2053 - DYNAMICS OF Cr-eGFR WITH ONE OR MORE ANTIRETROVIRALS THAT INHIBIT CR TUBULAR SECRETION- **GeSIDA 9316.**

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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/emtricitabine (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]
- Cobicistat (C), dolutegravir (DLT) and rilpivirine (RPV) all are modest antiretroviral drugs that inhibit proximal tubular creatinine secretion (IPTCrS) and hence a moderate and early non progressive creatinine estimated glomerular filtration (Cr-eGFR) reduction has been observed in clinical trials[6]. Neither in vitro, nor clinical trials have explored whether combination of these drugs may have an additive effect in the inhibition of creatinine secretion.

• OBJECTIVE

- To estimate Cr-eGFR changes after starting DRV/c alone or in combination with DTG and/or RPV (one or more IPTCrS), in clinical practice.

• METHODS

- Nation-wide retrospective cohort study of consecutive HIV-infected patients initiating DRV/c, from June/2014 to March/2017. **GeSIDA study 9316.**
- The Cr-eGFR was calculated with CrCKD-EPI in mL/min/1.73m2, baseline values and change over time were recorded along with variables in the table.
- Univariable and multivariable models where created to assess factors influencing baseline Cr-eGFR, variables recorded in table were investigated, including TDF use in prior regimen.
- The relationship between Cr-eGFR change over time and the use of DRV/c as the unique IPTCrS or in combination with other IPTCrS DTG and/or RPV was explored by analyzing factors influencing the Cr-eGFR and comparing directly changes in both groups, both analyses were adjusted by different factors that might influence Cr-eGFR such as HIV patient´s characteristics, socio-demographics, HIV severity, use of TDF in prior and in concomitant regimen, and medication use other than antiretroviral.
- Ethics approval was obtained and patients signed informed consent.
- Clinical 59 Trial.gov No NCT03042390.

• RESULTS

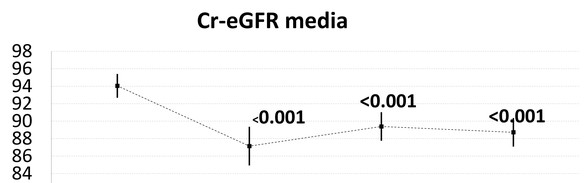
- 761 patients from 21 Spanish HIV Units initiating DRV/c were included in the overall cohort. Thirty-six (5%) patients were excluded due to the lack of cr-eGFR data.

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)
Heterosexual (%)	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)
Prior ART	
No (%)	12 (2)
DRV/r regimen (%)	610 (80)
No DRV/r regimen (%)	139 (18)
TDF (%)	220 (29)
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)
Number of IPTCrS in the regimen	
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)**
Concomitant TDF	195 (26)

Baseline Cr-eGFR and Factors Influencing its Value

- Baseline (mean ±SD) Cr-eGFR was **94±19** and **4.8 % had eGFR below 60** mL/min/1.73m², **increasing to 8.47% at 48 week**.
- In multivariable analysis, **higher age** was independently associated with a **lower** baseline Cr-eGFR Adjusted Mean Difference (AMD) (per **10** 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 Cr-eGFR.
- Only 6/761 (0.8%) switched a DRV/c containing regimen due to renal adverse event.

Change of Cr-eGFR 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

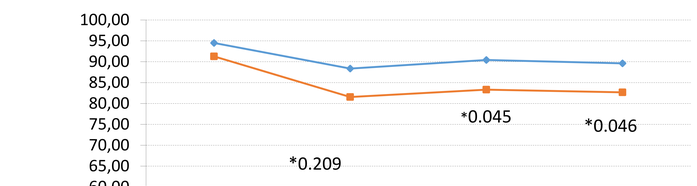
In clinical practice, DRV/c Initiation significantly decreases Cr-eGFR followed by a plateau , as it was previously described in clinical trials.

Factors influencing Change of Cr-eGFR after starting DRV/c

- After 12 weeks of starting DRV/C we did not observe any factor associated with higher or lower Cr-eGFR changes.
- After 48 weeks in patients receiving DRV/c, female sex was associated with a significant increase of eFGR while the combination of DRV/c with either RPV and /or DTG decreases Cr-eGFR.

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

Cr-eGFR at 12, 24 and 48 Weeks, DRV/c vs. DRV/c with RPV and/or DTG



	W 0	W 12	W 24	W 48
No RPV or DTG	94,49	88,36	90,42	89,61
RPV and/o DTG	91,28	81,55	83,31	82,68

DRV/c	N	623	256	514	463
RPV and/or DTG	N	102	56	86	69

After Adjustment for center clustering and baseline characteristics (sex, age, Aids stage, HCV- coinfection, DRV/c starting reason, prior DRV/c TAR type including TDF, baseline CD4 and Viral Load**,** a higher significant decrease in eGFR was observed in patients taking two or more creatinine IPTCrS at 24 weeks DRV/c +RPV and/or DTG, and a strong trend at 48 week.
*Adjusted p-value

• CONCLUSIONS

- An expected small Cr-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 Cr-eGFR change were gender, females experienced lower decrease of eGFR, while concomitant use of Dolutegravir, Rilpivirine or both increases Cr-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 Cr-eGFR decrease at 12, 24 and 48 weeks.

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