Treatment discontinuation in HIV-1 infected individuals starting their first-line antiretroviral regimen after 2008 in Italy: data from the Icona Foundation Study Cohort

A. Di Biagio[1], A. Cozzi-Lepri[2], R. Prinapori[1], G. Angarano[3], A. Gori[4], T. Quirino[5], A. De Luca[6], A. Costantini[7], C. Mussini[8], G. Rizzardini[9], A. Antinori [10], A. d'Arminio Monforte [11]; on behalf of Icona, Foundation Study

Infectious Diseases Unit, IRCCS AOU S. Martino-IST, Genoa, Italy[1]; ; Department of Infection and Population Health, Division of Population Health, UCL Medical School, Royal Free Campus, London, United Kingdom[2] Department of Biomedical Science and Human Oncology, University of Bari, Bari, Italy [3]; Clinic of Infectious Diseases, AO San Gerardo, Monza, Italy[4]; Infectious Diseases Unit, Busto Arsizio Hospital, Busto Arsizio (VA), Italy [5]; Infectious Diseases Unit, Siena University Hospital, Siena, Italy [6]; Department of Health Sciences, University of Ancona, Ancona, Italy[7]; Infectious Diseases Clinic, Policlinico of Modena, University of Modena, Modena, Italy[8] National Institute for Infectious Diseases IRCCS L. Spallanzani, Rome, Italy[10]; Clinic of Infectious and Tropical Diseases, Department of Health Sciences, S Paolo pital, University of Milan, Milan, Italy [11]

BACKGROUND

Rates and reasons for discontinuation or modifications of the first HAART regimens have been investigated in a number of recent study

Data updated from the Italian Cohort of Antiretroviral-Naive Patients (ICONA) on 2008 highlighted a first cART stopping rate of 36.1%;

Moreover it has been noticed that the incidence of discontinuation because of intolerance/toxicity has declined over time while simplification strategies have become more frequent in recent years

OBJECTIVE

The aim of this study was to analyze predictors associated with treatment interruption (TI) of first-line antiretroviral drugs and their evolution in more recent years, in a population of HIV-infected antiretroviral-naive patients starting their first cART regimen in Italy.

PATIENTS AND METHODS

HIV-1-infected patients from the ICONA Foundation Study who had initiated their first-line HAART regimen after 01/01/2008 were included in this analysis. TI was defined as stop and/or switch of at least one drug contained in the regimen, with the exclusion of simplification of TDF/FTC plus EFV with a STR containing TDF/FTC/EFV. All causes of TI, were evaluated and cumulative risk of stopping was investigated according to age, gender, comorbidity, years since starting cART, CD4 cell count, HIV-RNA, third drug and backbone combined in the regimen.

Statistical analysis

Standard survival analysis was used to estimate the time to TI. Patients' follow-up accrued from the date of starting their first cART-regimen from ART-naïve up to the date of TI or last clinical visit. Kaplan-Meier (KM) curves were drawn using a competing risk approach such as follow-up of patients who discontinued for a reason different from that of interest was truncated at the date of last clinical follow-up (administrative censoring). Overall cumulative risk of stopping was estimated using the KM method and all curves stratified by reason for stopping were plotted on the same graph. Cox regression analysis was used to identify factors associated with the risk of TI.

RESULTS

In this study 1759 patients, who started first antiretroviral regimen and had at least one month of clinical follow-up, were included. Male were 1,363 (77.5%), 419 patients (23.8%) were 18-30 years old, 1,113 (63.3%) were 31-50 years old and 227 (12.9%) were more than 50 old. Over a median follow-up of 12 months, 576 patients stopped their cART with an overall discontinuation risk of 32.7%. Demographic characteristics of population and differences between discontinuation and not discontinuation group are shown in Table 1.

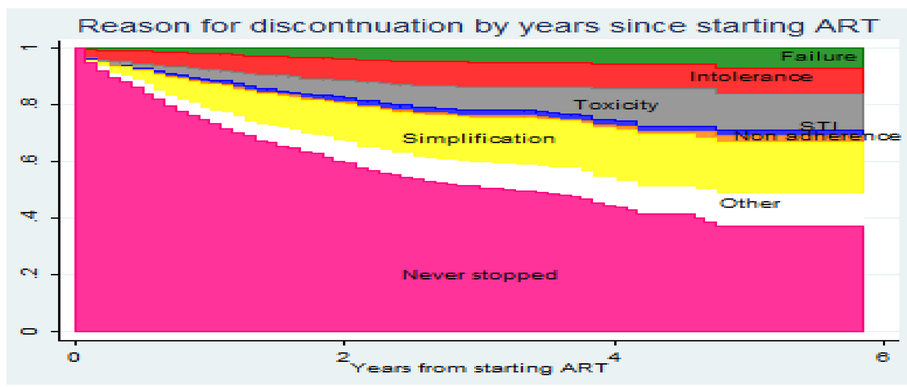
Table 1. Main characteristics

Characteristics	Discontinuation			
	Yes N= 572	No N= 1187	p-value*	Total N= 1759
Gender, n(%)			0.694	
Female	132 (23.1%)	264 (22.2%)		396 (22.5%)
Mode of HIV Transmission, n(%)			0.865	
IDU	53 (9.3%)	106 (8.9%)		159 (9.1%)
Homosexual contacts	251 (44.0%)	501 (42.3%)		752 (42.8%)
Heterosexual contacts	235 (41.1%)	504 (42.5%)		739 (42.0%)
Other/Unknown	32 (5.6%)	74 (6.2%)		106 (6.0%)
Nationality, n(%)			0.145	
Not Italian	102 (17.8%)	254 (21.4%)		356 (20.2%)
AIDS diagnosis, n(%)			0.118	
Yes	45 (7.9%)	70 (5.9%)		115 (6.5%)
HBsAg, n(%)			0.313	
Negative	479 (83.7%)	997 (84.0%)		1476 (83.9%)
Positive	12 (2.1%)	14 (1.2%)		26 (1.5%)
Not tested	81 (14.2%)	176 (14.8%)		257 (14.6%)
Hepatitis co-infection*, n(%)			0.341	
No	395 (69.1%)	857 (72.2%)		1252 (71.2%)
Yes	80 (14.0%)	141 (11.9%)		221 (12.6%)
Not tested	97 (17.0%)	189 (15.9%)		286 (16.3%)
Calendar year of baseline			<.001	
Median (IQR)	2010 (2009, 2011)	2012 (2010, 2013)		2011 (2010, 2012)
Age, years			0.156	
Median (IQR)	39 (32, 47)	38 (32, 46)		38 (32, 46)
CD4 count, cells/mmc			0.112	
Median (IQR)	320 (228, 414)	331 (244, 420)		327 (240, 420)
CD4 count nadir, cells/mmc			0.040	
Median (IQR)	301 (214, 382)	316 (230, 395)		311 (224, 392)
Viral load, log10 copies/mL			0.740	
Median (IQR)	4.37 (3.85, 4.71)	4.35 (3.85, 4.69)		4.35 (3.85, 4.70)
Time from HIV diagnosis to date of starting cART, months			0.144	
Median (IQR)	16 (2, 49)	13 (2, 42)		14 (2, 44)
Antivirals started, n(%)				
Zidovudine	41 (7.2%)	39 (3.3%)		80 (4.5%)
Lamivudine	95 (16.6%)	194 (16.3%)		289 (16.4%)
Abacavir	47 (8.2%)	147 (12.4%)		194 (11.0%)
Tenofovir	477 (83.4%)	969 (81.6%)		1446 (82.2%)
Emtricitabine	470 (82.2%)	963 (81.1%)		1433 (81.5%)
Efavirenz	225 (39.3%)	361 (30.4%)		586 (33.3%)
Nevirapine	15 (2.6%)	36 (3.0%)		51 (2.9%)
Rilpivirine	2 (0.3%)	117 (9.9%)		119 (6.8%)
Liponavir/r	109 (19.1%)	95 (8.0%)		204 (11.6%)
Atazanavir/r	115 (20.1%)	284 (23.9%)		399 (22.7%)
Darunavir/r	77 (13.5%)	238 (20.1%)		315 (17.9%)
Raltegravir	23 (4.0%)	71 (6.0%)		94 (5.3%)
Education, n(%)			0.737	
Primary school	30 (5.2%)	75 (6.3%)		105 (6.0%)
Secondary school	124 (21.7%)	236 (19.9%)		360 (20.5%)
College	164 (28.7%)	352 (29.7%)		516 (29.3%)
University	58 (10.1%)	108 (9.1%)		166 (9.4%)
Other/Unknown	196 (34.3%)	416 (35.0%)		612 (34.8%)
Employment, n(%)			<.001	
Unemployed	62 (10.8%)	155 (13.1%)		217 (12.3%)
Employed	283 (49.5%)	509 (42.9%)		792 (45.0%)
Self-employed	73 (12.8%)	148 (12.5%)		221 (12.6%)
Occasional	12 (2.1%)	50 (4.2%)		62 (3.5%)
Student	20 (3.5%)	42 (3.5%)		62 (3.5%)
Retired	24 (4.2%)	29 (2.4%)		53 (3.0%)
Invalid	4 (0.7%)	4 (0.3%)		8 (0.5%)
Housewife	23 (4.0%)	21 (1.8%)		44 (2.5%)
Other/unknown	71 (12.4%)	229 (19.3%)		300 (17.1%)

*Chi-square or Kruskal-Wallis test as appropriate

The likelihood of discontinuation by KM was 27% by 1 year (95% CI: 25-29) and 41% by 2 years (95% CI: 38-44). Main reason for stopping at least one drug in regimen was simplification (31,8%), followed by intolerance (19,6%), other causes (16,8%), toxicity (16,3%), failure (9,4%), planned interruption (4%) and non adherence (2%). Figure 1

Figure 1



The Kaplan-Meier estimates of drug discontinuation for any reason were in those who initiated ATV/r 28.2%, 26.1% for DRV/r, 53.77% for LPV/r and 31.6% for other third agents (p<0.001) (Figure 2).

Figure 2 KM estimates of discontinuation by PI/r

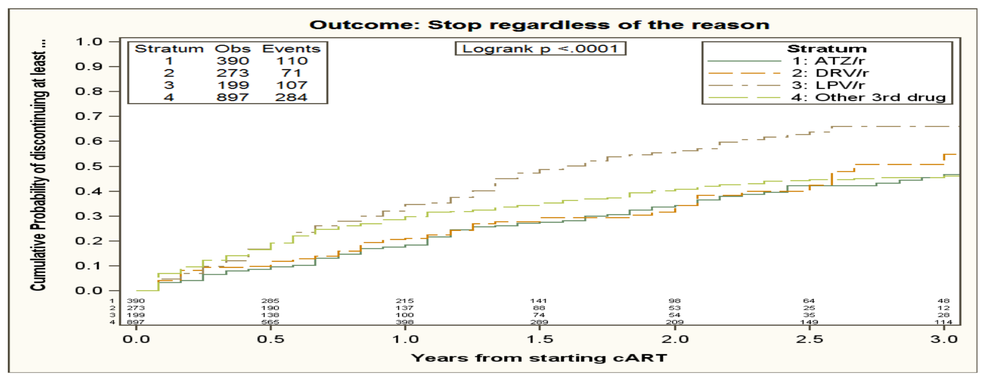


Table 2. Relative hazards from fitting four separate Cox regression models

	Relative hazards of discontinuation regardless of reason			
	Unadjusted RH (95% CI)	p-value	Adjusted RH (95% CI)	p-value
Gender, n(%)				
Female vs. male	1.08 (0.89, 1.31)	0.462	1.20 (0.77, 1.86)	0.431
Mode of HIV Transmission, n(%)				
IDU	1.00		1.00	
Homosexual contacts	1.00 (0.74, 1.35)	0.999	1.17 (0.59, 2.32)	0.651
Heterosexual contacts	0.96 (0.72, 1.30)	0.812	1.21 (0.62, 2.36)	0.569
Other/Unknown	1.16 (0.75, 1.80)	0.509	1.36 (0.55, 3.37)	0.502
Nationality, n(%)				
Not Italian vs. Italian	1.04 (0.84, 1.29)	0.697	1.06 (0.68, 1.64)	0.811
AIDS diagnosis, n(%)				
Yes vs. No	1.06 (0.78, 1.44)	0.711	1.01 (0.54, 1.91)	0.966
Hepatitis co-infection*, n(%)				
No	1.00		1.00	
Yes	1.15 (0.90, 1.46)	0.262	1.35 (0.81, 2.24)	0.250
Not tested	1.37 (1.09, 1.71)	0.006	1.52 (0.99, 2.32)	0.055
Calendar year of baseline				
per more recent year	0.97 (0.91, 1.03)	0.267	0.94 (0.84, 1.06)	0.320
Age				
per 10 years older	1.04 (0.96, 1.12)	0.383	1.11 (0.92, 1.34)	0.293
CD4 count				
per 100 cells/mm3 higher	1.00 (0.95, 1.05)	0.895	1.02 (0.77, 1.35)	0.903
CD4 count nadir				
per 100 cells/mm3 higher	0.99 (0.94, 1.05)	0.714	1.08 (0.80, 1.48)	0.608
Viral load				
per log10 copies/mL higher	0.94 (0.82, 1.08)	0.378	1.23 (0.95, 1.60)	0.119
Time from HIV diagnosis to date of starting cART				
per year longer	0.99 (0.97, 1.01)	0.186	0.96 (0.93, 1.00)	0.039
NRTI started, n(%)				
Tenofovir/Emtricitabine	1.00		1.00	
Zidovudine/lamivudine	2.25 (1.62, 3.14)	<.001	2.86 (1.42, 5.76)	0.003
Abacavir/Lamivudine	0.87 (0.64, 1.18)	0.380	0.83 (0.46, 1.51)	0.545
Other NRTI pair	0.86 (0.44, 1.66)	0.646	0.93 (0.31, 2.78)	0.891
3rd drug started, n(%)				
NNRTI (Yes vs. No)	1.80 (1.03, 3.14)	0.040	2.47 (0.91, 6.72)	0.077
PI or PI/r (Yes vs. No)	1.61 (0.92, 2.79)	0.093	1.86 (0.69, 5.04)	0.223
Other class (Yes vs. No)	0.98 (0.56, 1.70)	0.934	1.02 (0.35, 2.98)	0.975
Education, n(%)				
Primary school	1.00		1.00	
Secondary school	1.22 (0.82, 1.82)	0.331	0.98 (0.51, 1.88)	0.949
College	1.15 (0.78, 1.69)	0.495	0.63 (0.32, 1.24)	0.182
University	1.46 (0.94, 2.26)	0.095	0.66 (0.30, 1.46)	0.301
Other/Unknown	1.46 (0.99, 2.15)	0.054	1.25 (0.63, 2.48)	0.517
Employment, n(%)				
Unemployed	1.00		1.00	
Employed	1.15 (0.88, 1.52)	0.312	2.19 (1.28, 3.77)	0.004
Self-employed	1.09 (0.78, 1.53)	0.624	1.25 (0.61, 2.60)	0.541
Occasional	0.62 (0.33, 1.15)	0.127	0.53 (0.12, 2.34)	0.400
Student	1.20 (0.73, 1.99)	0.472	2.65 (1.12, 6.27)	0.027
Retired/invalid	1.59 (1.02, 2.48)	0.042	1.16 (0.40, 3.35)	0.779
Housework	1.74 (1.08, 2.81)	0.023	2.91 (1.36, 6.21)	0.006
Other/unknown	1.04 (0.74, 1.46)	0.827	1.82 (0.92, 3.61)	0.086

CONCLUSIONS

In a previously reported analysis of the Icona data, the overall risk of discontinuation of first-line HAART was 36% with 21% due to intolerance/toxicity. In this updated analysis, the main reason for stopping is simplification (accounting for 32% of stops), reflecting the recent changes in recommendations aimed to minimize drug toxicity, enhancing adherence and quality of life.

Contact information: Antonio Di Biagio; adibigioa@gmail.com IRCCS AOU San Martino-IST, Genoa, IT