Evolution of comorbidities in HIV patients in Italian ICONA cohort: *cross sectional analysis in 2004 and 2014*
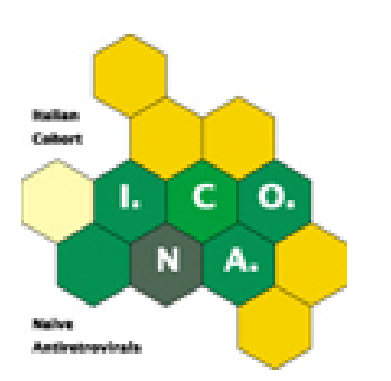
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Introduction and Objective

Significant advances in antiretroviral therapy (ART) have increased life expectancy of people living with HIV (PWHIV)[1]. Prevalence of non-HIV related comorbidities is increased in PWHIV compared to the general population[2].

The objective of this study is to describe the impact of ageing on demographics, HIV markers and comorbidities in the same PWHIV followed in ICONA cohort, 10 years apart.

Methods

- ICONA is an open cohort of PWHIV in Italy. All ICONA participants seen at least once in both 2004 and 2014 were included in the analysis.
- A cross-sectional analysis was performed comparing demographics, HIV markers and comorbidities in the same set of PWHIV ten years apart. This analysis is a descriptive analysis.
- A sub analysis was performed based on previous treatment history. Two mutually exclusive groups were defined: naïve to ART (never on ART through end of 2004 or initiated ART during 2004) and experienced (on ART prior to January 1st 2004).
- The following definitions were used:
  - eGFR: lowest value observed ever, calculated using CKD-EPI formula.
  - Cardiovascular event: myocardial infarction, invasive coronary procedure, stroke or cardiovascular related deaths;
  - Hypertension: systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg or taking antihypertensive drugs at least once over the year;
  - Diabetes: clinical diagnosis of diabetes, fasting glucose ≥100 mg/dL in two consecutive determinations, casual glucose > 140 mg/dL or taking antidiabetic drugs or insulin at least once over the year;
  - Dyslipidemia: elevated total cholesterol ≥6.2 mmol/l (240 mg/dL), and/or decreased HDL-cholesterol ≤0.9 mmol/l (35mg/dL), and/or elevated triglycerides ≥2.3 mmol/l (200 mg/dL) at least once over the year.

Results

- 1,517 met the inclusion criteria. Demographic and social characteristics of this population are depicted in *Table 1*.
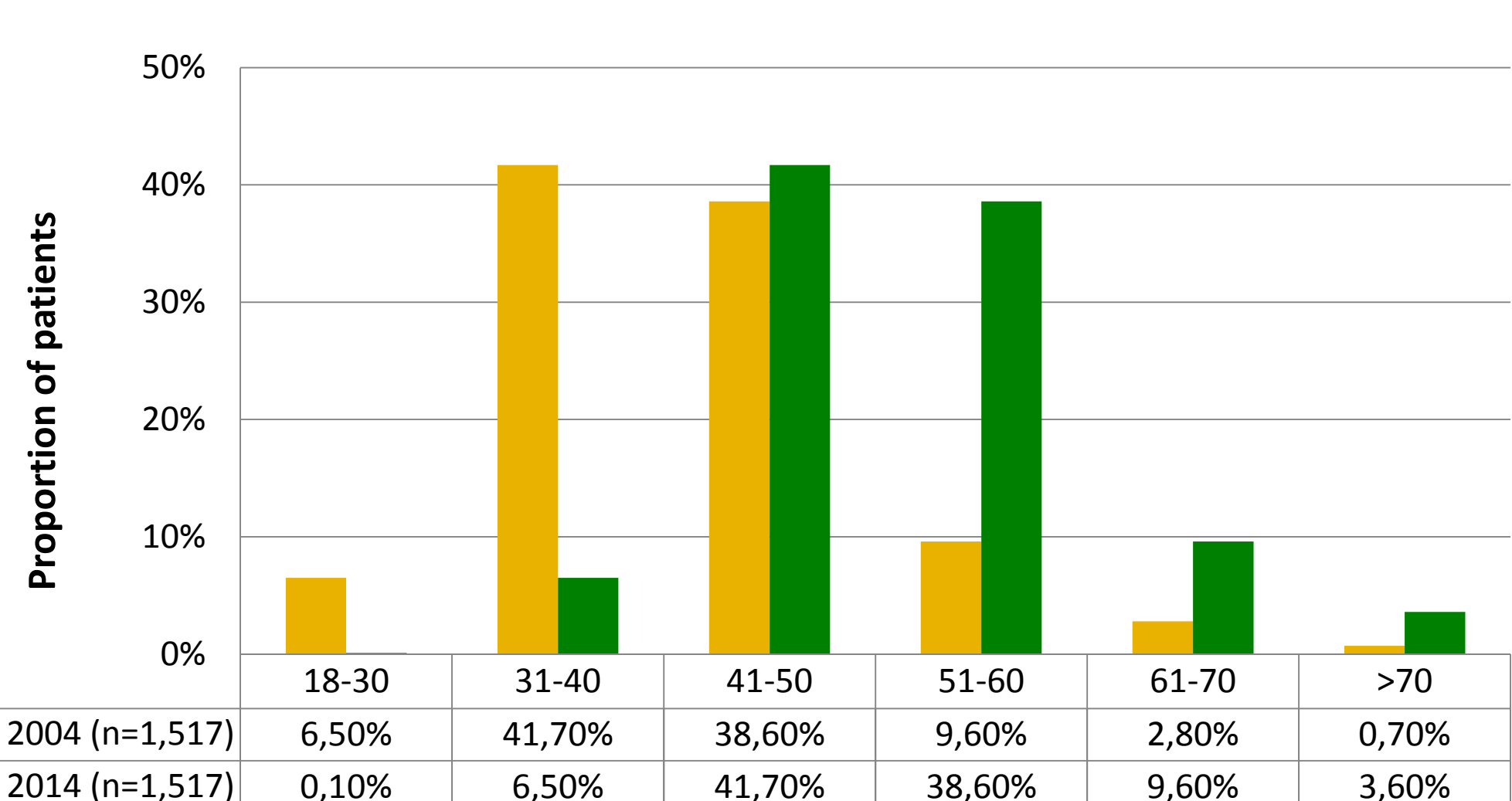
Table 1 – Patients Characteristics

Characteristics	2004 (N=1,517)	2014 (N=1,517)
Female, %		33.3
Mean age, years (SD)	42 (8)	52 (8)
Region of origin, %		
Italy		94.5
Europe		0.9
Africa		2.3
Others		2.3
Months from HIV diagnosis, median (IQR)	84 (48 - 144)	204 (168 - 264)
BMI, Kg/m², median (IQR)	23.4 (21.5 - 25.6)	23.8 (21.7 - 26.4)
Mode of HIV transmission, %		
Heterosexual contacts		43.6
IVDU		27.2
MSM		23.2
Other/unknown		5.9
Education, %		
Primary		11.1
Secondary		71.3
University		7.2
Other/unknown		10.3

Legend: BMI, Body Mass Index; MSM, men who have sex with men; IQR, Inter Quartile Range; IVDU, Intravenous drug users; SD, standard deviation

- As shown in *Figure 1*, the proportion of patients older than 50 years increased from 13.1% in 2004 to 51.8% in 2014, as expected.

Figure 1 – Distribution of patients by age group, in 2004 and 2014

	18-30	31-40	41-50	51-60	61-70	>70
2004 (n=1,517)	6,50%	41,70%	38,60%	9,60%	2,80%	0,70%
2014 (n=1,517)	0,10%	6,50%	41,70%	38,60%	9,60%	3,60%

Significant clinical improvements on HIV disease markers and management occurred over time (Table 2):

- There was a 57% increase in the proportion of patients with CD4 count > 500 cells/mm3;
- The proportion of patients who were suppressed (viral load ≤40 log10 copies/mL) increased from 4.5% in 2004 to 83.8% in 2014;
- The proportion of patients on a 2NRTI+PI/r overall decreased from 22.5% in 2004 to 7.9% in 2014.

Table 2 – Patients' Characteristics: ART and HIV infection

Characteristics	Overall 2004 (n=1,517)	Overall 2014 (n=1,517)	ART-naïve 2004 (n=445)	ART-naïve 2014 (n=445)	ART-experienced 2004 (n=1,072)	ART-experienced 2014 (n=1,072)
Proportion of patients (naïve / experienced)			29.3%		70.7%	
Months on ART, median (IQR)	54 (26 - 79)	152 (117 - 186)	7 (3 - 10)	96 (66 - 117)	59 (35 - 81)	171 (146 - 195)
Type of ART regimen, %						
On therapy (ever or on that year)	78.5	98.1		26.7		100
2NRTI + NNRTI	38.0	35.7	30.3	43.7	38.8	34.8
2 NRTI + PI/r	22.5	7.9	16.8	6.7	23.1	7.9
2 NRTI + INSTI	0.0	4.2	0.0	1.7	0.0	4.4
NRTI-sparing	16.4	10.1	43.7	4.2	13.3	10.4
Dual therapy	6.3	1.7	4.2	1.7	6.5	2.0
Other	16.9	40.5	5.0	42	18.2	40.5
CD4 count, cells/mm³						
CD4 count, cells/mm³, median (IQR)*	507 (357 - 713)	706 (518 - 912)	462 (346 - 633)	698 (518 - 847)	530 (366 - 739)	711 (515 - 942)
0-350, %	23.0	7.8	24.3	6.1	22.5	8.5
351-500, %	25.2	14.7	29.4	15.1	23.5	14.6
>500, %	49.8	77.5	39.8	78.9	54.0	77.0
AIDS diagnosis ever before end of the year, %	13.8	16.4	6.7	10.3	16.8	18.9

*Legend: *, percentages do not sum 100%, due to the patients with unknown status; ART, anti-retroviral treatment; NRTIs, nucleoside reverse-transcriptase inhibitors; NNRTIs, non-nucleoside reverse-transcriptase inhibitors; PI, protease inhibitors; PI/r, ritonavir boosted protease inhibitor; INSTI, Integrase Strand Transfer Inhibitor; IQR, Interquartile range.*

- Between 2004 and 2014, there was an overall increase in prevalence of comorbidities *(Figure 2)*. The prevalence of dyslipidemia significantly increased by +16.6%, hypertension by +16.3%, cardiovascular events by +14.2%.
- The prevalence of other modifiable characteristics, such as, obesity and abusive alcohol consumption, also increased over time. Only tobacco consumption was significantly reduced over time.

Results (cont')

Figure 2 – Prevalence of patients' comorbidities and behavioral risk factors, in 2004 and 2014

	eGFR<60	Cardiovascular event	Diabetes	Hypertension	Dyslipidemia	HCV	HBV	Obesity (BMI>30)	Current tobacco consumption	Abusive alcohol consumption
2004 (n=1,517)	4,90%	17,50%	4,20%	67,20%	74,60%	31,80%	5,0%	5,40%	54,50%	4,60%
2014 (n=1,517)	30,20%	31,70%	8,60%	83,50%	91,20%	33,1%	5,1%	8,50%	46,10%	6,90%

+25.3% (p<0.001); +14.2% (p<0.001); +4.4% (p<0.001); +16.3% (p<0.001); +16.6% (p<0.001); +1.3% (p<0.001); +0.1% (p<0.001); +3.1%; -8.4% (p<0.001); +2.3%

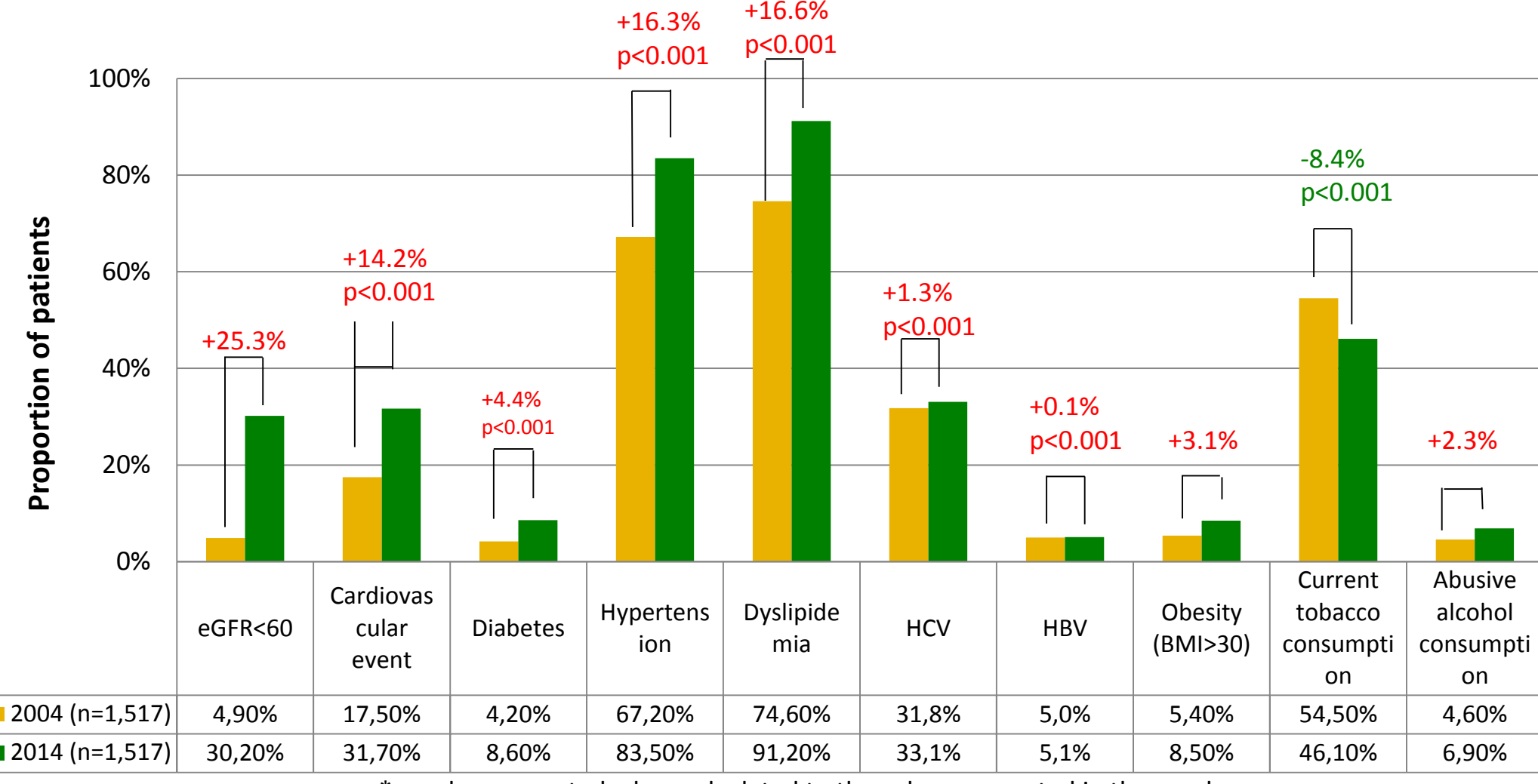** p-value presented when calculated to the values presented in the graph.*

Figure 3 – Distribution of patients by eGFR in 2004 and 2014, overall, ART-naïve and ART-experienced

	<30	30-60	60-89	≥90
2004 ART-naïve (n=445)	0.1%	0.5%	11.7%	14.6%
2004 ART-experienced (n=1072)	0.7%	3.7%	35.6%	28.9%
2014 ART-naïve (n=445)	1.1%	6.7%	18.0%	3.6%
2014 ART-experienced (n=1072)	3.8%	18.7%	43.8%	4.4%

- Overall, there was a decrease of the renal function over time, regardless of ART status. Particularly the proportion of patients with renal impairment (eGFR <60) increased from 4.9 % in 2004 to 30.2% in 2014 - *Figure 3*.
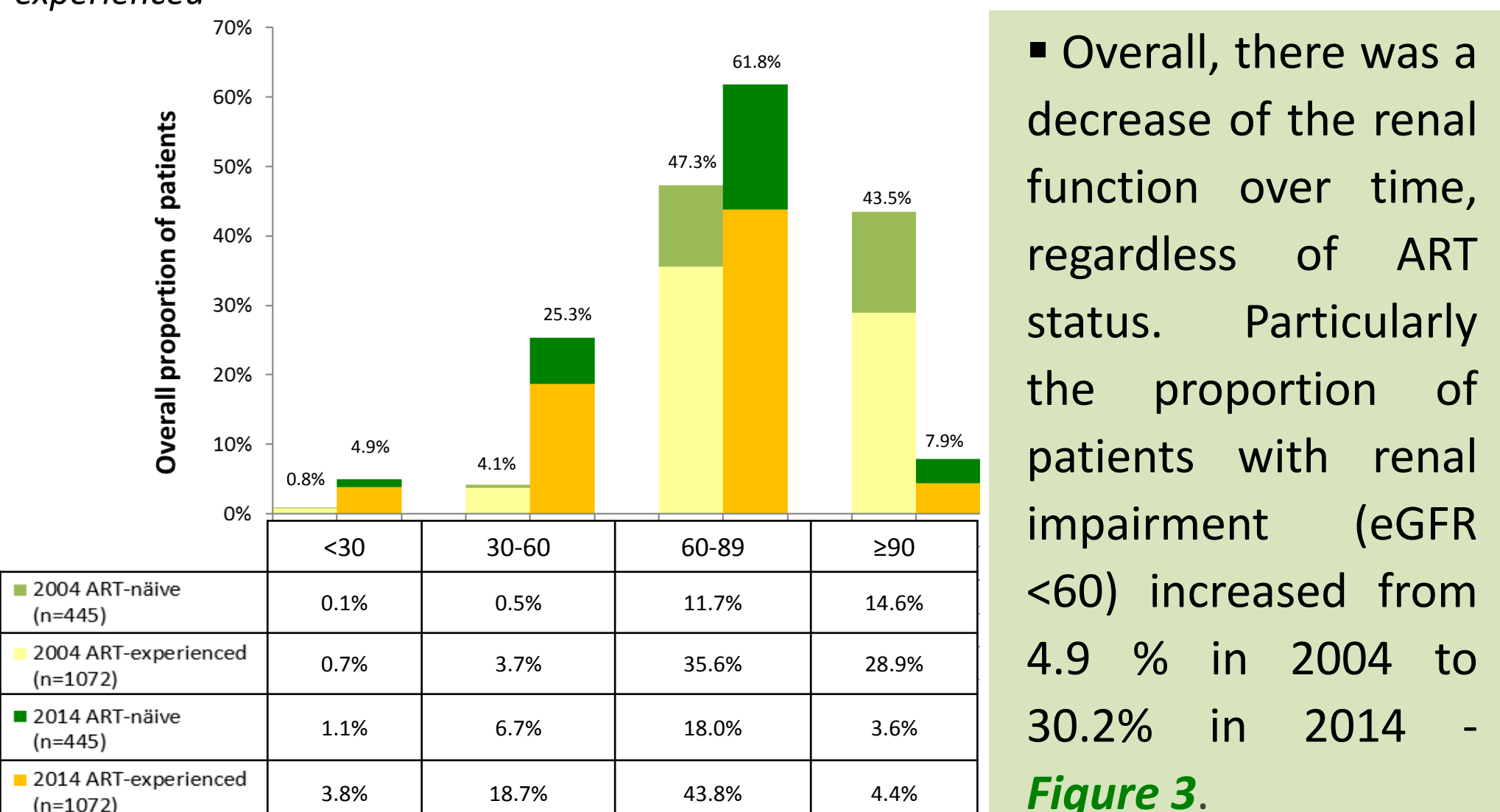
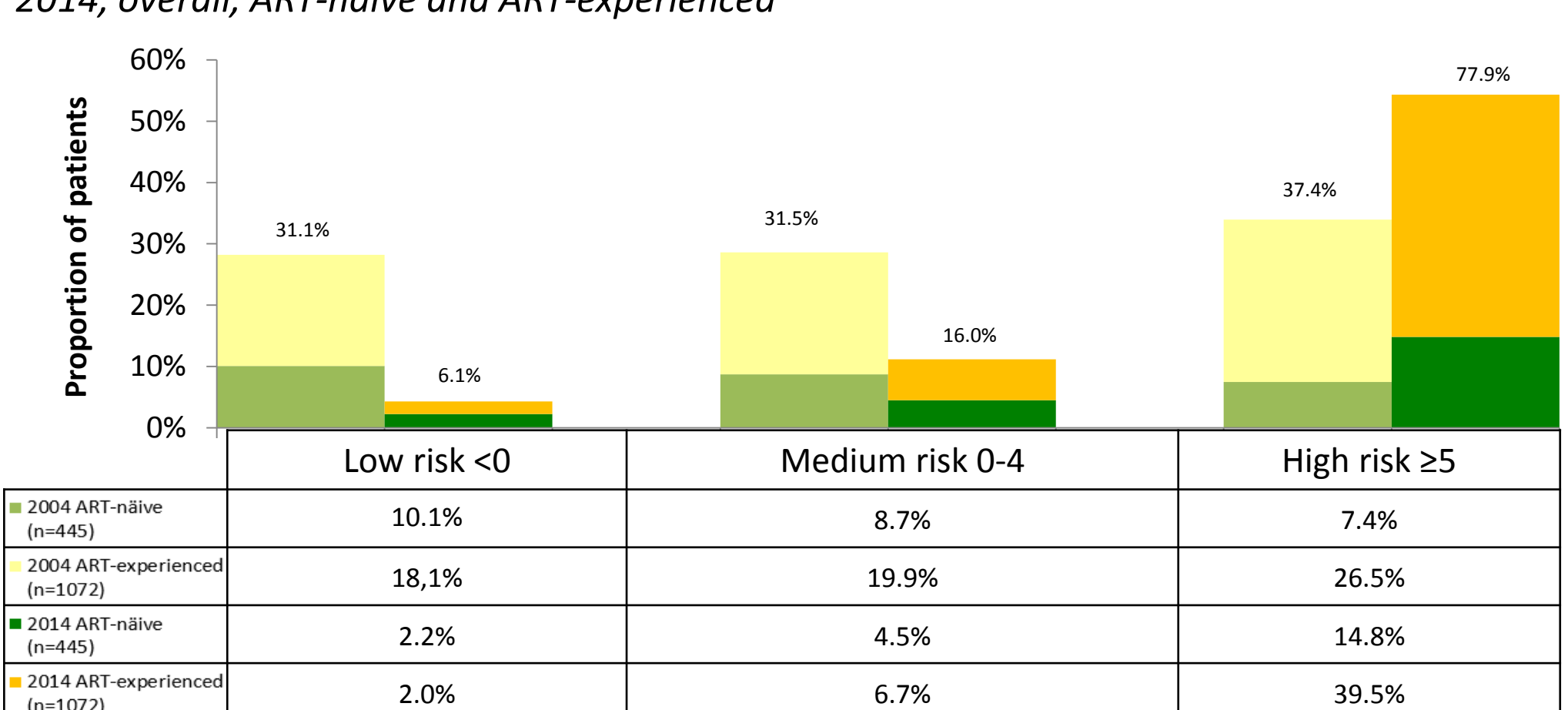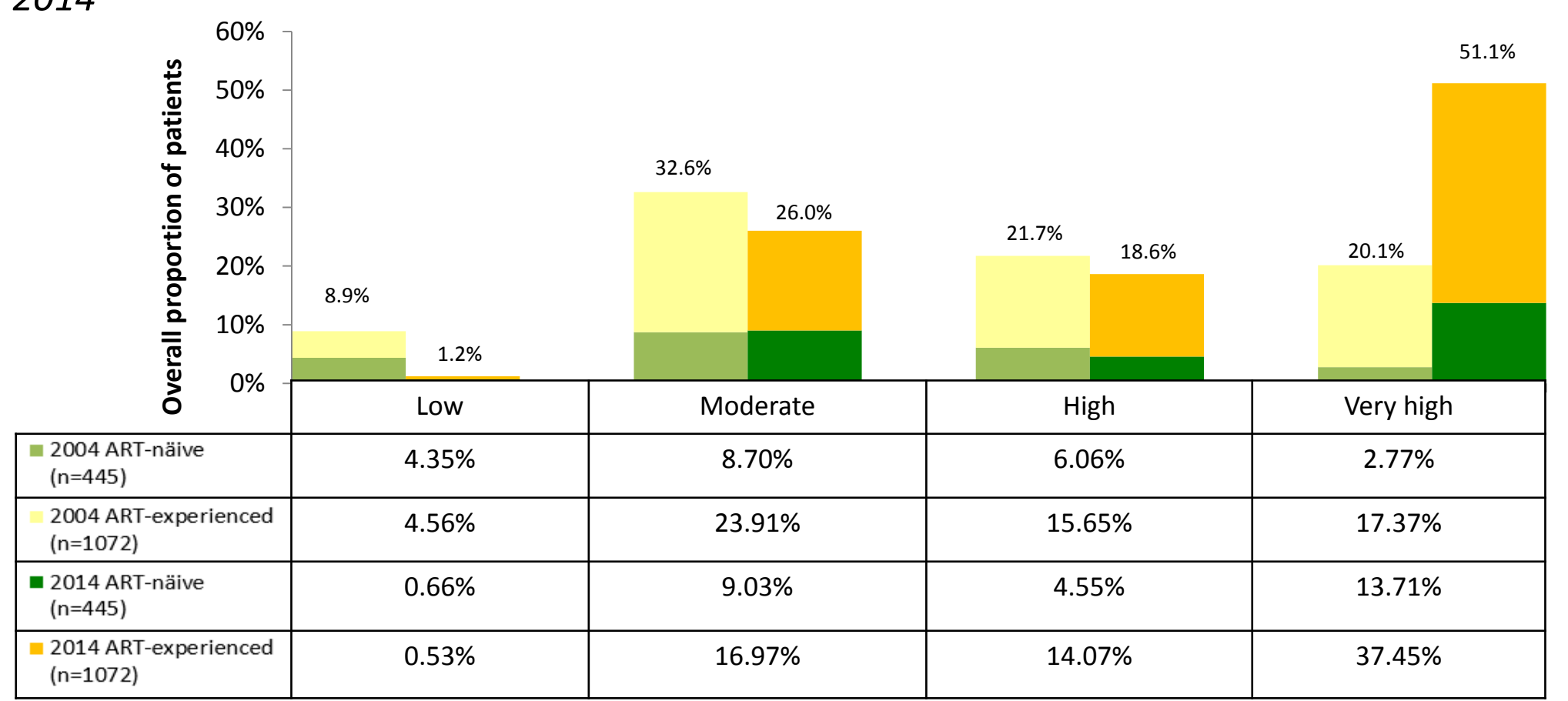### Figure 4 – Distribution by D.A.D. Progression to Chronic Kidney Disease Score in 2004 and 2014, overall, ART-naïve and ART-experienced

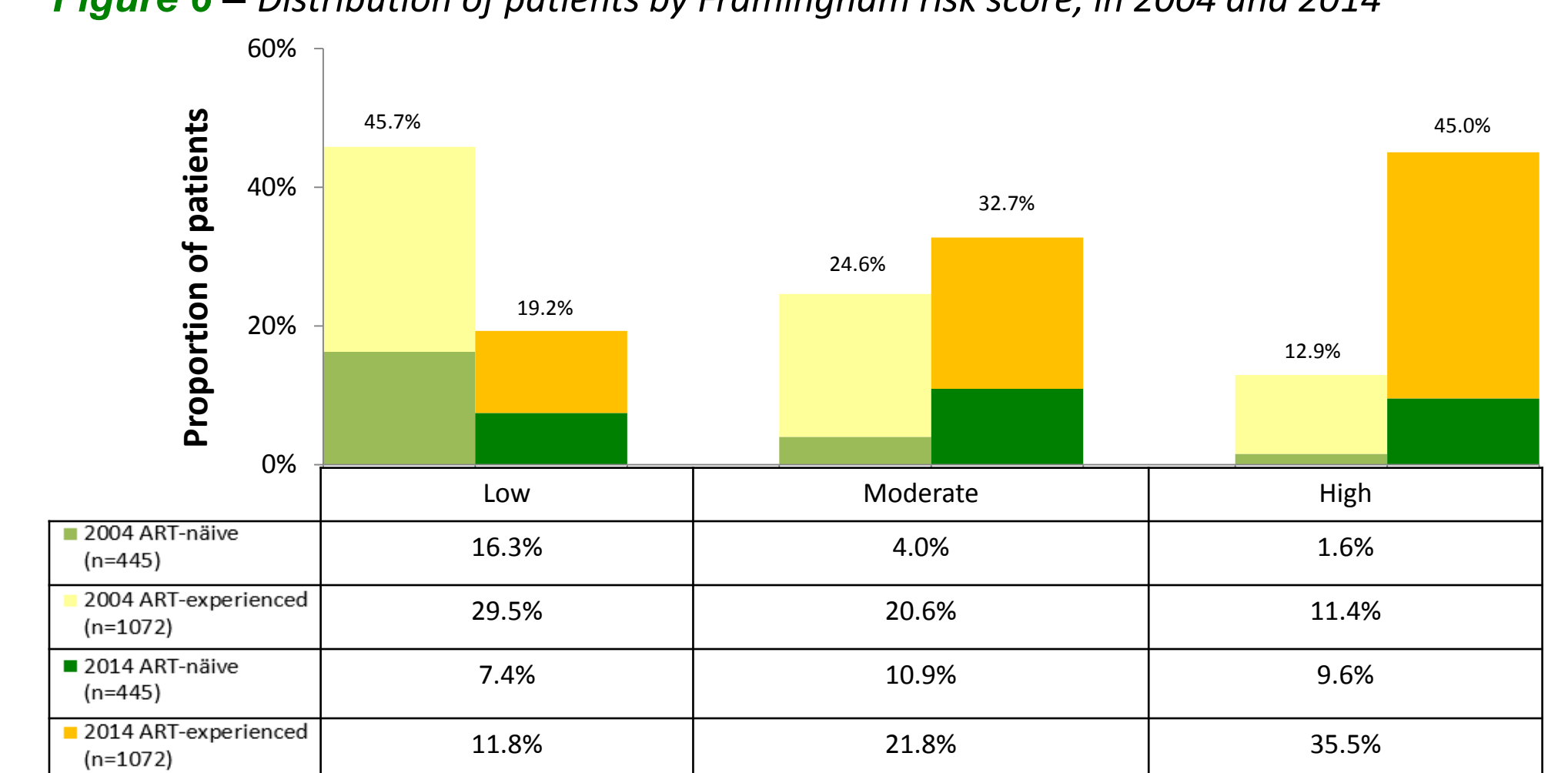|	Low risk <0	Medium risk 0-4	High risk ≥5
2004 ART-naïve (n=445)	10.1%	8.7%	7.4%
2004 ART-experienced (n=1072)	18,1%	19.9%	26.5%
2014 ART-naïve (n=445)	2.2%	4.5%	14.8%
2014 ART-experienced (n=1072)	2.0%	6.7%	39.5%

* calculations were based on patients on therapy.

- The mean (±SD) D:A:D CKD score significantly increased over time, from 8.2 (±3.0) in 2004 to 10.5 (±3.6) in 2014 (p<0.001).
- Particularly, the proportion of patients at high risk of progression to CKD doubled between 2004 and 2014 (37.4% vs 77.9%)- *Figure 4*.

Figure 5 – Distribution of patients by D.A.D. cardiovascular disease risk score, in 2004 and 2014*

	Low	Moderate	High	Very high
2004 ART-naïve (n=445)	4.35%	8.70%	6.06%	2.77%
2004 ART-experienced (n=1072)	4.56%	23.91%	15.65%	17.37%
2014 ART-naïve (n=445)	0.66%	9.03%	4.55%	13.71%
2014 ART-experienced (n=1072)	0.53%	16.97%	14.07%	37.45%

* Percentages will not sum 100% due to the number of patients with unknown risk score (245, in 2004 and 47 in 2014); calculations were based on patients on therapy

- The mean (±SD) D:A:D cardiovascular score significantly increased over time, from 21.6 (±14.7) in 2004 to 27.9 (±19.1) in 2014 (p<0.001).
- The proportion of patients in the highest CV risk class more than doubled according to both the Framingham and D:A:D risk equations *(Figure 5 and Figure 6)*.

Figure 6 – Distribution of patients by Framingham risk score, in 2004 and 2014*

	Low	Moderate	High
2004 ART-naïve (n=445)	16.3%	4.0%	1.6%
2004 ART-experienced (n=1072)	29.5%	20.6%	11.4%
2014 ART-naïve (n=445)	7.4%	10.9%	9.6%
2014 ART-experienced (n=1072)	11.8%	21.8%	35.5%

* Percentages will not sum 100% due to the number of patients with unknown risk score (245, in 2004 and 47 in 2014); calculations were based on patients on therapy.

- There was a significant increase in the mean (±SD) Framingham score over time, from 31.2 (±10.1) in 2004 to 35.0 (±13.3) in 2014 (p<0.001).

CONCLUSIONS

- Between 2004 and 2014, a significant improvement in HIV markers (CD4 count and viral load) was observed. Simultaneously, the population is older and with higher prevalence of comorbidities, namely renal and cardiovascular along with increased associated risk factors for these.
- Careful HIV management, including adequate selection of ART and regular monitoring and screening of the major comorbidities, could lead to an early management of these comorbidities and to a continuous improvement of quality of life in PLHIV.
- These data will be further used to inform a stochastic model to predict Italian patients comorbidity status in 2030 and beyond.

ACKNOWLEDGEMENTS

Bibliography

[1] Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: A collaborative analysis of 14 cohort studies. Lancet 2008; 372(9635): 293–9.
[2] Guaraldi G, et al. Clinical Infectious Diseases 2011;53(11):1120–6.