Evolution of renal function during treatment with direct antiviral agents (DAA-t) in HIV/HCV infected patients in ICONA/Hepalcona cohorts

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Italian Cohort I. C. O. N. A. Naive Antiretrovirals

Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS
Conceived by Professor Mauro Moroni

16th EUROPEAN AIDS CONFERENCE
October 25–27, 2017
Milan, Italy
EACS European AIDS Clinical Society

BACKGROUND

- Eradication of HCV after therapy with interferon plus ribavirin in HIV/HCV-coinfected patients is associated not only with a reduction in liver-related events but also with a reduction in HIV progression and mortality not related to liver disease (*Berenguer, Clin Infect Dis 2012*).

- HCV-HIV patients had a 50-75% increased risk of CKD compared with HIV patients (*Mocroft, AIDS 2007; Wyatt, AIDS 2008*).

- Successful HCV treatment seems to slightly reduce the incidence of chronic kidney diseases (*Kovari, Clin Infect Dis 2017*).

- Concomitant treatment with ledipasvir/sofosbuvir and tenofovir has been reported as detrimental on kidney function (*Bunnell, Pharmacother 2016*).

OBJECTIVES

In HIV/HCV co-infected patients, we aimed to assess:

- changes in renal function (eGFR) during and after treatment with direct acting antiviral drug (DAA) treatment,

- factors associated with eGFR changes during and after DAA treatment.

METHODS

HIV/HCV patients from the ICONA/Hepaicona Cohort in active follow-up after January 2013 (N=3012) :

- ✓ Treated with DAA (February 2013 - December 2016);
- ✓ With at least 12 weeks follow-up after the end of DAA treatment (SVR12);
- ✓ With regular eGFR determinations (CKD-EPI formula*)* during and after DAA treatment [median number of eGFR determinations on the overall follow-up: 6 (IQR: 3-8); during DAA: 3 (IQR: 1-4); post DAA: 3 (2-4)].

Follow-up accrued from the date of DAA start (baseline, within 3 months) to the date of last visit after the end of DAA treatment.

STATISTICAL ANALYSIS

Patients were stratified by baseline eGFR :

<60 mL/min/1.73m^2, 60-90 mL/min/1.73m^2, >90 mL/min/1.73m^2.

Baseline characteristics of subjects with different baseline eGFR values compared using chi-square and Kruskal-Wallis test.

Mixed linear models with random intercept and slope fitted to:

- ✓ estimate mean eGFR changes (slopes) from baseline at different time points [end of DAA treatment (EOT), at SVR12, at the end of follow-up];
- ✓ identify factors associated with eGFR changes (slopes) on the overall follow-up.

RESULTS – Characteristics at DAA start (1)

		Overall (n=394)	eGFR <60* (n=16)	eGFR 60-90* (n=112)	eGFR >90* (n=266)	P-value
Age (years)	Median (IQR)	53 (50 - 55)	52.5 (51 - 56.5)	53 (51 - 55.5)	52 (50 - 55)	0.139
Gender	Male	308 (78%)	11 (69%)	84 (75%)	213 (80%)	0.357
Previous AIDS		65 (17%)	5 (31%)	23 (21%)	37 (14%)	0.076
Nadir CD4+ (cells/µL)	Median (IQR)	159 (70 - 254)	45 (20 - 78)	128 (52 - 190)	180 (81 - 275)	0.0001
Years of ART	Median (IQR)	17.1 (12.2 - 19.3)	15.7 (6.1 - 22.9)	17.6 (13.2 - 19.8)	17.1 (11.6 - 19.2)	0.557
Diabetes		24 (9%)	1 (6%)	17 (15%)	24 (9%)	0.176
Hypertension		104 (26%)	10 (63%)	35 (31%)	59 (22%)	0.0007
Cirrhosis		172 (44%)	5 (32%)	47 (42%)	120 (45%)	0.506
Previous kidney disease		26 (7%)	7 (44%)	8 (7%)	11 (4%)	<0.0001

** by CKD-EPI formula (mL/min/1.73m²)*

RESULTS – Characteristics at DAA start (2)

		Overall (n=394)	eGFR <60* (n=16)	eGFR 60-90* (n=112)	eGFR >90* (n=266)	P-value
PI-including regimens		132 (34%)	6 (38%)	36 (32%)	90 (34%)	0.896
INSTI-including regimens		215 (55%)	10 (63%)	63 (56%)	142 (53%)	0.710
TDF-includign regimens		264 (68%)	9 (56%)	74 (66%)	181 (69%)	0.539
BL CD4+ (cells/µL)	Median (IQR)	562 (354 - 769)	450 (279 - 590)	527 (335 - 777)	573 (410 - 762)	0.154
BL HIV-RNA	<50 cps/mL	358 (94%)	16 (100%)	101 (93%)	242 (95%)	0.484
BL eGFR* (mL/min/1.73m²)	Median (IQR)	99 (85 – 105)	57 (50 - 58)	79 (72 - 85)	103 (99 – 108)	<0.0001
HCV genotype	1/1a	177 (46%)	7 (44%)	47 (44%)	123 (48%)	0.665
	1b	55 (15%)	2 (13%)	22 (21%)	31 (12%)	
	3	77 (20%)	4 (25%)	16 (15%)	57 (22%)	
	4	67 (18%)	3 (19%)	22 (21%)	42 (16%)	
	Other/Mixed	4 (1.1%)	0 (0%)	0 (0%)	4 (1.4%)	

** by CKD-EPI formula (mL/min/1.73m²)*

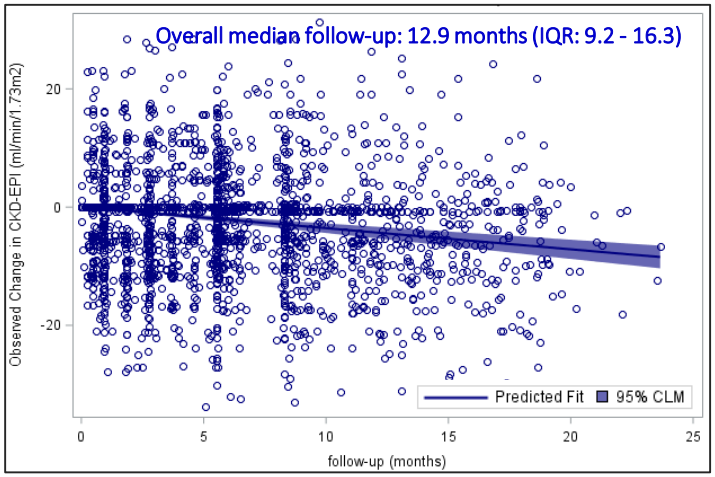
RESULTS – Characteristics at DAA start (3)

		Overall (n=394)	eGFR <60* (n=16)	eGFR 60-90* (n=112)	eGFR >90* (n=266)	P-value
BL Stiffness (Kpa)	Median (IQR)	14 (10 - 23)	11 (9 - 16)	14 (10 - 23)	14 (10 - 23)	0.562
Type of DAA regimen	LDV/SOF	117 (30%)	4 (25%)	40 (36%)	73 (27%)	0.303
	SOF-including	170 (43%)	7 (44%)	46 (41%)	117 (44%)	
	SOF-sparing	107 (27%)	5 (31%)	26 (23%)	76 (29%)	
Use of ribavirin		268 (68%)	11 (69%)	66 (59%)	191 (72%)	0.050
Previously treated with IFN/RBV		196 (50%)	11 (69%)	50 (45%)	135 (51%)	0.166
SVR 12		337 (93%)	12 (86%)	95 (90%)	230 (95%)	0.141

** by CKD-EPI formula (mL/min/1.73m^2)*

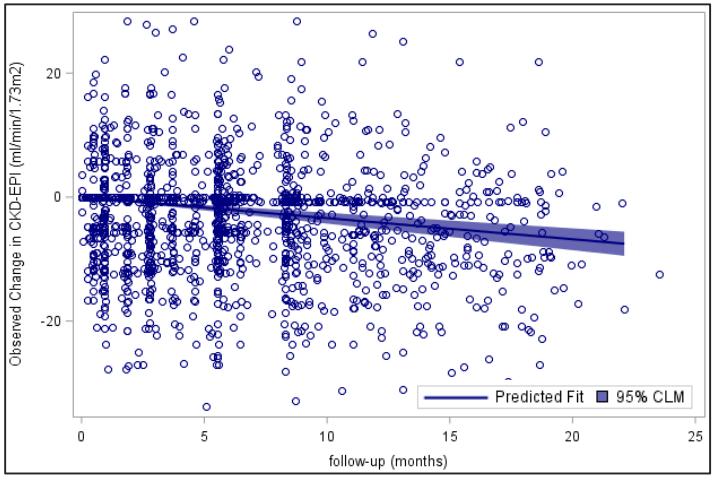
Results - eGFR changes over time and slopes

ALL subjects (n=394)



		Mean eGFR* change (slope) from baseline (95% Confidence Interval) (mL/min/1.73m2 per month)	P-value
OVERALL FOLLOW-UP		-0.36 (-0.44, -0.28)	<.0001
During DAA	**EOT**	-0.39 (-0.58, -0.21)	<.0001
Post DAA	**12W**	-0.26 (-0.37, -0.14)	<.0001
	24W	-0.42 (-0.55, -0.30)	<.0001

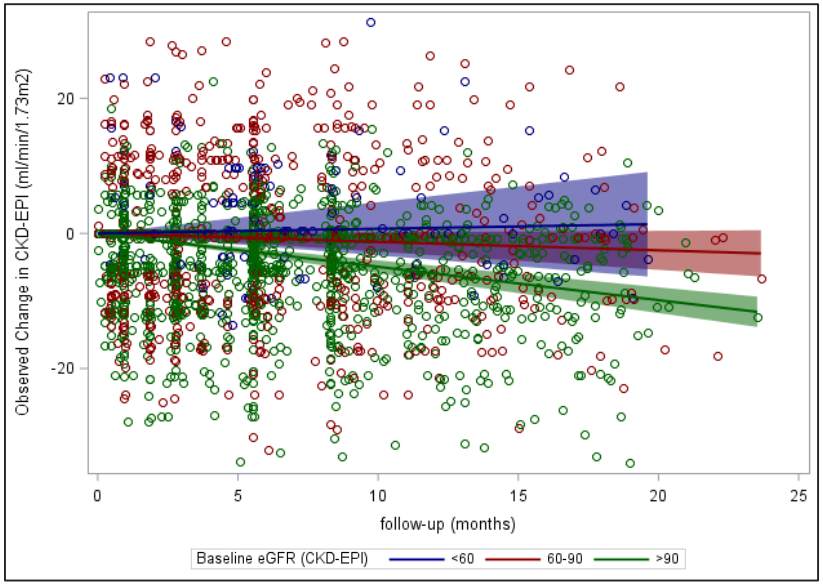
Excluded subjects on DVG,RPV,cobi (n=299)



		Mean eGFR* change (slope) from baseline (95% Confidence Interval) (mL/min/1.73m2 per month)	P-value
OVERALL FOLLOW-UP		-0.34 (-0.43, -0.25)	<.0001
During DAA	**EOT**	-0.40 (-0.64, -0.16)	0.001
Post DAA	**12W**	-0.38 (-0.53, -0.23)	<.0001
	24W	-0.59 (-0.76, -0.42)	<.0001

** by CKD-EPI formula (mL/min/1.73m²)*

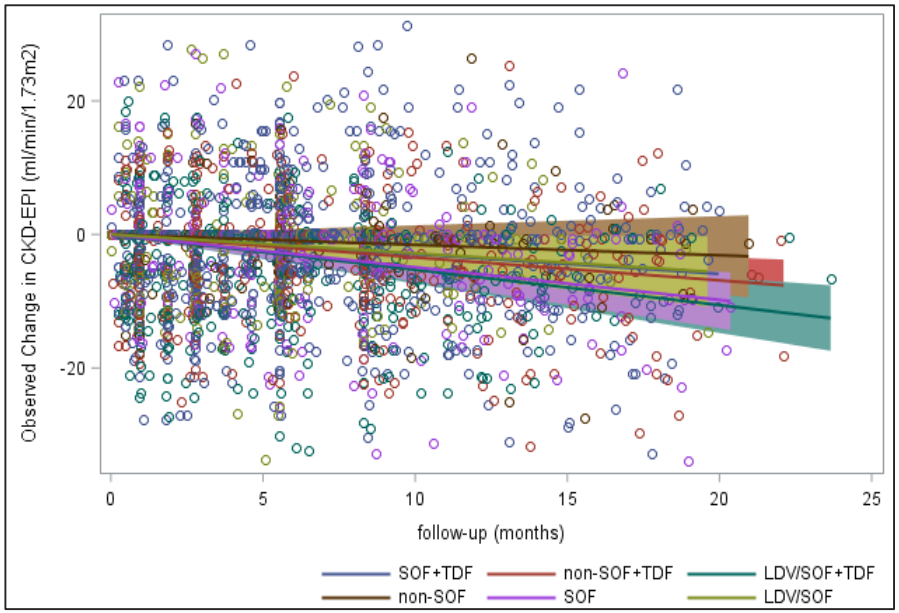
Results - eGFR changes over time and slopes according to baseline eGFR



Baseline eGFR*	Mean eGFR* change (slope) from baseline (95% Confidence Interval) (mL/min/1.73m2 per month)		
	OVERALL FOLLOW-UP	EOT	12W post EOT
<60 (n=16)	0.07 (-0.33, 0.46) P=0.732	-0.97 (-1.70, -0.24) P=0.010	0.62 (0.03, 1.20) P=0.039
60-90 (n=112)	-0.13 (-0.30, 0.02) P=0.089	0.30 (0.02, 0.58) P=0.039	0.18 (-0.02, 0.38) P=0.082
>90 (n=266)	-0.49 (-0.59, -0.40) P<.0001	-0.80 (-1.05, -0.54) P<.0001	-0.52 (-0.66, -0.38) P<.0001

** by CKD-EPI formula (mL/min/1.73m²)*

Results - eGFR changes over time and slopes according to DAA regimen



Type of DAA regimen	Mean eGFR* change (slope) from baseline (95% Confidence Interval) (mL/min/1.73m2 per month)		
	OVERALL FOLLOW-UP	EOT	12W post EOT
LDV/SOF (n=45)	-0.28 (-0.55, -0.02) P=0.039	-0.16 (-0.73, 0.41) P=0.585	-0.41 (-0.75, -0.07) P=0.017
LDV/SOF+TDF (n=72)	-0.53 (-0.74, -0.32) p<.0001	-0.68 (-1.06, -0.31) P=0.0004	-0.51 (-0.77, -0.24) P=0.0002
SOF (n=53)	-0.49 (-0.70, -0.28) P<.0001	-0.65 (-1.18, -0.11) P=0.017	-0.33 (-0.64, -0.01) P=0.043
SOF+TDF (n=115)	-0.30 (-0.44, -0.16) P<.0001	-0.36 (-0.68, -0.03) P=0.030	-0.02 (-0.23, 0.19) P=0.839
Non-SOF (n=29)	-0.16 (-0.45, 0.14) P=0.297	-0.23 (-1.30, 0.85) P=0.678	-0.22 (-0.71, 0.28) P=0.392
Non-SOF+TDF (n=77)	-0.34 (-0.52, -0.17) P=0.0001	-0.14 (-0.63, 0.34) P=0.560	-0.25 (-0.52, 0.03) P=0.081

** by CKD-EPI formula (mL/min/1.73m²)*

Results - Factors associated with eGFR changes over time

The adjusted mean change in eGFR on the overall follow-up was -0.27 mL/min/1,73m^2 (95%CI: -0.37, -0.18), p<0.0001

Characteristic	Adjusted* difference in eGFR change (95% Confidence Interval) (mL/min/1.73m2 per month)	P-value
Age (per year older)	**-0.23 (-0.41/-0.05)**	**0.013**
Diabetes (yes vs no)	**-3.45 (-6.09/ -0.80)**	**0.011**
Type of DAA regimen		0.652
LDV/SOF	-1.09 (-3.44/ +1.26)	0.364
SOF	-0.79 (-3.12/ +1.54)	0.508
non-SOF	Ref	
Use of tenofovir (yes vs no)	-1.72 (-3.59/ +0.16)	0.072
Baseline eGFR (mL/min/1.73m^2)		**<0.0001**
<60	**+6.07 (+0.51/ +11.63)**	**0.032**
60-90	**+5.13 (+3.19/ +7.08)**	**<.0001**
>90	**Ref**	

** Adjusted also for Nadir CD4+, HCV genotype (1/1a vs other), Years of ART, Use of ribavirin in the DAA regimen, Baseline CD4+, Cirrhosis.*

LIMITATIONS

- The eGFR decline prior to DAA treatment was not accounted for when considering eGFR changes.
- The analysis of the relationship between DAA regimens and TDF use may have been impaired by a limited number of available subjects.
- The impact of drugs other than cART concomitantly administered could not be ruled out

CONCLUSIONS

- A slight overall reduction of renal function was observed during DAA treatment.
- Baseline eGFR may determine different trajectories, leading to improvement in pts with more impaired baseline kidney function and to worsening in pts with higher baseline eGFR.
- The concomitant use of TDF, independently of DAA regimens, tended to negatively affect renal function during DAA.
- Age and metabolic comorbidities seem to have a more detrimental role than concomitant potentially nephrotoxic drugs in renal function during DAA treatment.

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Funding:

ICONA Foundation is supported by unrestricted grants from Bristol Myers Squibb, Gilead Science, Janssen, Merck Sharpe and Dohme and ViiV Healthcare Italy.