

## Background

Prevalence of prolonged QT interval on electrocardiograms (ECG) of HIV infected individuals has been described as being higher than in the general population (13% to 20%). Various factors might explain cardiac repolarization changes in HIV infected individuals, including direct effect of HIV, immunodepression, drug toxicity (protease inhibitors [PI]) and potential confounding cardiovascular co-factors.

## Inclusion criteria

- HIV-infected adults
- Followed in the Infectious Diseases Dpt (CHU Nantes) between Jan. 2010 and Feb. 2016
- ECG performed before antiretroviral therapy initiation
- Current ARV therapy
- Oral informed consent

## Results

- 255 ART-naïve adults had a pre-ART ECG between January 2010 and February 2016 : median age 36.4 years, 72.6% male, median CD4 428/mm<sup>3</sup>, median HIV RNA 4.6 log<sub>10</sub> c/ml, smoker 42.5%, IVDU 14.4%, CDC Stage C 14%.
- Pre-ART and on-ART ECGs were both performed in 175 patients (Table 1).
- 6 /255 pre-ART ECGs (2,3 %) and 4/175 on-ART ECGs (2,3 %) showed a prolonged QTc interval (Tables 2 and 3) with values ranging from 443 to 474 ms both in pre-ART and on-ART ECGs.

Fig. 1 - Flowchart

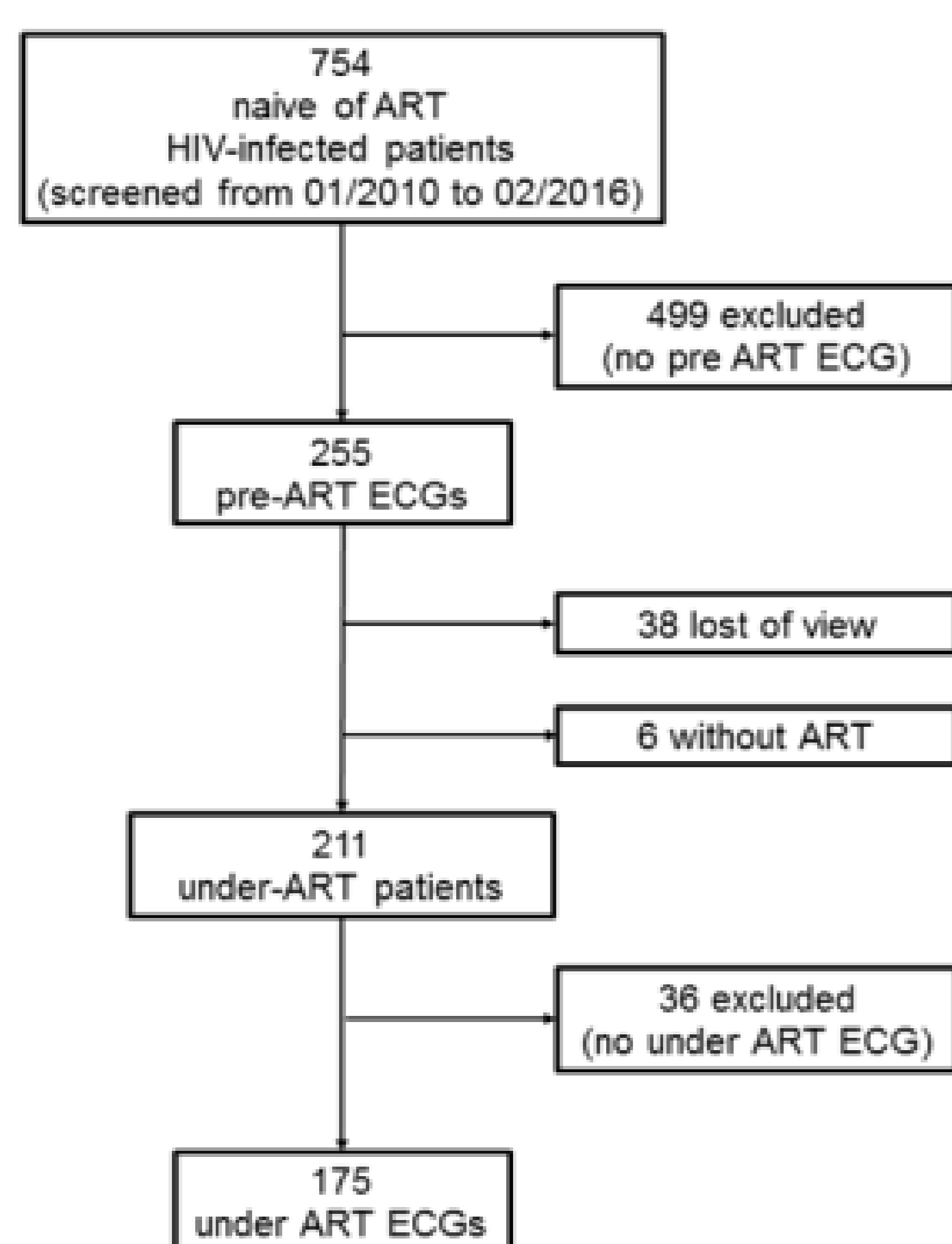
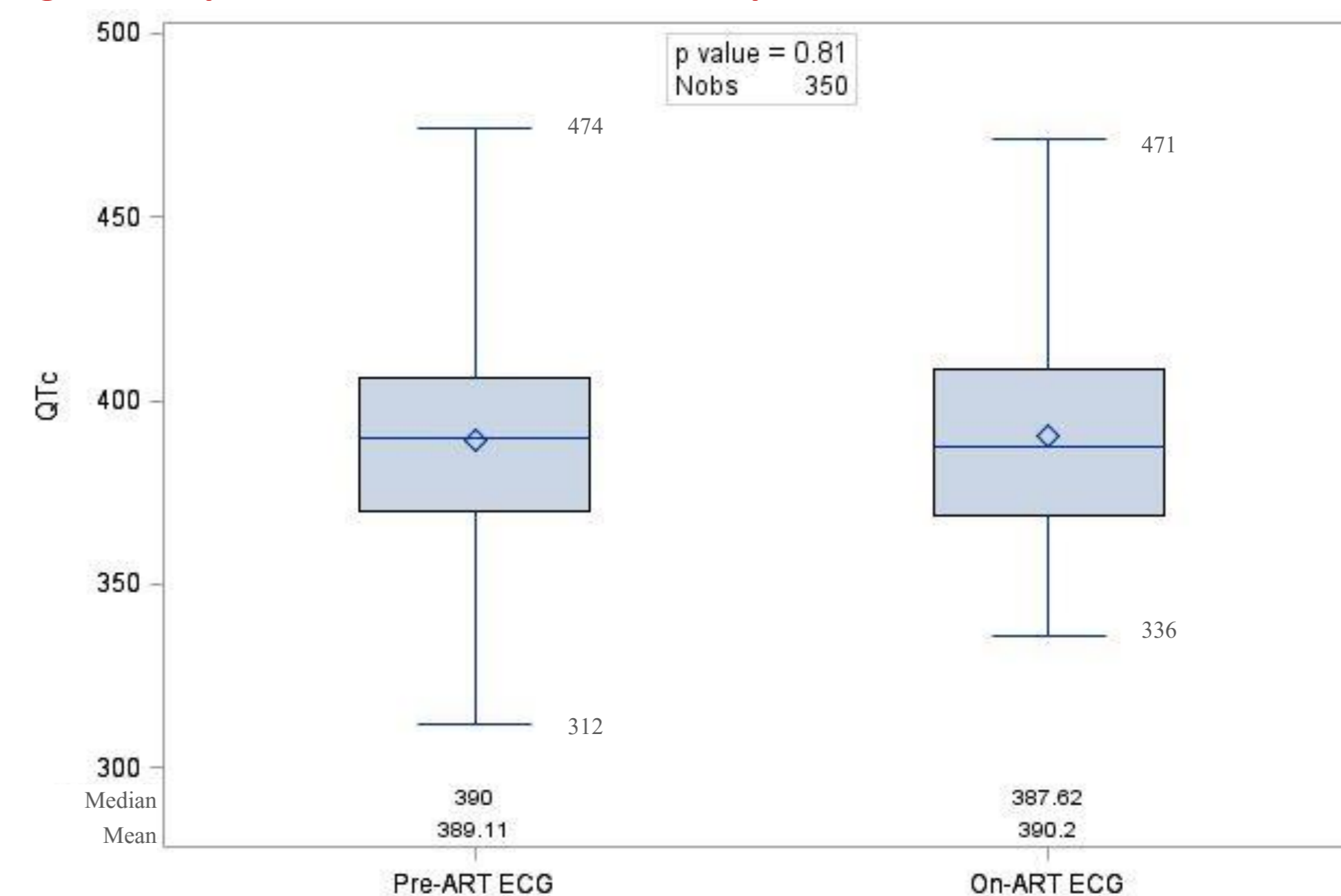


Table 1 - Characteristics of 175 patients with both pre-ART and on-ART ECGs

n (%) or median (IQR)	Pre-ART ECG	On-ART ECG	P value
Age, years	37.2 (30.6;46.9)	41.7 (33.8;50.8)	<0.0001
Body Mass Index, kg/m <sup>2</sup>	23.2 (20.9;26.7)	24.0 (21.6;28.4)	<0.0001
HIV infection			
Duration of HIV infection, months	1.2 (0.5;4.6)	42.0 (24.6;69.5)	<0.0001
CD4+ cell count, cells/mm <sup>3</sup>	432 (280;619)	669 (513;873)	<0.0001
HIV RNA, log <sub>10</sub> copies/ml	4.6 (4.1;5.1)	0 (0;1.3)	<0.0001
Antiretroviral therapies			
Mono and dual therapies	-	15 (8.6)	
2 NRTIs + INSTI	-	57 (32.6)	
2 NRTIs + bPI	-	40 (22.9)	
2 NRTIs + NNRTI	-	61 (34.9)	
2 NRTIs + bPI or NNRTI	-	2 (1.1)	
Comorbidities			
Smoker	77 (46)	67 (41)	0.07
Alcohol use >20 g/day	81 (48)	48 (29)	0.001
Drug use	17 (18)	22 (14)	<0.0001
QT-related medications*	9 (5)	21 (13)	0.014
HBV or HCV coinfection	14 (8)	15 (9)	0.99
MDRD creatinine clearance, ml/min	101 (90;113)	83 (76;97)	<0.0001

\* Antihistaminics, selective serotonin reuptake inhibitors (SSRIs), macrolides and quinolones.

Fig. 2 - Boxplots of QTc interval between pre-ART and on-ART ECGs



A prolonged QTc interval was identified in 6/255 (2,3%) ECGs of ART-naïve patients (4/6 patients had an on-ART ECG) Table X. A prolonged QTc interval was identified in 4/175 (2,3%) ECGs of patients under ART Table XX.

Table 2 - Characteristics of the 6 patients with prolonged QTc interval on "pre-ART ECG"

Sex	Age (yrs)	Pre-ART ECG			Context	On-ART ECG			ΔQTc (ms)		
		CD4 count (/mm <sup>3</sup> )	HIV VL (log <sub>10</sub> /ml)	QTc (ms)		Delay between 2 ECGs (months)	Duration under ART (months)	CD4 count (/mm <sup>3</sup> )		HIV VL (log <sub>10</sub> /ml)	QTc (ms)
M	49	22	5.0	474	ER (inferior) Fever, PCP	26	7.1	209	<1.4	449	-25
F	29	53	5.1	462	Flat T waves	N/A	N/A	N/A	N/A	N/A	N/A
M	63	48	5.8	452		61	29.0	298	<1.4	382	-70
M	69	280	5.6	449	High BP	31	31.1	455	<1.4	419	-30
M	32	370	5.6	446	Flat T waves	N/A	N/A	N/A	N/A	N/A	N/A
M	36	39	5.3	443	Smoker-cannabis	15	9.2	1032	<1,4	394	-49

Table 3 - Characteristics of the 4 patients with prolonged QTc interval on "on-ART ECG"

Sex	Age (yrs)	Pre-ART ECG			Delay between 2 ECGs (months)	On-ART ECG			ART	QTc (ms)	ΔQTc (ms)
		CD4 count (/mm <sup>3</sup> )	HIV VL (log c/ml)	QTc (ms)		CD4 count (/mm <sup>3</sup> )	HIV VL (log c/ml)	Duration under ART (months)			
F	31	105	5.5	434	45.9	842	2.7	45.4	TDF/FTC/DRV/r	465	+31
F	48	364	5.0	458	18.5	515	3.5	17.2	ABC/3TC-DTG	471	+13
M	51	22	5	474	26.4	209	0	24.7	TDF/FTC/EFV	441	-33
M	31	577	4.2	373	17.9	554	1.3	16.3	ABC/3TC-DTG	455	+82

Table 4 - Factors associated with QTc duration pre-ART and on-ART

Average QTc difference from reference level*	Pre-ART ECG (n=255)				On-ART ECG (n=175)			
	Univariate*	p	Multivariable*	p	Univariate*	p	Multivariable*	p
Sex (female vs male)	9.66 (2.27;17.06)	0.01	12.09 (4.77;19.42)	0.001	16 (6.8;25.2)	0.0007	12.82 (4.5;21.1)	0.003
Age, years	0.48 (0.18;-0.78)	0.002	0.57 (0.27;0.87)	0.0002	0.11 (-0.25;0.46)	0.56		
Body Mass Index, kg/m <sup>2</sup>	0.35 (-0.40;1.09)	0.36			0.82 (0.05;1.59)	0.04		
C CDC status	12.78 (3.19;22.37)	0.01			8.5 (-2.8;19.8)	0.14		
HIV transmission							0.01	
Heterosexual	10.4 (3.6;17.2)	0.003			12.0 (4.0;20.1)	0.0036		
MSM	Ref.				Ref.			
Other	16.9 (4.0;29.8)	0.01			5.3 (-12.7;23.4)	0.56		
CD4+ cell count, cells/mm <sup>3</sup>	-0.01 (-0.02;0.00)	0.14			-0.001 (-0.02;0.01)	0.86		
Drug use	9.03 (-4.15;22.22)	0.18			-3.38 (-15.4;8.7)	0.58		
Creatinine, μmol/l	-0.30 (-0.53;-0.06)	0.01			-0.29 (-0.55;-0.04)	0.02		
GGT, UI/l	0.04 (-0.01;0.09)	0.09			0.03 (-0.095;0.16)	0.61		
Albumin, g/l	-0.74 (-1.66;0.17)	0.11			-2.19 (-4.5;0.12)	0.06		
QTc before ART, ms					0.46 (0.32;0.60)	<0.0001	0.44 (0.30;0.57)	<0.0001

\* Variables included in the analysis : ethnic origin, duration of HIV infection, viral load, sub-type, smoker, alcohol use, hepatitis coinfection, MDRD creatinine clearance, LDL cholesterol, duration of ART, protease inhibitor.

Table 5 - Pre-ART and on-ART ECG comparison (n=175)

n(%) or median (IQR)	Pre-ART ECG	On-ART ECG	P value
Early repolarization	50 (28.6)	26 (14.9)	<0.0001
Notch	7 (14)	5 (22)	0.45
Flat/decreasing ST segment	32 (64)	2 (9)	0.0005
Heart rate, bpm	74 (63;84)	68 (62;79)	0.008
PR space, ms	159 (143;173)	162 (148;176)	0.02
QRS complex, ms	77 (65.5;87.5)	75 (64.5;86)	0.16
QT interval, ms	353 (333;374)	360 (341;380)	0.002
QTc interval, ms	390 (370;406)	388 (369;408)	0.81
Prolonged QTc interval*	4 (2.3)	4 (2.3)	

\* >440 ms for men and >460 ms for women.

## Discussion / Conclusion

- Prevalence of QTc prolongation was low (2,3 %) both in ART-naïve and on-ART individuals.
- Neither excess risk of prolongation of the QTc interval in the ART-naïve population nor prolongation of QTc interval after onset of ART were observed.
- In multivariable analysis, the only variable associated to QTc interval for both pre- and on-ART ECGs was female gender. Neither comorbidities nor current ART exposure, including protease inhibitors, showed statistical association to QTc interval.
- A careful methodology is needed to evaluate QTc interval in order to discard potential measurement biases, as the method of QT interval measurement remains a major issue. The strenght of our study is the manual measurement of the QT interval with the Bazett's formula. The limitations are the lack of electronic levels and potential under-reporting of co-medications with known effects on the cQT interval. ECGs were not systematically performed at time of time at the ARV Cmax that could have pinpointed a transient QTc prolongation.
- A high prevalence of Early Repolarization was unexpectedly found in HIV-infected patients, prior to ART initiation, with a decrease of the ER prevalence under ART.
- We also found a decrease of heart rate after ART initiation that may be related to the effect of HIV on the autonomous nervous system or to patient anxiety that is likely to be greater close after HIV diagnosis.