Discontinuation of initial antiretroviral therapy in clinical practice: moving towards individualized therapy.

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AUTHOR CONTRIBUTION

AD, RP, ACL, ADM conceived of and designed the study; ACL performed statistical analyses. All author contributed to the interpretation of the data. AD and RP drafted the manuscript. All authors reviewed the manuscript critically for important intellectual content and approved final version.

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PRESENTATION OF PRELIMINARY RESULTS

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RUNNING HEAD: Discontinuation of first-line regimen in the recent antiretroviral era

Abstract

Background

Study aim was to estimate the rate and identify predictors of discontinuation of first antiretroviral treatment (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 one drug of the regimen, regardless of the reason. All causes of discontinuation were evaluated and three main endpoints were considered: toxicity, intolerance and simplification. Predictors of discontinuation were examined separately for all three endpoints. Kaplan Meier (KM) 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 due to the three reasons considered.

Results

A total of 4052 patients were included. Main reason for stopping at least one drug were simplification (29%), intolerance (21%), toxicity (19%), other causes (18%), failure (8%), planned discontinuation (4%) and non-adherence (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). Looking at 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, quality of life and minimize drug toxicity.

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

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, since long term toxicity and persistency are fundamental features driving 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 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 while 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 naïve 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: (I) 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 (II) to evaluate factors associated with treatment discontinuation.

METHODS

Patient population

ICONA Foundation Study (ICONA) is a multi-center 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 01/01/2008 and had at least one month of clinical follow-up were included in this analysis; follow-up lasts up to the end of October2014. Discontinuation of the first regimen was defined as stopping and/or switching of at least one drug contained in the regimen, we had ignored all changes in formulations that did not imply a modification in the drugs used [e.g. changing from tenofovir/emtricitabine (TDF/FTC) plus efavirenz (EFV) to a single tablet regimen (STR) containing tenofovir/emtricitabine/efavirenz (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 (e.g. unwillingness or refusal to tolerate the prescribed drug in 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); non-adherence; planned discontinuation (including structured treatment discontinuation, end of pregnancy and medical decision); other causes (including patients decision, pregnancy, enrolment or ending of a clinical trial and drug-drug interaction), as reported by the treating physician. Three main discontinuation endpoints have been considered: i) due to toxicity, ii) due to intolerance and iii) due to simplification. These have been decided a priori as likely to be the three 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 three endpoints, included: gender, mode of HIV transmission, nationality (an immigrant patient was considered a patient that was born outside of 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 (HDL) cholesterol (categorical variable, above and below 40 mg/dl for males and 50 mg/dl for females), use of statins, use of blood pressure lowering drugs, time from HIV diagnosis to date of starting cART, estimated glomerular filtration rate (eGFR), blood glucose, third drug and backbone combined in the regimen, mental health disorder.

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 for stopping were plotted on the same graph. Cox regression analysis was used to identify factors associated with the risk of treatment discontinuation due to the three reasons described. We used a cause-specific hazard approach as our main analysis and the Fine-Gray's approach as an alternative analysis with the objective of prediction (Supplementary data). All variabile considered in the univariable model have been also included in the multivariable model.

RESULTS

We included in the study 4,052 patients, satisfying the entry criteria. Males were 3,197 (78.9%), mean age was 39 years (range 32-47 years), 796 patients (19.6%) were 18-30 years old, 2,562 (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 overtime are showed in Table 2. Globally, protease inhibitor (PI)- containing regimens accounted for the 55.6% of the patients (n=2,252), non-nucleoside reverse transcriptase inhibitors (NNRTI)-containing regimens were the first line choice in 39.5% of the patients (n= 1,601); 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 3,472 patients (85.7%) TDF/FTC was used; in 375 (9.2%) and 145 (3.6%) the backbone was represented by abacavir/lamivudine (ABC/3TC) and zidovudine/lamivudine (AZT/3TC) respectively.

Over a median follow-up of 12 months 1,389 patients stopped their cART with an overall discontinuation rate of 34.3%.

The likelihood of discontinuation by KM was 26% by 1 year (95% CI: 23.8-28.2), 39.7 % by 2 years (95% CI: 37.0-42.4) and 48.5% by 3 years (95% CI: 45.4-51.6), as showed in Figure 1. Main reason for stopping at least one 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 non adherence (1.7%). Reasons for discontinuation by year since starting cART are illustrated in Figure 2. Three hundred and seven patients (76%) simplified their regimens to STR as second line cART (268 patients in TDF/FTC/EFV and 39 patients in TDF/FTC/rilpilvirine (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 (HR 5.13; CI 95% 1.57, 16.74; p=0.007) and a higher nadir lymphocyte T CD4+ cell (HR 1.72; CI 95% 1.13, 2.61; p=0.011), while being immigrant (HR 0.39; CI 95% 0.18, 0.85; p=0.017), higher pre-treatment lymphocyte T CD8+ cell count (HR 0.89; CI 95% 0.81, 0.99; p=0.025) were associated with lower likelihood.

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

Among available data (n=3,638) about virological status at two years after starting cART 3,597 patients (98.9%) achieved viral suppression with HIV-RNA<50 copies/ml (Figure 3).

DISCUSSION

In this analysis from the ICONA cohort we offer new data for estimating the proportion of HIV-infected naïve patients who discontinue their first-line cART and for identifying characteristics associated with treatment discontinuation in clinical practice. 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 in order to enhance patient adherence, improve quality of life, minimize drug related toxicity and eventually provide a cost containment, thanks to an increase in the number of available drugs and regimen combination options and according to the changes in national and international recommendations (18, 23).

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% due to 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 demonstrated 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 getting older and suffering of age-related co-morbidities 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 regimen, might have played a role in influencing the decision of clinicians on behalf of switches strategies (28). In fact in our country single tablet regimens (TDF/FTC/EFV and TDF/FTC/RPV) are cheaper than PI/r-based regimes and TDF/FTC/EVG/cobi 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.

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 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 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 tenofovir/emtricitabine/elvitegravir/cobicistat and dolutegravir were not available in Italy, while 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 (tenofovir/emtricitabine/elvitegravir/cobicistat, abacavir/lamivudine/dolutegravir) and the new formulations containing protease inhibitors (darunavir and atazanavir) plus cobicistat. Further, due to evolving guidelines recommendations, more 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 persistent reduction of virological failure rate has been observed in our cohort (8.2 % vs 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, immigrants patients represent a more vulnerable population: it has been already demonstrated that immigrants are more likely to delay in access to HIV care and with concurrent advanced AIDS (34) because of language, socio cultural and educational barriers with limited knowledge of HIV infection and its prevention that determine delayed testing and diagnosis (35). Furthermore in HIV-infected immigrants the rate of retention to care is lower (36) as well as the rate of adherence to cART (37). For these reasons Italian physician might have used different patterns of prescription for this population (e.g. 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 recent study the median lymphocyte CD4+ at switch to TDF/FTC/RPV were over 500/mmc and probabilities of discontinuations or virological failure were lymphocyte CD4+ cell count below 200/mmc at time of the 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 late diagnosed and present advanced disease (39), probably due to 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 due to 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 in order 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 (LDL) cholesterol, they reduce the risk of heart disease, stroke, diabetes and death (40). When considering treatment switches to improve tolerability, it is critical to consider the agent with less impact on lipid profile.

As previously reported (12,41) the individuals starting a zidovudine/lamivudine-based regimens were more likely to modify their treatment due to toxicity compared those treated with tenofovir/emtricitabine-based regimens. Switch from zidovudine was associated with significant improvements in hemoglobin level and neutrophil counts parameters (42). Also, switch from a thymidine analogue to tenofovir leads to significant improvement in limb fat mass, metabolic parameters and mithocondrial toxicity (43-46).

The impressive number of patients that achieve HIV-RNA below <50 copies/ml gives the magnitude of the success of cART in the ICONA cohort. 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 (though 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 due to 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. On the other hand, the strength of this study is the large sample size and the ability to represent the prescription trend including very recent years of enrolment.

In conclusion, the choice of different first-line cART regimens in ICONA confirmed that there are differences in prescription practices in different Italian sites, while 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/mL, is well defined also in practice. A clear trend towards tailored cART was highlighted. Further research evaluating the impact of the introduction in clinical practice of integrase inhibitors is needed.

**Appendix

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Table 1 Characteristics of patients according to discontinuation

Table 2 Most frequent regimens and their prescriptive distribution overtime

Figure 1 Overall Kaplan-Meier estimates of the risk of stopping

Figure 2 Kaplan-Meier estimates according to reason for stopping

Abbreviations: STI: Structured Treatment Interruptions; ART: Antiretroviral treatment

Table 3 Indipendent predictors of discontinuation due to simplification, intolerance and toxicity

Legend: NNRTI non nucleoside reverse transcriptase inverse; PI: protease inhibitors; r:ritonavir

Figure 3 Overall Kaplan-Meier estimates of viral suppression