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

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• 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 eGFR[7].
- **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

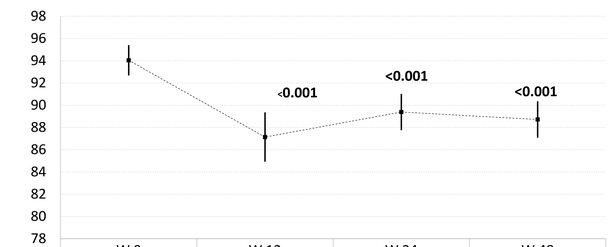
- 761 patients from 21 Spanish HIV Units initiating DRV/c were included in the overall cohort. Thirty-six (5%) patients were excluded due to the lack of eGFR data.

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 etniticity** 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



	W 0	W 12	W 24	W 48
lim sup	95,40424334	89,3566006	91,02273343	90,3561573
lim inf	92,67843666	84,9277794	87,75476657	87,0806427
Mean	94,04134	87,14219	89,38875	88,7184
N=	725	329	615	543

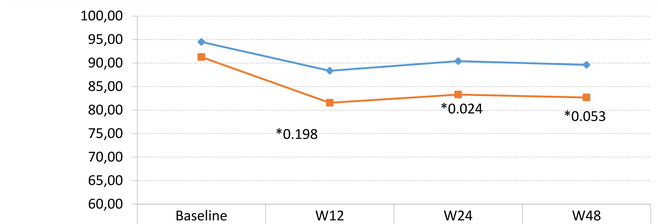
In clinical practice DRV/c Initiation significantly decreases eGFR followed by a plateau , as described in clinical trials.

Factors influencing Change of eFGR after DRV/c initiation

- Univariated and Multivariated models were performed to evaluate factors influencing eFGR change at 12 and 48 weeks. All baseline (Table-1) variables were investigated.
- At 12 weeks any factor was associated with higher or lower eFGR changes.
- **At 48 weeks in patients receiving DRV/c, only female sex was associated with a significant increase of eFGR while the combination of DRV/c with either RPV and /or DTG or both decreases eFGR.**

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**

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



	Baseline	W12	W24	W48
No RPV or DTG	94,49	88,36	90,42	89,61
RPV and/o DTG	91,28	81,55	83,31	82,68
No RPV or DTG N	623	256	514	463
RPV and/or DTG N	102	56	86	69

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.

• 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) produces and additive effect in the eGFR decrease at 12, 24 and 48 weeks.

• REFERENCES

1. Kakuda TN, et al: Bioequivalence of a darunavir/cobicistat fixed-dose combination tablet versus single agents and food effect in healthy volunteers. Antivir Ther 2014, 19:597–606.
2. Kakuda TN, et al. : Pharmacokinetics of darunavir in fixed-dose combination with cobicistat compared with coadministration of darunavir and ritonavir as single agents in healthy volunteers. J Clin Pharmacol 2014, 54:949–957.
3. Tashima et al.: Cobicistat-boosted darunavir in HIV-1-infected adults: week 48 results of a Phase IIIb, open-label single-arm trial. AIDS Research and Therapy 2014 11:39.
4. Orkin C, Molina JM, Negredo E, et al. Efficacy and safety of switching from boosted protease inhibitors plus emtricitabine and tenofovir disoproxil fumarate regimens to single-tablet darunavir, cobicistat, emtricitabine, and tenofovir alafenamide at 48 weeks in adults with virologically suppressed HIV-1 (EMERALD): a phase 3, randomised, non-inferiority trial.Lancet HIV. 2018 Jan;5(1):e23-e34
5. Eron JJ, Orkin C, Gallant J, et al. A week-48 randomized phase-3 trial of darunavir/cobicistat/emtricitabine/tenofovir alafenamide in treatment-naive HIV-1 patients. AIDS 2018 Jul 17;32(11):1431-1442.
6. Mocroft A, Lundgren JD, Ross M, et al.Cumulative and current exposure to potentially nephrotoxic antiretrovirals and development of chronic kidney disease in HIV-positive individuals with a normal baseline estimated glomerular filtration rate: a prospective international cohort study.Lancet HIV. 2016 Jan;3(1):e23-32.
7. Fisher M, McDonald C, Moyle G. Switching from ritonavir to cobicistat in HIV patients with renal impairment who are virologically suppressed on a protease inhibitor.J Int AIDS Soc. 2014 Nov 2;17(4 Suppl 3):19824.

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