Discontinuation of Initial Antiretroviral Therapy in Clinical Practice: Moving Toward Individualized Therapy

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Background: Study aim was to estimate the rate and identify predictors of discontinuation of first combination antiretroviral therapy (cART) in recent years.

Methods: Patients who initiated first cART between January 2008 and October 2014 were included. Discontinuation was defined as stop of at least 1 drug of the regimen, regardless of the reason. All causes of discontinuation were evaluated and 3 main endpoints were considered: toxicity, intolerance, and simplification. Predictors of discontinuation were examined separately for all 3 endpoints. Kaplan–Meier analysis was used for the outcome discontinuation of ≥1 drug regardless of the reason. Cox regression analysis was used to identify factors associated with treatment discontinuation because of the 3 reasons considered.

Results: A total of 4052 patients were included. Main reason for stopping at least 1 drug were simplification (29%), intolerance (21%), toxicity (19%), other causes (18%), failure (8%), planned discontinuation (4%), and nonadherence (2%). In a multivariable Cox model, predictors of discontinuation for simplification were heterosexual transmission ($P = 0.007$), being immigrant ($P = 0.017$), higher nadir lymphocyte T CD4$^+$ cell ($P = 0.011$), and higher lymphocyte T CD8$^+$ cell count ($P = 0.025$); for discontinuation due to intolerance: the use of statins ($P = 0.029$), higher blood glucose levels ($P = 0.050$). About toxicity: higher blood glucose levels ($P = 0.010$) and the use of zidovudine/lamivudine as backbone ($P = 0.044$).

Conclusions: In the late cART era, the main reason for stopping the initial regimen is simplification. This scenario reflects the changes in recommendations aimed to enhance adherence and quality of life, and minimize drug toxicity.

Key Words: antiretroviral therapy, HIV-1, discontinuation, resumption treatment, single-tablet regimen, first-line therapy

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INTRODUCTION

The expanded use of combination antiretroviral therapy (cART) since 1996 has resulted in a marked and sustained decrease in AIDS-related morbidity and mortality,[1–3] with a range of benefits to HIV-infected patients, such as increased survival, improved immune status, and decreased of opportunistic infections.[4–6] Current regimen options are more effective, better tolerated, less toxic, than regimens used in the early years of the cART era[7]; therefore, optimization of initial antiretroviral therapy in terms of both virological efficacy and tolerability is essential because long-term toxicity and persistency are fundamental features in the choice of first-line cART. Rates and reasons for discontinuation or modifications of the first-line cART regimens have been investigated in a number of recent studies[8–17] in which it has been underlined how discontinuation of initial therapy has decreased over time, but is still quite high even for the latest drug combinations.[16] Data updated from the Italian Cohort

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R.P. and A.D.B. contributed equally to this study.

The ICONA Foundation Study Group is listed in Appendix 1.

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of Antiretroviral-Naive Patients (ICONA) on 2008 highlighted a 1-year probability of first cART stopping of 36.1%; moreover, it has been noticed that the incidence of discontinuation because of intolerance/toxicity has declined over time, whereas simplification strategies have become more frequent in recent years.[11] The latest advances in refinement of cART strategies, regarding both new drugs and fixed dose formulations, have led to reconsider and change current guidelines for first antiretroviral regimens in naive patients,[18] as has already happened for multiple other drugs in the past years.[19]

Furthermore, evaluations of the prevalence and predictors of initial cART discontinuation have demonstrated that certain patients are more likely to discontinue treatment.[20–22] For this reason, identifying groups at increased risk of cART discontinuation could support clinicians in the choice and optimization of first-line therapy for the individual patient.

The aims of this analysis were (1) to estimate the frequency and causes of discontinuation of treatment regimens initiated in very recent years in HIV-infected patients seen for care in Italy and (2) to evaluate factors associated with treatment discontinuation.

METHODS

Patient Population

ICONA Foundation Study (ICONA) is a multicenter prospective observational study of HIV-1–infected patients, which was set up in 1997. Eligible patients were those starting cART when they were naive to antiretrovirals, regardless of the reason for which they had never been treated and the stage of the disease. All patients signed consent forms to participate to the ICONA, in accordance with the ethical standards of the committee on human experimentation and the Helsinki Declaration (1983 revision). Demographic, clinical and laboratory data, and information on therapy are collected for all participants and recorded online www.icona.org.

Patients who had initiated their initial cART regimen after January 1, 2008 and had at least 1 month of clinical follow-up were included in this analysis; follow-up lasts up to the end of October 2014. Discontinuation of the first regimen was defined as stopping and/or switching of at least 1 drug contained in the regimen; we had ignored all changes in formulations that did not imply a modification in the drug used [eg, changing from tenofovir/emtricitabine (TDF/FTC) plus efavirenz (EFV) to a single-tablet regimen (STR) containing TDF/FTC/EFV]. All causes of discontinuation were coded in the ICONA database, including simplification (defined either as the reduction of drugs included in the regimen or the decrease in daily doses or pills); intolerance defined as patient's related lack of tolerance (eg, unwillingness or refusal to tolerate the prescribed drug in the absence of any clinical and laboratory signs of drug harmfulness); toxicity defined as a stop likely to be caused by adverse effects related to exposure to that drug. This includes drug-related side effects and adverse reactions, defined as the response to a drug, which is noxious and unintended and which occurs at normally used doses; failure (either virological or clinical); nonadherence; planned discontinuation (including structured treatment discontinuation, end of pregnancy, and medical decision); other causes (including patients decision, pregnancy, enrollment, or ending of a clinical trial and drug–drug interaction), as reported by the treating physician. Three main discontinuation endpoints have been considered: (1) because of toxicity, (2) intolerance, and (3) simplification. These have been decided a priori as likely to be the 3 main reasons for stopping drugs in the modern era of cART, as previously shown.[11] Potential predictors of the risk of stopping, which have been examined separately for all 3 endpoints, included: sex, mode of HIV transmission, nationality (an immigrant patient was considered a patient born outside Italy), AIDS diagnosis, cardiovascular disease diagnosis, hepatitis B and C diagnosis, calendar year of baseline, age, lymphocyte T $CD4^+$ and $CD8^+$ cell count, HIV-RNA plasma level, diabetes, total cholesterol, and high-density lipoproteins cholesterol (categorical variable, above and below 40 mg/dL for men and 50 mg/dL for women), use of statins, use of blood pressure lowering drugs, time from HIV diagnosis to date of starting cART, estimated glomerular filtration rate, blood glucose, third drug and backbone combined in the regimen, mental health disorders.

Statistical Analysis

Standard survival analysis was used to estimate the time to treatment discontinuation (endpoints defined as above). Patients' follow-up accrued from the date of starting their first cART regimen from ART-naive up to the date of discontinuation or last clinical visit. Kaplan–Meier (KM) curves were drawn using a marginal model 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 fore stopping were plotted on the same graph. Cox regression analysis was used to identify factors associated with the risk of treatment discontinuation because of the 3 reasons described. We used a cause-specific hazard approach as our main analysis and the Fine–Gray approach as an alternative analysis with the objective of prediction (see Table S1, S2, S3, Supplemental Digital Content, http://links.lww.com/QAI/A754). All variables considered in the univariable model have been also included in the multivariable model.

RESULTS

We included in the study 4052 patients, satisfying the entry criteria. Men were 3197 (78.9%), mean age was 39 years (range: 32–47 years), 796 patients (19.6%) were 18–30 year old, 2562 (63.2%) were 31–50 years old and 694 (17.1%) were more than 50 old. In Table 1, demographic characteristics of patients included in the study are illustrated. The most frequently prescribed regimens and their prescriptive distribution over time are showed in Table 2. Globally, protease inhibitor (PI)–containing regimens accounted for the

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TABLE 1. ART Discontinuation and Reasons in Late cART Era

	Discontinuation			
Characteristics	**Yes (N = 1389)**	**No (N = 2663)**	***P****	**Total (N = 4052)**
Gender, n (%)			0.043	
Female	318 (22.9)	537 (20.2)		855 (21.1%)
Mode of transmission, n (%)			0.166	
Intravenous drug use	103 (7.4)	229 (8.6)		332 (8.2)
Homosexual contacts	569 (41.1)	1068 (40.3)		1637 (40.6)
Heterosexual contacts	617 (44.4)	1133 (42.5)		1750 (43.2)
Other/unknown	95 (6.9)	222 (8.4)		317 (7.9)
Nationality, n (%)			0.169	
Being immigrant	253 (18.2)	598 (22.5)		851 (21.0)
AIDS diagnosis, n (%)			0.062	
Yes	168 (12.1)	271 (10.2)		439 (10.8)
Calendar year of baseline			<0.001	
Median (IQR)	2011 (2009, 2012)	2012 (2011, 2013)		2012 (2010, 2013)
Age, years			<0.001	
Median (IQR)	40 (33, 48)	39 (32, 47)		39 (32, 47)
CD4 count, cells/mmc			0.007	
Median (IQR)	297 (159, 400)	313 (185, 422)		308 (176, 413)
CD4 count nadir, cells/mmc			0.029	
Median (IQR)	284 (155, 382)	300 (173, 394)		294 (166, 391)
CD8 count, cells/mmc			0.683	
Median (IQR)	655 (473, 820)	660 (474, 832)		659 (473, 826)
Viral load, log10 copies/mL			0.019	
Median (IQR)	4.77 (4.13, 5.27)	4.68 (4.02, 5.21)		4.71 (4.05, 5.23)
Total cholesterol, mg/dL			0.266	
Median (IQR)	160 (136, 184)	161 (137, 187)		161 (136, 186)
HDL cholesterol, mg/dL			0.592	
Median (IQR)	38 (31, 47)	38 (31, 47)		38 (31, 47)
Use of statins, n (%)			0.054	
Yes	26 (1.9)	30 (1.1)		56 (1.4)
Blood glucose, mg/dL			0.838	
Median (IQR)	86 (79, 94)	86 (79, 94)		86 (79, 94)
Antivirals started, n (%)				
Zidovudine	96 (6.9)	52 (2.0)		148 (3.7)
Lamivudine	199 (14.3)	360 (13.5)		559 (13.8)
Abacavir	90 (6.5)	285 (10.7)		375 (9.3)
Tenofovir	1192 (85.8)	2310 (86.7)		3502 (86.4)
Emtricitabine	1181 (85.0)	2295 (86.2)		3476 (85.8)
Efavirenz	503 (36.2)	704 (26.4)		1207 (29.8)
Nevirapine	23 (1.7)	56 (2.1)		79 (1.9)
Rilpivirine	8 (0.6)	304 (11.4)		312 (7.7)
Liponavir/r	279 (20.1)	200 (7.5)		479 (11.8)
Atazanavir/r	308 (22.2)	611 (22.9)		919 (22.7)
Darunavir/r	206 (14.8)	630 (23.7)		836 (20.6)
Raltegravir	48 (3.5)	115 (4.3)		163 (4.0)
Age (yrs), n (%)			0.002	
18–30	246 (17.7)	550 (20.7)		796 (19.6)
31–50	870 (62.6)	1692 (63.5)		2562 (63.2)
50+	273 (19.7)	421 (15.8)		694 (17.1)

*Chi-square or Kruskal–Wallis test as appropriate.
HDL, high-density lipoprotein; IQR, interquartile range; r, ritonavir.

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TABLE 2. Most Frequent Regimens and Their Prescriptive Distribution Over Time

Regimens	Years			
Frequency	2008–2010	2011–2012	2013–2014	Total
Abacavir/lamivudine +atazanavir/ritonavir	23	52	37	112
	0.57	1.28	0.91	2.76
	20.54	46.43	33.04	
	1.95	3.15	3.02	
Abacavir/lamivudine +darunavir/ritonavir	9	52	51	112
	0.22	1.28	1.26	2.76
	8.04	46.43	45.54	
	0.76	3.15	4.17	
Other	172	196	106	474
	4.24	4.84	2.62	11.70
	36.29	41.35	22.36	
	14.61	11.87	8.66	
Tenofovir/emtricitabine +atazanavir/ritonavir	220	385	177	782
	5.43	9.50	4.37	19.30
	28.13	49.23	22.63	
	18.69	23.32	14.46	
Tenofovir/emtricitabine +darunavir/ritonavir	94	341	256	691
	2.32	8.42	6.32	17.05
	13.60	49.35	37.05	
	7.99	20.65	20.92	
Tenofovir/emtricitabine +lopinavir/ritonavir	230	69	44	343
	5.68	1.70	1.09	8.46
	67.06	20.12	12.83	
	19.54	4.18	3.59	
Tenofovir/emtricitabine +raltegravir	27	41	58	126
	0.67	1.01	1.43	3.11
	21.43	32.54	46.03	
	2.29	2.48	4.74	
Tenofovir/emtricitabine/ efavirenz	402	512	203	1117
	9.92	12.64	5.01	27.57
	35.99	45.84	18.17	
	34.15	31.01	16.58	
Ttenofovir/emtricitabine/ rilpivirine	0	3	292	295
	0.00	0.07	7.21	7.28
	0.00	1.02	98.98	
	0.00	0.18	23.86	
Total	1177	1651	1224	4052
	29.05	40.75	30.21	100.00

55.6% of the patients (n = 2252), non-nucleoside reverse transcriptase inhibitors–containing regimens were the first-line choice in 39.5% of the patients (n = 1601); in 199 patients (4.9%), integrase inhibitors and/or CCR5 inhibitors were the third drugs of combinations (raltegravir was used as part of 126 regimens). Looking at the NRTI backbone, in 3472 patients (85.7%), TDF/FTC was used; in 375 (9.2%) and 145 (3.6%), the backbone was represented by abacavir/lamivudine and zidovudine/lamivudine respectively.

Over a median follow-up of 12 months, 1389 patients stopped their cART with an overall discontinuation rate of 34.3%.

The likelihood of discontinuation by KM was 26% by 1 year [95% confidence interval (CI): 23.8 to 28.2], 39.7% by 2 years (95% CI: 37.0 to 42.4), and 48.5% by 3 years (95% CI: 45.4 to 51.6), as showed in Figure 1. Main reason for stopping at least 1 drug in regimen was simplification (29.1%), followed by intolerance (21.1%), toxicity (18.6%), other causes (17.8%), failure (8.2%), planned interruption (3.5%), and poor adherence (1.7%). Reasons for discontinuation by year since starting cART are illustrated in Figure 2. Three hundred seven patients (76%) simplified their regimens to STR as second-line cART [268 patients in TDF/FTC/EFV and 39 patients in TDF/FTC/rilpivirine (RPV)].

In a multivariable Cox model, independent predictors of discontinuation for the main reasons (simplification, intolerance, and toxicity) were analyzed (Table 3). Independent predictors associated with higher likelihood of simplification were heterosexual intercourse as risk factor for HIV transmission [hazard ratio (HR) 5.13; CI: 95% 1.57 to 16.74; $P = 0.007$] and a higher nadir lymphocyte T CD4$^+$ cell (HR 1.72; CI: 95% 1.13 to 2.61; $P = 0.011$), whereas being immigrant (HR 0.39; CI: 95% 0.18 to 0.85; $P = 0.017$), higher pretreatment lymphocyte T CD8$^+$ cell counts (HR 0.89; CI: 95% 0.81 to 0.99; $P = 0.025$) were associated with lower likelihood.

For discontinuation due to intolerance, an association was found using statins (HR 2.99; CI: 95% 1.11 to 7.69; $P = 0.029$) and higher blood glucose levels (HR 2.11 CI: 95% 1.00 to 4.47). Independent predictors of discontinuation due to toxicity were higher blood glucose levels (HR 3.12; CI: 95% 1.31 to 7.41; $P = 0.010$) and the use of zidovudine/lamivudine as backbone (HR 3.72 CI: 95%1.04 to 13.34; $P = 0.044$).

Among available data (n = 3638) about virological status at 2 years after starting cART, 3597 patients (98.9%) achieved viral suppression with HIV-RNA$<$ 50 copies per milliliter (see Figure S1, Supplemental Digital Content, http://links.lww.com/QAI/A754).

DISCUSSION

In this analysis from the ICONA cohort, we offer new data for estimating the proportion of HIV-infected naive patients who discontinue their first-line cART and for identifying characteristics associated with treatment discontinuation in clinical practice. By our data, in the late of antiretroviral therapy era, the main reason for stopping the first-line treatment is simplification. These data suggest that there is an ongoing prescriptive trend, which leads to prioritize the regimen choice by simplifying the cART to enhance patient adherence, improve quality of life, minimize drug-related toxicity, and eventually provide a cost containment, because of an increase in the number of available drugs and regimen combination options and according to the changes in national and international recommendations.[18,23]

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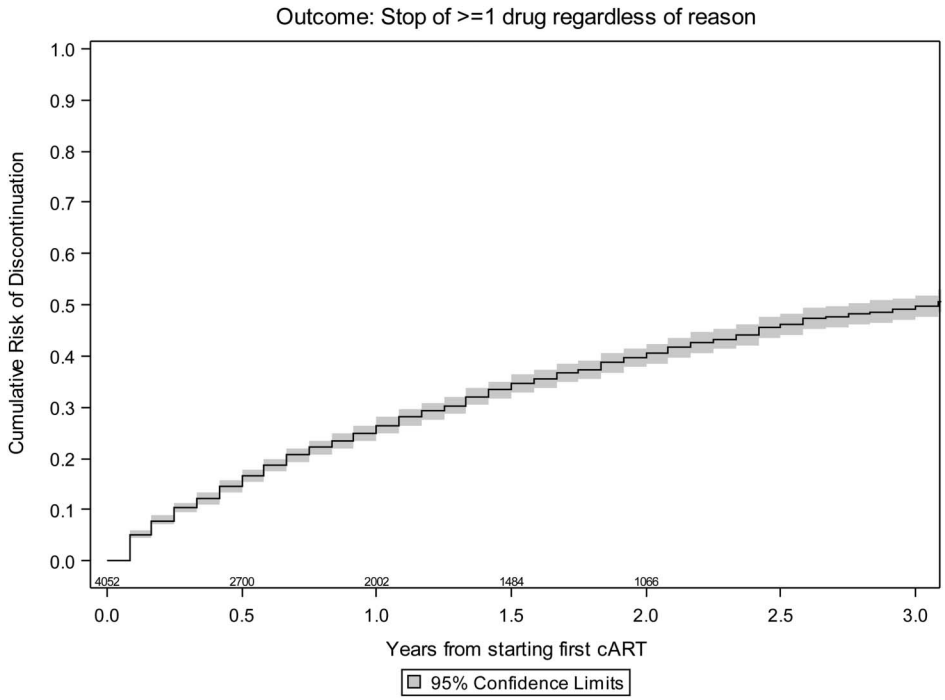

FIGURE 1. Overall Kaplan–Meier estimates of the risk of stopping.

In a previously reported analysis of the ICONA cohort conducted from January 2007 to June 2008[11] in the first year after cART initiation, the overall risk of discontinuation of initial therapy was 36% with 5.2% because of simplification. In this analysis, the simplification reaches 29%: the use of new drug combinations aimed to simplify dosing frequency and reduce pill burden as STR. In this cohort, it has been highlighted a great rate of simplification to STR (76.%). In fact, it has been suggested that the performance of patients who switched to an STR compared to patients remaining on a more complex regimen is better, both in terms of virological response and persistence.[24–26] Furthermore, this high rate of simplifications may also reflect the increase frequency of pro-active switches in virologically suppressed patients finalized to prevent long-term toxicity in a population that is expected to become older and have age-related comorbidities similarly to non-HIV–infected people.[27] Moreover, the Italian economic crisis, with the contraction of the government budget, favors cheaper drugs and/or alternative treatment regimens, might have played a role in influencing the decision of clinicians on behalf of switches strategies.[28] Indeed, in our country, STRs (TDF/FTC/EFV and TDF/FTC/RPV) are cheaper than PI/r-based regimes and TDF/FTC/EVG/cobicistat price is comparable to that of PI/r-based regimens. We were not referring to the comparison of the price of STR with that of its non-STR equivalent.

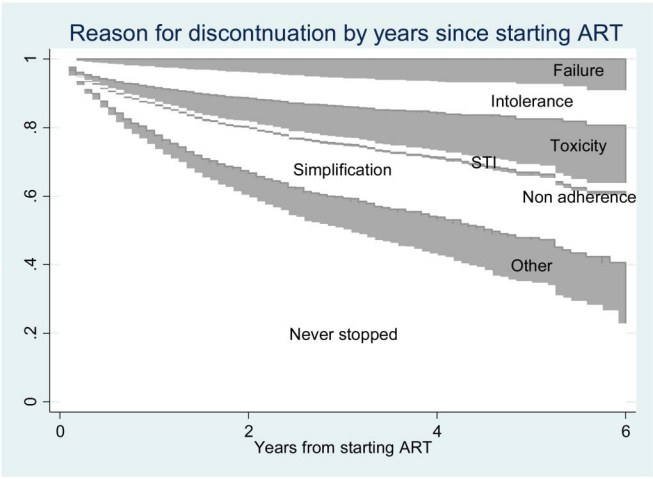

FIGURE 2. Kaplan–Meier estimates according to reason for stopping. STI, structured treatment interruptions.

In our cohort rate of treatment, discontinuation due to poor adherence was only 1.7% versus 24% in the previous ICONA analysis; these data reflect the improvements of drug formulation and regimen convenience, and the trend of clinicians in favor of individualization of cART. Moreover, the recent introduction of the fixed-dose, single-tablet formulation of TDF/FTC/RPV for the treatment of HIV-infected adults with a more favorable tolerability profile than TDF/FTC/EFV have contributed in improving patient adherence.[29–33]

It is important to underline that at the time of this analysis TDF/FTC/elvitegravir/cobicistat and dolutegravir were not available in Italy, whereas the use of TDF/FTC/RPV was not available for the switch on the whole Italian peninsula. These data may support the auspice that in a next future, discontinuation rate due to low adherence and intolerance will decrease over time thanks to the second wave of STR (TDF/FTC/elvitegravir/cobicistat, abacavir/lamivudine/dolutegravir) and the new formulations containing protease inhibitors (darunavir and atazanavir) plus cobicistat. Furthermore, because of evolving guidelines recommendations, more

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TABLE 3. Independent Predictors of Discontinuation Due to Simplification, Intolerance, and Toxicity

	Relative Hazards of Discontinuation Due to Simplification			Relative Hazards of Discontinuation Due to Intolerance			Relative Hazards of Discontinuation Due to Toxicity		
	Adjusted Relative Hazards (95% CI)	*P*	Global *P*	Adjusted Relative Hazards (95% CI)	*P*	Global *P*	Adjusted Relative Hazards (95% CI)	*P*	Global *P*
Gender									
Female versus male	1.15 (0.72 to 1.19)	0.640		1.36 (0.70 to 2.65)	0.366		1.10 (0.49 to 2.51)	0.813	
Mode of HIV transmission									
Injection drug user	1.00		0.009	1.00		0.789	1.00		0.790
Homosexual contacts	3.79 (1.16 to 12.34)	0.027		0.94 (0.30 to 2.89)	0.910		0.60 (0.21 to 1.75)	0.352	
Heterosexual contacts	5.13 (1.57 to 16.74)	0.007		1.14 (0.39 to 3.32)	0.809		0.37 (0.14 to 1.01)	0.053	
Other/unknown	5.94 (1.47 to 24.08)	0.013		1.39 (0.35 to 5.46)	0.637		0.42 (0.13 to 3.10)	0.247	
Nationality									
Being immigrant versus Italian	0.39 (0.18 to 0.85)	0.017		1.05 (0.51 to 2.16)	0.897		0.98 (0.40 to 2.38)	0.958	
AIDS diagnosis									
Yes versus no	1.76 (0.80 to 3.84)	0.159		0.27 (0.06 to 1.26)	0.097		1.37 (0.51 to 3.63)	0.531	
Cardiovascular disease									
Yes versus no	5.81 (0.67 to 50.76)	0.112					1.83 (0.19 to 18.02)	0.604	
Hepatitis coinfection,* n (%)									
No	1.00		0.962	1.00		0.470	1.00		
Yes	1.57 (0.74 to 3.35)	0.244		1.00 (0.37 to 2.66)	0.997		1.14 (0.43 to 3.02)	0.787	
Not tested	0.78 (0.39 to 1.58)	0.490		1.68 (0.85 to 3.33)	0.134		1.21 (0.53 to 2.75)	0.655	
Calendar year of baseline									
Per more recent year	0.90 (0.77 to 1.05)	0.186		0.98 (0.81 to 1.19)	0.856		1.27 (1.00 to 1.62)	0.054	
Age									
Per 10 yrs older	0.91 (0.71 to 1.18)	0.498		1.07 (0.80 to 1.43)	0.644		1.02 (0.73 to 1.42)	0.924	
CD4 count									
Per 100 cells/mm3 higher	0.75 (0.51 to 1.09)	0.136		1.00 (0.64 to 1.55)	0.986		0.62 (0.44 to 1.81)	0.751	
CD4 count nadir									
Per 100 cells/mm^3 higher	1.72 (1.13 to 2.61)	0.011		1.16 (0.71 to 1.89)	0.546		0.96 (0.29 to 1.34)	0.259	
CD8 count									
Per 100 cells/mm3 higher	0.89 (0.81 to 0.99)	0.025		1.06 (0.94 to 1.20)	0.339		0.99 (0.86 to 1.13)	0.847	
HIV-RNA viral load									
Per log10 copies/mL higher	0.94 (0.77 to 1.16)	0.587		1.25 (0.96 to 1.63)	0.102		0.82 (0.62 to 1.08)	0.161	
Diabetes, n (%)									
Yes versus no		0.977		0.59 (0.05 to 7.10)	0.674		1.46 (0.21 to 10.45)	0.704	
Total cholesterol									
Per 100 mg/dL higher	1.22 (0.68 to 2.20)	0.504		0.56 (0.28 to 1.14)	0.199		0.99 (0.48 to 2.05)	0.976	
HDL cholesterol									
Altered versus normal	1.08 (0.70 to 1.66)	0.723		1.41 (0.83 to 2.40)	0.029		0.52 (0.27 to 1.03)	0.060	
Use of statins									
Yes versus no	1.30 (0.42 to 4.06)	0.651		1.41 (0.83 to 2.40)	0.199		0.94 (0.26 to 3.45)	0.926	
Use of blood pressure lowering drugs (%)									
Yes versus no	0.69 (0.08 to 5.92)	0.731		1.36 (0.25 to 7.39)	0.029		2.12 (0.38 to 11.75)	0.391	

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TABLE 3. (*Continued*) Independent Predictors of Discontinuation Due to Simplification, Intolerance, and Toxicity

	Relative Hazards of Discontinuation Due to Simplification			Relative Hazards of Discontinuation Due to Intolerance			Relative Hazards of Discontinuation Due to Toxicity		
	Adjusted Relative Hazards (95% CI)	*P*	Global *P*	Adjusted Relative Hazards (95% CI)	*P*	Global *P*	Adjusted Relative Hazards (95% CI)	*P*	Global *P*
Time from HIV diagnosis to date of starting cART									
Per year longer	1.02 (0.97 to 1.07)	0.449		0.98 (0.92 to 1.03)	0.421		0.98 (0.93 to 1.04)	0.496	
eGFR (CKD_Epi formula)									
Per 60 mL/min per 1.73 m higher	0.56 (0.12 to 2.62)	0.462		0.82 (0.14 to 4.84)	0.823		0.63 (010 to 4.07)	0.623	
Blood glucose									
Per 100 mg/dL higher	0.66 (0.30 to 1.46)	0.304		2.11 (1.00 to 4.47)	0.050		3.12 (1.31 to 7.41)	0.010	
NRTI started									
Tenofovir/ emtricitabine	1.00		<0.001	1.00		<0.001	1.00		<0.001
Zidovudine/lamivudine	0.62 (0.14 to 2.74)	0.527		2.26 (0.80 to 6.39)	0.125		3.72 (1.04 to 13.34)	0.044	
Abacavir/lamivudine	0.88 (0.41 to 1.87)	0.734		015 (0.02 to 1.09)	0.060		0.55 (0.16 to 1.87)	0.340	
Other NRTI pair	2.05 (0.28 to 15.04)	0.478		3.18 (0.79 to 12.82)	0.104		1.87 (0.11 to 32.21)	0.667	
Third drug started									
NNRTI (yes versus no)	3.14 (0.15 to 65.49)	0.461		5.01 (0.47 to 52.76)	0.180		8.46 (0.51 to 141.8)	0.138	
PI or PI/r (yes versus no)	1.58 (0.08 to 32.02)	0.765		3.12 (0.30 to 32.05)	0.338		14.26 (0.83 to 245.5)	0.067	
Other class (yes versus no)	0.78 (0.05 to 12.02)	0.861		1.42 (0.22 to 9.05)	0.710		1.69 (0.11 to 27.16)	0.710	
Mental health disorders (yes versus no)	0.23 (0.03 to 1.73)	0.154					2.50 (0.65 to 9.54)	0.181	

*HDL level: >40 mg/dL for men and >50 mg/dL for women.
eGFR, estimated glomerular filtration rate; NRTI, nucleoside analog reverse transcriptase inhibitors; NNRTI, non-nucleoside analog reverse transcriptase inhibitors; r, ritonavir.

patients will start their first cART regimen directly with STR or with integrase inhibitor including regimens and it could be foreseen that the rate of switches due to simplification will dramatically decrease.

A reduction of virological failure rate has been observed in our cohort (8.2% versus 10.6% of previous analysis): this could be due to the correct use of genotypic resistance test at baseline in clinical practice and also to more potent, more tolerated regimens.

Looking at simplification issues, in this analysis, we found that being immigrants was correlated with a lower rate of simplification. Notably, immigrant patients represent a more vulnerable population: it has been already demonstrated that immigrants are more likely to have a delayed in access to HIV care and with concurrent advanced AIDS.[34,35] Furthermore in HIV-infected immigrants, the rate of retention to care is lower[36] and the rate of adherence to cART.[37] For these reasons, Italian physicians might have used different patterns of prescription for this population (eg, using regimens with high barrier to resistance) and subsequently immigrants have reduced possibility to discuss treatment simplifications with their treating physician. A predictor of simplification in this cohort was a higher nadir of lymphocyte T $CD4^+$, indicating that antiretroviral simplification is primarily performed in safer conditions. In a study, the median lymphocyte $CD4^+$ at switch to TDF/FTC/RPV was over 500/mmc and risk factors for discontinuations or virological failure were lymphocyte $CD4^+$ cell count below 200/mmc at the time of switch.[38] Another predictor of simplification is heterosexual contact as risk factor for HIV transmission. Similarly to immigrants, heterosexual HIV-infected subjects are more likely to be diagnosed late and present advanced disease,[39] probably because of a lower perception of being at risk of HIV infection that may have led to delayed testing: simplification strategies are justified in this population that starts first-line cART with a more complex regimen because of the wide immunological impairment or owing to opportunistic infections.

Discontinuation due to intolerance is more likely to be in patients with a concomitant use of statins indicating a pre-existing alteration of lipid profile that can lead more frequently to cART switch to improve metabolic profile and reduce cardiovascular risk. The statins are more effective than other classes of lipid-lowering drugs at reducing low-density lipoproteins cholesterol; they reduce the risk of heart disease, stroke, diabetes, and death.[40] When considering treatment

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switches to improve tolerability, it is critical to consider the agent with less impact on lipid profile.

As previously reported,[12,41] individuals starting a zidovudine/lamivudine-based regimens were more likely to modify their treatment because of toxicity compared to those treated with TDF/FTC-based regimens. Switch from zidovudine was associated with significant improvements in hemoglobin level and neutrophil counts parameters.[42] Also, switch from a thymidine analog to TDF leads to significant improvement in limb fat mass, metabolic parameters, and mitochondrial toxicity.[43–46]

The impressive number of patients (99%) who achieve HIV-RNA below <50 copies per milliliter gives the magnitude of the success of cART in the ICONA cohort and in Italian population. In fact, despite the discontinuation of the first-line cART, almost all patients resume therapy and are able to obtain a virological success.

Some limitations should be recognized when interpreting the results of our study: the heterogeneity of the collection of the data on the single reason for discontinuation in cases of concomitant reasons (although this bias has been partially corrected by close central monitoring of all data), the potential poor ascertainment of mental health disorders that might have introduced bias because of residual confounding, the low number of events of interest. Another limitation is that patients' mental health disorders and depression are recorded in the ICONA database although likely to be underestimated, and for this reason, they are not included in the analysis of predictors of discontinuation. However, the strength of this study is the large sample size and the ability to represent the prescription trend including very recent years of enrollment.

In conclusion, the choice of different initial antiretroviral regimens in ICONA confirmed that there are differences in prescription practices in different Italian sites, whereas in second-line regimen simplification to STR appeared the preferred choice. As observed in clinical studies, virological success, measured with HIV-RNA below 50 copies per milliliter, is well defined also in practice. A clear trend toward tailored cART was highlighted. Further research evaluating the impact of the introduction in clinical practice of integrase inhibitors is needed.

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