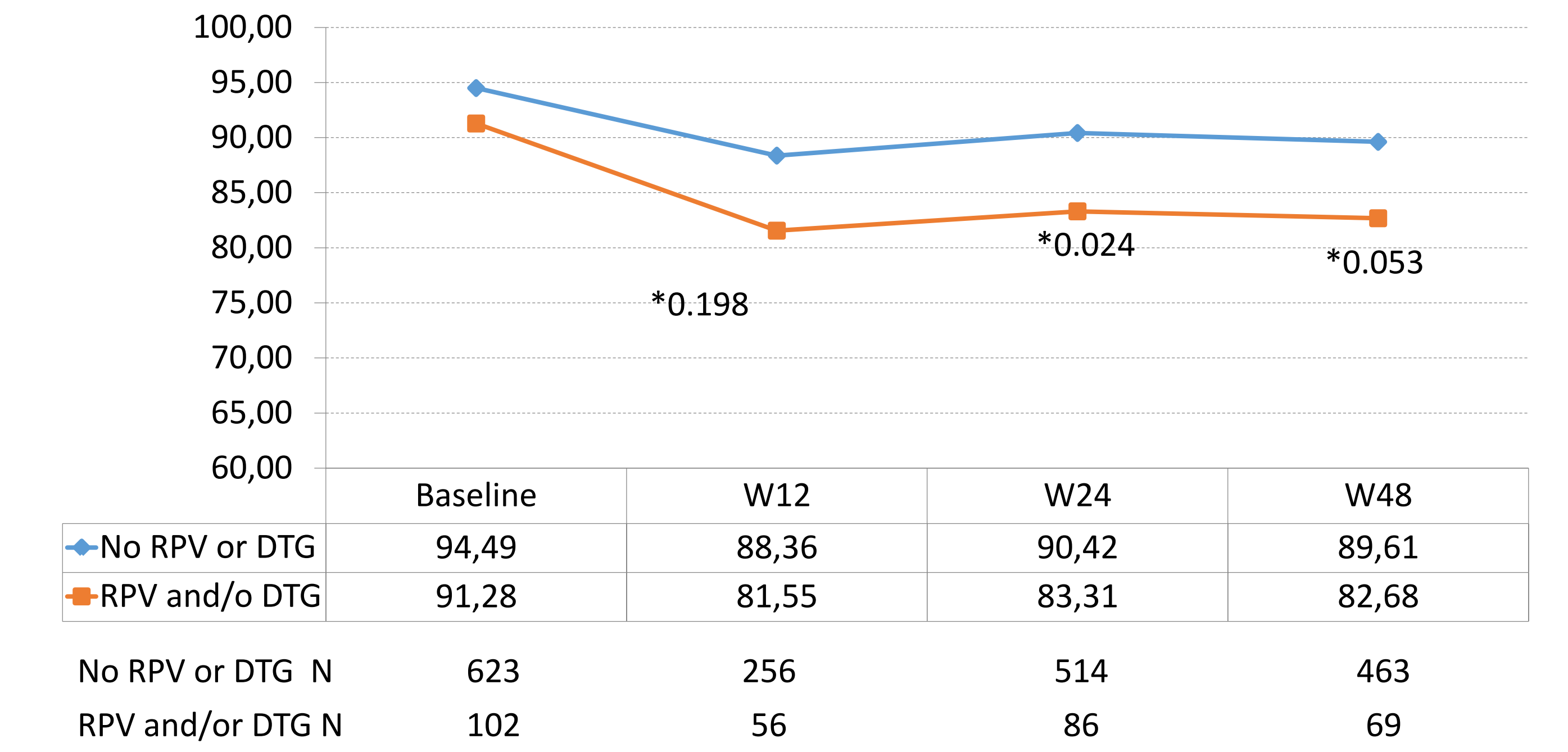
❖ Univariate and Multivariate models were performed to evaluate factors influencing eGFR change at 12 and 48 weeks. All baseline (Table-1) variables were investigated.

❖ At 12 weeks any factor was associated with higher or lower eGFR changes.

❖ At 48 weeks in patients receiving DRV/c, only female sex was associated with a significant increase of eGFR while the combination of DRV/c with either RPV and /or DTG or both decreases eGFR.

| Multivariate analysis, at 48 weeks | AMD | CI 95% | P |
|------------------------------------|----------|---------------|-------|
| Sex (Female) | 2.5±1.3 | (0.4; 5.1) | 0.047 |
| DRV/c+ RPV and/or DTG | -3.5±1.6 | (-6.6 ; -0.3) | 0.032 |

eGFR at 12, 24 and 48 Weeks, DRV/c vs. DRV/c plus Rilpivirine (RPV) and/or Dolutegravir (DTG) or both.



After Adjustment for center clustering and baseline characteristics (sex, Aids stage, HCV- coinfection, age, DRV/c initiation reason, pre-REZOLSTA TAR type, baseline CD4 and Viral Load), a higher significant decrease in eGFR was observed in patients taking two or more creatinine active tubular secretion inhibitors at 24 weeks (DRV/c +DTG, RPV or both), and a strong trend at 48 week.

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