I pazienti naive delle coorti SCOLTA: motivi di interruzione durante il primo anno di trattamento.

Naive patients enrolled in the SCOLTA HIV cohorts: reasons for interruption during the first year of treatment.

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Riassunto

Il progetto SCOLTA (Surveillance Cohort Long-term Toxicity Antiretrovirals) è un sistema di sorveglianza online degli eventi avversi dei farmaci antiretrovirali di recente commercializzazione. È uno studio di farmacovigilanza prospettico, multicentrico, che prevede una coorte di pazienti per ciascun nuovo farmaco. In questa analisi, sono stati inclusi tutti i pazienti naïve che hanno iniziato un trattamento di prima linea con lopinavir (LPV), atazanavir (ATZ), raltegravir (RTG), darunavir (DRV), rilpivirina (RPV), elvitegravir (EVG), e dolutegravir (DTG). Dal 2002, abbiamo incluso 697 pazienti naïve. Le caratteristiche basali dei pazienti erano diverse nelle diverse coorti, in termini sia epidemiologici che di variabili relative all'infezione. Utilizzando DTG come gruppo di riferimento, i pazienti in LPV avevano una probabilità maggiore di interrompere il trattamento durante il primo anno (HR 2.89, 95% CI 1.68-4.98, p=0.0001) e quelli in RPV una probabilità inferiore (HR 0.28, 95% CI 0.10-0.83, p=0.02). In tutte le coorti, i pazienti presentavano meno interruzioni rispetto a LPV, con differenza significativa per DRV, RPV, EVG e DTG. Colesterolo totale e HDL aumentavano in LPV, EVG e DTG, mentre in DRV oltre al colesterolo totale anche i trigliceridi presentavano un aumento significativo. La variazione del peso era positiva in tutte le coorti. I CD4 aumentavano significativamente in tutti i farmaci in studio, ma la soppressione virale a 6 mesi era meno frequente nelle coorti più vecchie. Questa analisi riflette la storia della terapia antiretrovirale di prima linea degli ultimi 20 anni. Nelle nostre coorti, abbiamo osservato che la durability aumenta nel tempo, in concomitanza con l'inizio del trattamento in pazienti con infezione meno avanzata e con la disponibilità di terapie antiretrovirali in combinazione più tollerabili.

Abstract

The SCOLTA project (Surveillance Cohort Long-term Toxicity Antiretrovirals) is a system for online surveying of adverse reactions to recently commercialized antiretroviral drugs. It is a prospective, multicenter, observational pharmacovigilance study involving one cohort of patients for each new drug. In this analysis, all naive patients consecutively starting a first line treatment with lopinavir (LPV), atazanavir (ATZ), raltegravir (RTG), darunavir (DRV), rilpivirine (RPV), elvitegravir (EVG), and dolutegravir (DTG) were included. Since 2002, 697 naïve patients were enrolled.

Baseline characteristics of patients were different across cohorts, in term of epidemiologic and HIV infection features. As regards durability, using DTG as the reference group, during the first year of treatment patients on LPV were more likely to interrupt (HR 2.89, 95% CI 1.68-4.98, p=0.0001) and RPV less likely (HR 0.28, 95% CI 0.10-0.83, p=0.02). As compared to LPV, interruptions were less likely in all cohorts, significantly so in DRV, RPV, EVG and DTG. Both total and HDL-cholesterol increased in LPV, EVG and DTG, total cholesterol and triglycerides in DRV. Weight modification from baseline was positive in all cohorts. CD4 increased significantly on all study drugs, but viral suppression at 6-month visit was achieved less frequently in older cohorts. Our analysis reflects the history of antiretroviral therapy over the last 20 years. In our study cohorts, we observed that durability increased over time, concurrently with starting therapy in patients with less advanced disease, and with availability of more tolerable combination antiretroviral therapy.

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Introduction

Introduction of combination antiretroviral therapy (cART) reduced morbidity and mortality among HIV-infected persons (1). Over time, new drug combinations presented with reduced pill burden and improved toxicity profiles, leading to longer durability.

Among HIV-infected U.S. adults in routine HIV care, durability of first and second cART regimens and the likelihood of prompt virologic suppression increased during 1996–2011, when more tolerable, less complex cART options became available (2). A single-center study of HIV-infected patients initiating cART in 2000–2007 indicated that the median duration of first cART lengthened from about 2.1 years to 2.9 years after the introduction of once-daily, fixed-dose combination regimens in 2004 (3), suggesting improved regimen durability as a result of regimen simplification. A more recent analysis of data from the Multicenter AIDS Cohort Study found that median duration of first cART regimens for antiretroviral-naïve men initiating cART in 2006–2009 was over 3 years, a substantial improvement since earlier years (4). To offer information about Italian situation, we analyzed the characteristics of naïve patients entering the SCOLTA cohort from 2002 to 2018, reasons for interruption during the first year of treatment, and durability by first line cART.

Materials and methods

We analyzed data from SCOLTA (Surveillance Cohort Long-Term Toxicity Antiretrovirals) prospective database. The SCOLTA project is a multicenter observational study started in 2002. We follow prospectively HIV-infected people who start to take new antiretroviral drugs, with the aim of identifying toxicities and adverse events in real life setting (5). Both ART naïve and experienced patients can be included in the SCOLTA cohort, if they are more than 18 years old and agree study entry. Clinical data collected include sex, age, ethnicity, weight, height, and history of previous ART, if any. Laboratory data include HIV-RNA, CD4+T cell count, total cholesterol (TC), HDL cholesterol (HDL), triglycerides (TG), and fasting blood glucose (BG), and are prospectively collected in anonymous form in a central database every six months.

We performed a query to this prospectively collected database, to select all naïve patients included in lopinavir (LPV), atazanavir (ATV), raltegravir (RTG), darunavir (DRV), rilpivirine (RPV), elvitegravir (EVG) and dolutegravir (DTG) cohorts, who had at least 1 follow-up.

The absolute change in variables was defined as the difference between each subsequent measurement and baseline value of the variable. Patients were described using frequency for categorical variables and mean (standard deviation, SD) or median (interquartile range, IQR) for continuous variables. Comparisons of patient demographics and baseline characteristics among different groups was performed using the chi-square test, the analysis of variance and the Mann-Whitney U test respectively.

Change from baseline was described as mean ± standard error (SE) and assessed throughout paired t-test in the univariate analysis at 6 months of follow-up. A general linear model was run to compare change from baseline among groups, including potential confounders (different between treatment groups).

We also analyzed treatment interruptions during the first year of treatment, using the survival analysis (Kaplan Meier curve).

Treatment interruptions were compared among cohorts, using hazard ratios (HR) and 95% confidence interval (95% CI) according to the Cox proportional hazard regression model.

The study protocol of the SCOLTA Group was approved by local ethical committees and conducted in accordance with the ethical principles stated in the Declaration of Helsinki. Written consent was obtained from all participants.

Results

Overall, during the course of the SCOLTA Project, 697 naïve patients started their first line treatment including one of the study drugs.

Naïve subjects represented 21% of patients starting LPV, 5% of those starting ATV, 7% in RTG, 11% in DRV, 27% in RPV, 30% in EVG and 26% in DTG.

Main characteristics of naïve patients at enrolment in one of the SCOLTA cohorts are reported in *Table 1*.

Mean age was not significantly different among groups, but for patients starting RPV, that were significantly younger than LPV and in DTG. Gender varied between 14.3% in DRV and 40.9% in ATV cohort. Over time, patients with history of intravenous drug use were less frequent among naïve subjects, whereas sexual transmission increased.

After 12 months of observation, 80 (11.5%) subjects interrupted the cohort drug, with remarkable difference between cohorts *(Table 2)*.

	LPV N=134		ATV N=22		RTG N=29		DRV N=49		RPV N=136		EVG N=103		DTG N=224		P
N and %															
Sex															
F	32	23.9	9	40.9	4	13.8	7	14.3	34	25.0	15	14.6	39	17.4	
M	102	76.1	13	59.1	25	86.2	42	85.7	102	75.0	88	85.4	185	82.6	0.03
Etnicithy															
Caucasian	124	92.5	20	90.9	27	93.1	45	91.8	125	91.9	87	84.5	196	87.5	
Latin-American	7	5.2	0	0	0	0	1	2.0	3	2.2	4	3.9	13	5.8	
Black	3	2.2	2	9.1	2	6.9	3	6.1	7	5.1	9	8.7	11	4.9	
Other	0	0	0	0	0	0	0	0	1	0.7	3	2.9	4	1.8	0.42
Risk factor for HIV acquisition															
Heterosexual	66	49.3	11	50.0	12	41.4	20	40.8	59	43.4	32	31.1	80	35.7	
MSM	37	27.6	1	4.5	12	41.4	16	32.7	63	46.3	60	58.3	105	46.9	
IDU	20	14.9	9	40.9	2	6.9	2	4.1	8	5.9	1	1.0	15	6.7	
Other/unknown	11	8.2	1	4.5	3	10.3	11	22.4	6	4.4	10	9.7	24	10.7	<0.0001
HCV positive															
N	106	79.1	12	54.5	28	96.6	43	87.8	123	90.4	101	98.1	209	93.3	
Y	28	20.9	10	45.5	1	3.4	6	12.2	13	9.6	2	1.9	15	6.7	<0.0001
CDC stage															
A	45	33.6	9	40.9	19	65.5	15	30.6	105	77.2	65	63.1	129	57.6	
B	34	25.4	7	31.8	3	10.3	12	24.5	25	18.4	22	21.4	51	22.8	
C	55	41.0	6	27.3	7	24.1	22	44.9	6	4.4	16	15.5	44	19.6	<0.0001
Advanced*															
N	83	61.9	18	81.8	23	79.3	29	59.2	134	98.5	91	88.3	186	83.0	
Y	51	38.1	4	18.2	6	20.7	20	40.8	2	1.5	12	11.7	38	17.0	<0.0001
Mean and standard deviation or median and interquartile range															
Age at enrolment	41.4	9.5	41.8	8.3	42.1	12.5	39.9	12.6	38.0	10.3	39.1	11.9	41.4	11.7	0.07
Weight (Kg)	65.6	10.4	69.0	13.3	71.8	13.7	63.7	22.0	69.9	11.5	70.6	11.3	69.6	12.6	0.0002
CD4 (cells/mm3)	74	41-191	253	92-319	385	174-567	135	30-270	381	299-486	371	189-527	326	125-528	<0.0001
HDL cholesterol (mg/dL)	51	30	43	18	36	10	37	17	41	13	41	13	39	13	<0.0001
Total cholesterol (mg/dL)	165	52	186	53	172	45	153	53	165	35	161	35	162	45	0.14
Blood glucose (mg/dL)	91	11	92	10	91	18	87	14	88	22	90	17	87	14	0.47
Triglycerides (mg/dL)	165	117-218	146	94-171	125	90-171	118	91-138	99	68-135	88	69-116	104	78-142	<0.0001

MSM: male having sex with male; IDU: intravenous drug user; HCV: hepatitis C virus; *CDC stage C and CD4 at starting treatment < 200 cells/mL

Table 1. Main characteristics of 697 naïve patients enrolled in the SCOLTA study by cohort (2002-2019).

	LPV N=134		ATV N=22		RTG N=29		DRV N=49		RPV N=136		EVG N=103		DTG N=224		P
N and %															
Interruption															
N	97	72.4	20	90.9	23	79.3	45	91.8	132	97.1	96	93.2	204	91.1	
Y	37	27.6	2	9.1	6	20.7	4	8.2	4	2.9	7	6.8	20	8.9	<0.0001
Adverse event	15		1		0		1		3		4		11		
Failure	2		1		1		0		1		2		0		
Simplification	8		0		4		1		0		0		6		
Death	1		0		0		1		0		0		1		
Patient's preference	6		0		0		0		0		1		0		
Other	5		0		1		1		0		0		2		

Table 2. Reason for interruptions during the first year of treatment by cohort.

Across cohorts, survival curves significantly differed, as shown in *Figure 1* (log-rank test p<0.0001). Using DTG as the reference group, patients on LPV were more likely to interrupt (HR 2.89, 95% CI 1.68-4.98, p=0.0001) and RPV less likely (HR 0.28, 95% CI 0.10-0.83, p=0.02).

As compared to LPV, interruptions were less likely in all cohorts, significantly so in DRV, RPV, EVG and DTG. *Figure 2* shows rates of interruptions (with 95% CI) during the first year of treatment.

Limiting the analysis to patients enrolled before 1 January 2018, that is those potentially treated for at least 2 years, we found that the median duration of first line treatment was 20 months in LPV, 24 in ATV, 16 in RTG, 18 in DRV, 19 in RPV, 28 in EVG and 30 in DTG (p<0.0001).

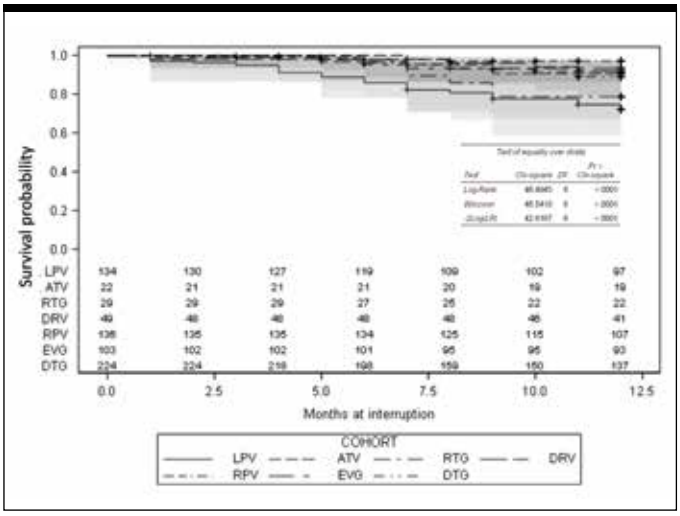

Figure 1. Survival curve over 12-month study period, by cohort.

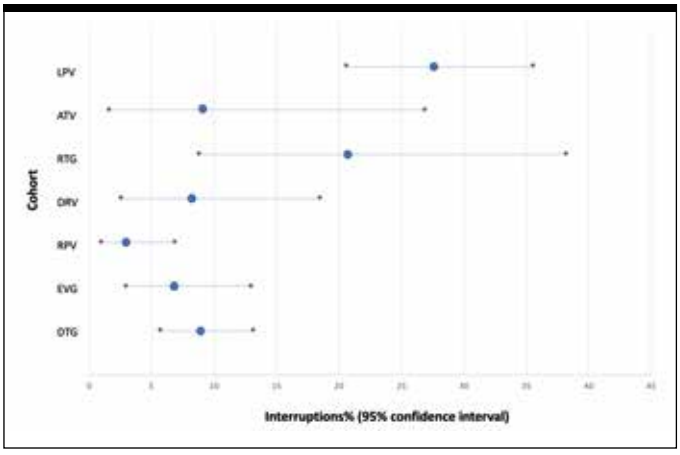

Figure 2. Rate of interruption (%) during the first year of treatment, by cohort.

At 6-month follow-up, blood lipids showed a different trend across cohorts, with significant increase in LPV and INSTI treated patients as regards HDL- and total cholesterol. (*Table 3*)

Median TG were significantly higher than at baseline in patients on DRV and EVG. BG remained stable in all cohorts. As regards weight, it increased in all cohorts, as well as CD4 level. Changes from baseline were significant in all cohorts but ATV and RTG, probably because of the low sample size of these groups. In the multivariate analysis, we found that CDC stage C was significantly associated with higher weight increase (0.7 Kg in stage A, 1.3 Kg in stage B and 3.0 Kg in stage C), with significant difference between A and C (p<0.0001) and B and C (p=0.0004). A strong positive relationship existed between weight gain and percentage CD4 increase (Pearson r=0.25, p<0.0001).

As regards HIV-RNA suppression, undetectable 6-month viral load was significantly different among cohort drugs *(Figure 3)*.

Discussion

Analyzing our cohorts, we observed marked differences in naïve patients entering the study. This was expected, because over time guidelines for starting ART changed and cohort drugs had different indications.

In our cohorts, patients were enrolled when starting treatment with any of the study drugs. Thus, their characteristics were different from naive subjects not undergoing drug treatment, even if they were referring to the centers participating into SCOLTA Project. Furthermore, it must be considered that immediately treating all HIV positive patients is recommended in 2015 Italian Guidelines (6): previously, the choice of starting treatment was affected by CD4 count and diseases progression.

Over the study period, characteristics of newly diagnosed HIV patients changed. Some discrepancies among cohorts are attributable to this variation, mainly due to epidemiology and general conditions of HIV positive subjects. For example, this is the case for risk factors for HIV acquisition, CDC stage and general health status of patients.

We found a different pattern of risk factors for HIV acquisition over the period: proportion of patients with history of intravenous drug use were steadily declining, and this shift was also reflected in a gradual lowering of naïve subjects with HCV coinfection. However, the irregular trend in HCV coinfection was also due to different indications for each drug.

Table 3. Change from baseline to 6-month follow-up for selected variables, by cohort.

	LPV N=134		ATV N=22		RTG N=29		DRV N=49		RPV N=136		EVG N=103		DTG N=224	
	Mean ± standard error													
Weight (Kg)	**3.0 ±**	**0.5**	1.0 ±	0.5	1.4 ±	0.9	**3.2 ±**	**0.9**	**0.7 ±**	**0.3**	**0.5 ±**	**0.2**	**1.2 ±**	**0.3**
CD4 (cells/mm3)	**139 ±**	**14**	**148 ±**	**36**	**152 ±**	**38**	**167 ±**	**18**	**170 ±**	**16**	**152 ±**	**17**	**199 ±**	**13**
CD4 % increase	**380 ±**	**66**	**326 ±**	**226**	**88 ±**	**26**	**296 ±**	**52**	**54 ±**	**5**	**83 ±**	**14**	**136 ±**	**13**
HDL cholesterol (mg/dL)	**17 ±**	**4**	7 ±	4	**6 ±**	**2**	4 ±	3	0 ±	1	**5 ±**	**1**	**5 ±**	**1**
Total cholesterol (mg/dL)	**34 ±**	**11**	-3 ±	10	14 ±	9	**51 ±**	**8**	-5 ±	2	**16 ±**	**3**	**12 ±**	**3**
Blood glucose (mg/dL)	-0 ±	2	-2 ±	4	-0 ±	2	0 ±	2	1 ±	1	2 ±	1	1 ±	1
Triglycerides (mg/dL)	36 ±	28	-74 ±	74	-22 ±	36	**40 ±**	**13**	-4 ±	8	**18 ±**	**5**	2 ±	4

Bold: p<0.05

On the same line of reasoning, as regards gender difference among cohorts, the higher frequency of women on ATV (40.9%) was due to the proven safety of this drug during pregnancy (7,8): thus, it was more frequently prescribed in reproductive age women.

LPV was more frequently interrupted than other drugs. This is due to higher number of adverse events, that have a higher number of simplifications as a further consequence. On the same line, EVG and DTG durability is also subsequent to the low rate of adverse events observed in these drugs. Overall, in our cohorts treatment withdrawals are consistent with safety and tolerability of study drugs.

Apart from this, different indications, patient's epidemiology and immunodeficiency degree may also contribute to the observed different durability. As regards mainly most recent drugs, our results are consistent with those of ICONA Cohort (9,10), where naïve patients are enrolled and followed up through all their antiretroviral treatments since 1997.

With respect to metabolic alterations, difference among drugs are expected. LPV causes triglycerides and total cholesterol increase, as well as HDL decrease, more frequently than other protease inhibitors (PI) (i.e. ATV) or drugs from other classes, such as RPV, RTG and DTG (11,12).

Findings about blood glucose are less consistent. In literature, blood glucose increase was observed, mainly during PI treatment (11-14), we did not observe significant modification of glycaemia during the first year of treatment, in any cohorts.

However, it is noteworthy that a recently emerged issue, that is weight gain, was already present in the SCOLTA LPV cohort.

Back then, the impact of weight gain was negligible as compared to other adverse events occurring during LPV treatment, such as metabolic and gastrointestinal events, frequently leading to treatment interruptions. Moreover, patients with advanced disease were more frequent and weight increase was more likely read as a return to health than as an adverse event.

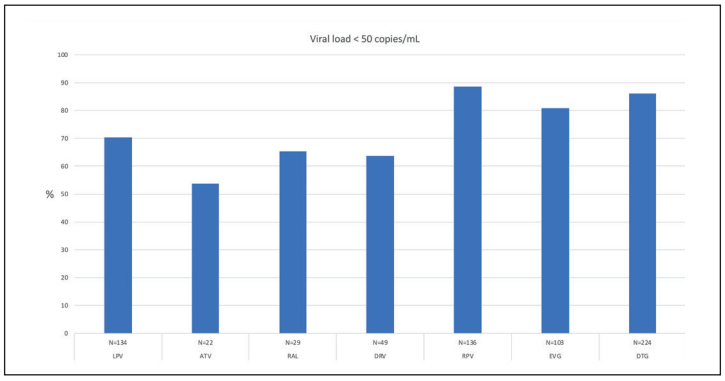

Figure 3. Undetectable viral load at 6-month follow-up, by cohort.

A discussion is currently ongoing about the role of integrase inhibitors in weight gain. Some authors report a significant weight gain in patients starting this class (15,16), although a similar effect could be observed in other classes (17), with differences existing between drugs from the same class.

The effectiveness of cohort drugs in naïve patients, at least during the first year of treatment, was comparable. Only seven failures caused treatment interruption, two in LPV and EVG, and one each in ATV, RTG and RPV. CD4 level increased similarly across cohorts, even if patients had a lower baseline level in some of them (LPV and DRV). Due to this fact, their percentage rise was, on the contrary, higher than in cohort with better absolute increase.

However, viral suppression at 6-month visit was achieved less frequently in older cohorts.

In conclusion, our analysis reflects the history of antiretroviral therapy over the last 20 years. In our study cohorts, we observed that durability increased over time, concurrently with starting therapy in patients with less advanced disease, and with availability of more tolerable cART. Long-term impact of these changes is longer and healthier life expectancy.

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