From naive to highly treated subjects. Efficacy of cART

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Title: **Lower response to antiretroviral therapy (ART) and persistently poor survival for AIDS presentation in people seen for care in Italy from 2009 to 2018**

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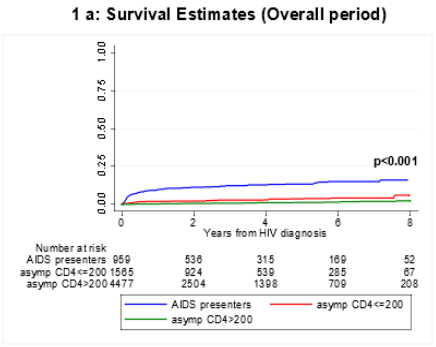
Abstract body
Background: Despite the universal access to care, advanced HIV presentation (HIV diagnosis in patients [pts] with CD4<200 cell/mL or with an AIDS-defining event), is still an issue. The aim of this study was to evaluate characteristics of ART regimens, treatment outcomes and survival probability in advanced HIV presenters compared to the rest of ART-naive pts in a large Italian cohort.
Material and Methods: All consecutive ART-naive HIV+ pts, enrolled in Icona Foundation Study Cohort from January 2009 to December 2018, with HIV diagnosis within 3 months from enrolment, were included and divided into 3 groups: 1) pts with an AIDS diagnosis at or within 3 months from HIV diagnosis (AIDS presenters); 2) asymptomatic pts with CD4 count≤200 cell/mL at the enrolment (asympt CD4≤200); 3) asymptomatic pts with CD4 count>200 cell/mL at the enrolment (asympt CD4>200). Characteristics of ART regimens started were compared in the three groups by non-parametric tests. Probability of virological failure (VF) (2 consecutive HIV-RNA >200 cp/ml after 6 months of ART), treatment discontinuation (TD) for toxicity of any drug, as well as of survival, was estimated by Kaplan Meier curves in both the overall period and separately, analyzing two consecutive time periods (2009-2013; 2014-2018). Independent risks for the same outcomes were identified by fitting a Cox regression model.
Results: Overall, 7,001 pts were included: 959 AIDS presenters, 1,565 asympt CD4≤200 and 4,477 asympt CD4>200. ART was started in 6,440 (92%) pts of whom 95%, 97%, 90% in group 1, 2 and 3, respectively. Pts with advanced HIV presentation were more likely to start PI/b and less likely to initiate NNRTI as third drug. On the contrary, INSTI-based regimens were similarly distributed among the groups [Table 1]. By multivariable Cox regression, AIDS presenters were associated with a greater risk of virological failure and of discontinuing ART for toxicity compared to asympt CD4>200 pts [Table 2]. At survival analysis, AIDS presenters showed the lowest probability of overall survival among the three treatment groups [Fig.1a] and 4-year survival estimates for the three groups remained substantially stable over the two different consecutive time periods [Fig.1b, 1c]. After adjusting for the main confounders, both the groups with advanced HIV presentation were associated to a higher risk of death compared to asympt CD4>200. This data was confirmed also restricting the analysis to subgroup of pts starting ART [Table 2].
Conclusions: Among ART-naive individuals, AIDS presenters showed an increased risk of virological

failure and more frequently discontinued ART due to toxicity. Patients presenting with advanced HIV disease, mainly AIDS presenters, remained at consistently higher risk of death, over the last 10 years. Public health strategies for emerging unknown infections and early treatment access are urgent to constrain the persistent mortality gap of this advanced vulnerable population.

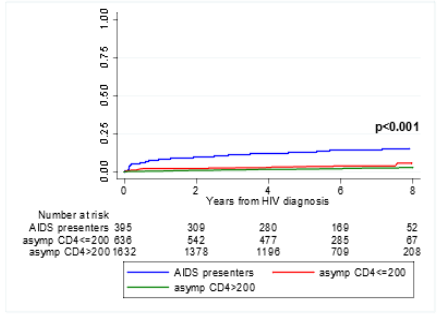
Table 1: Main characteristics of 7,001 HIV-infected naïve patients enrolled, according with grouped definitions at HIV diagnosis (AIDS presenter, asymptomatic with low CD4 count, and asymptomatic with high CD4 count).

	AIDS presenters (959, 13.7%)	asymp CD4<=200 (1,565, 22.3%)	asymp CD4>200 (4,477, 64.0%)	p-value
Female gender, n(%)	246 (25.6%)	335 (21.4%)	778 (17.4%)	**<0.001**
Age, yrs, median (IQR)	44 (36 - 53)	42 (34 - 51)	36 (28 - 45)	**<0.001**
Non-Italian nationality, n (%)	255 (26.6%)	343 (21.9%)	809 (18.1%)	**<0.001**
Days from HIV test to enrolment, median (IQR)	9 (3-20)	12 (4 - 23)	16 (6-35)	**< 0.001**
Mode of HIV transmission				**< 0.001**
MSM	272 (28.4%)	515 (32.9%)	2474 (55.3%)	
heterosexual	532 (55.5%)	808 (51.6%)	1515 (33.8%)	
IDU	45 (4.7%)	83 (5.3%)	186 (4.2%)	
Other/unknown	110 (11.5%)	159 (10.2%)	302 (6.8%)	
HCV coinfection				
positive	46 (4.8%)	93 (5.9%)	220 (4.9%)	**<0.001**
negative	732 (76.3%)	1223 (78.2%)	3717 (83.0%)	
not known	181 (18.9%)	249 (15.9%)	540 (12.1%)	
HBV coinfection				
positive	59 (6.2%)	56 (3.6%)	158 (3.5%)	**<0,001**
negative	729 (76.0%)	1244 (79.5%)	3685 (82.3%)	
not known	171 (17.8%)	265 (16.9%)	634 (14.2%)	
CD4 at enrolment, median (IQR)	42 (19 - 115)	94 (40 - 146)	447 (325 - 610)	**< 0.001**
HIV-RNA, copies/mL				
< 100.000 copies/mL	220 (22.9%)	524 (33.5%)	2972 (66.4%)	**< 0.001**
≥ 100.000 copies/mL	632 (65.9%)	950 (60.7%)	1254 (28.0%)	
Missing	107 (11.2%)	91 (5.8%)	251 (5.6%)	
Number of comorbidities				
0	776 (80.9%)	1329 (84.9%)	4051 (90.5%)	**< 0.001**
1	151 (15.7%)	190 (12.1%)	329 (7.4%)	
2	26 (2.7%)	43 (2.8%)	75 (1.7%)	
≥3	6 (0.6%)	3 (0.2%)	22 (0.5%)	
ART initiation	914 (95.3%)	1513 (96.7%)	4013 (89.6%)	**<0.001**
Days from first HIV test to ART, median (IQR)	20 (12 -36)	23 (13 - 40)	51 (24 -119)	**< 0.001**
ART regimen				
2NRTI+NNRTI	123 (13.5%)	198 (13.1%)	1216 (30.3%)	**< 0.001**
2NRTI+PI/b	393 (43.0%)	653 (43.2%)	991 (24.7%)	
2NRTI+II	329 (36.0%)	548 (36.2%)	1435 (35.8%)	
Other	69 (7.6%)	114 (7.5%)	371 (9.2%)	
Backbone				
Tenofovir-FTC	739 (77.0%)	1245 (79.6%)	3142 (70.2%)	**< 0.001**
ABC+3TC	119 (13.0%)	190 (12.6%)	696 (17.3%)	
AZT+3TC	19 (2.1%)	35 (2.3%)	53 (1.3%)	
other	37 (4.0%)	43 (2.8%)	122 (3.0%)	

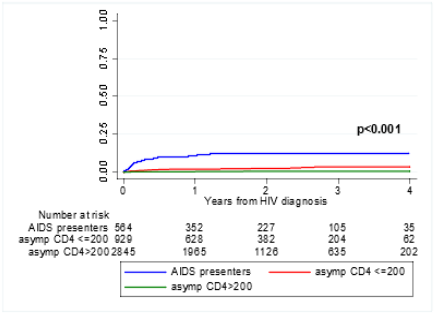
Figure 1: Estimated probabilities of survival in the overall period (a) and in the two consecutive time periods (2009-2013; 2014-2018) (b,c)



Survival Estimates (95% CI)			
	AIDS presenters	Asymp CD4 ≤ 200	Asymp CD4>200
1-year	90.3 % (88.1-92.1)	98.0 % (97.2-98.6)	99.7 % (99.4-99.8)
2-year	88.7 % (86.3-90.6)	97.8 % (96.9-98.5)	99.4 % (99.1-99.6)
4-year	86.6 % (83.8-88.9)	96.4% (94.9-97.4)	98.8 % (98.2-99.1)



Survival Estimates (95% CI)			
	AIDS presenters	Asymp CD4 ≤ 200	Asymp CD4>200
1-year	91.8 % (88.6-94.2)	97.9 % (96.4-98.8)	99.5 % (99.0-99.8)
2-year	90.1 % (86.6-92.7)	97.9 % (96.4-98.8)	99.1 % (98.5-99.5)
4-year	88.0 % (84.2-90.9)	97.1 % (95.4-98.2)	98.4 % (97.6-98.9)



Survival Estimates (95% CI)			
	AIDS presenters	Asymp CD4 ≤ 200	Asymp CD4>200
1-year	89.2 % (86.1-91.6)	98.1 % (96.6-98.9)	99.8 % (99.5-99.9)
2-year	87.8 % (84.4-89.4)	97.7 % (96.3-98.6)	99. 7% (99.2-99.8)
4-year	87.8 % (84.4-89.4)	96.7% (94.7-98.0)	99.7 % (99.2-99.8)

Table 2. Relative hazards of virological failure (VF), discontinuation for toxicity or death from fitting Cox regression models according to ART history.

	aRH* (95% CI) of VF^ (n=5,204)	p	aRH* (95% CI) of TD for toxicity (n=6,440)	p	aRH* (95% CI) of death (n=7,001)	p	aRH* (95% CI) of death# (n=6,440)	p
Asymptomatic with CD4 count >200 cells/mm^3	1.00		1.00		1.00			
Asymptomatic with CD4 count ≤200 cells/mm^3	0.96 (0.66-1.40)	0.821	1.10 (0.93, 1.30)	0.261	3.04 (1.88, 4.91)	**<0.001**	1.91 (1.16-3.14)	**0.011**
AIDS presenters	1.52 (1.03-2.26)	**0.037**	1.39 (1.14, 1.68)	**0.001**	11.79 (7.69, 18.09)	**<0.001**	7.48 (4.78-11.71)	**<0.001**

* Adjusted for: age, gender, mode of HIV transmission, nationality, days between HIV diagnosis and enrolment, days from HIV diagnosis and ART initiation (only in the model restricted to patients who started ART), n. of comorbidities, educational level, CD4 count and VL at baseline, HCV and HBV co-infection, NRTI backbone, third ARV drug class, calendar year of HIV diagnosis.
^ Virological failure (VF) definition: 2 consecutive HIV-RNA >200 copies/mL after 6 months of ART.
# Sensitivity analysis including only patients who started ART