Predictors of first-line antiretroviral therapy discontinuation due to drug-related adverse events in HIV-infected patients: a retrospective cohort study

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Abstract

Background: Drug-related toxicity has been one of the main causes of antiretroviral treatment discontinuation. However, its determinants are not fully understood. Aim of this study was to investigate predictors of first-line antiretroviral therapy discontinuation due to adverse events and their evolution in recent years.

Methods: Patients starting first-line antiretroviral therapy were retrospectively selected. Primary end-point was the time to discontinuation of therapy due to adverse events, estimating incidence, fitting Kaplan-Meier and multivariable Cox regression models upon clinical/demographic/chemical baseline patients’ markers.

Results: 1,096 patients were included: 302 discontinuations for adverse events were observed over 1,861 person years of follow-up between 1988 and 2010, corresponding to an incidence (95% CI) of 0.16 (0.14-0.18). By Kaplan-Meier estimation, the probabilities (95% CI) of being free from an adverse event at 90 days, 180 days, one year, two years, and five years were 0.88 (0.86-0.90), 0.85 (0.83-0.87), 0.79 (0.76-0.81), 0.70 (0.67-0.74), 0.55 (0.50-0.61), respectively. The most represented adverse events were gastrointestinal symptoms (28.5%), hematological (13.2%) or metabolic (lipid and glucose metabolism, lipodystrophy) (11.3%) toxicities and hypersensitivity reactions (9.3%). Factors associated with an increased hazard of adverse events were: older age, CDC stage C, female gender, homo/bisexual risk group (vs. heterosexual), HBsAg-positivity. Among drugs, zidovudine, stavudine, zalcitabine, didanosine, full-dose ritonavir, indinavir but also efavirenz (actually recommended for first-line regimens) were associated to an increased hazard of toxicity. Moreover, patients infected by HIV genotype F1 showed a trend for a higher risk of adverse events.

Conclusions: After starting antiretroviral therapy, the probability of remaining free from adverse events seems to decrease over time. Among drugs associated with increased toxicity, only one is currently recommended for first-line regimens but with improved drug formulation. Older age, CDC stage, MSM risk factor and gender are also associated with an increased hazard of toxicity and should be considered when designing a first-line regimen.

Keywords: HIV, HAART, Toxicity, Side effects, Therapy-naïve
Background
Combination antiretroviral therapy (cART) has markedly changed the prognosis of HIV-infected patients, reducing AIDS-related morbidity and mortality [1]. Rates of virological failure during first line regimens are decreasing both in clinical trials and in studies performed during routine clinical practice [2,3]. However, drug-related adverse events and toxicities are increasingly recognized [4-7] and represent one of the most common reasons for treatment discontinuation or switch [2,3,8-11]. In recent years, the introduction of newer antiretroviral agents with improved efficacy and tolerability profiles has allowed for a decline of treatment-limiting toxic effects; however, drug-related adverse events still represent an issue of concern.

Treatment-limiting cART toxicity has been associated with several factors such as demographical characteristics, drug-drug interactions, co-morbidities and recently genetic factors [12]. However, determinants of toxicity are not fully understood. In particular, the role of newer and apparently better tolerated antiretroviral drugs needs to be fully investigated. Moreover, the influence of baseline chemistry remains to be elucidated.

The aim of this study is to investigate predictors of first-line antiretroviral therapy discontinuation due to adverse events and their evolution in more recent years, characterized by an increased use of regimens with better tolerability profiles. In particular, the analysis is focused on the evaluation of baseline demographic and clinical characteristics, prescribed drugs and chemical parameters which could represent objective tools to tailor regimens on patients’ characteristics.

Methods
HIV-infected patients followed up at the Infectious Diseases Clinic of the Catholic University of the Sacred Heart (CUSH) in Rome, Italy, starting a first-line anti-HIV antiretroviral therapy, were screened retrospectively via the electronic CUSH data base, which includes data on more than 4,300 HIV-infected patients, with the first available anti-HIV therapy record dated 1988. All patients included in the data base had previously signed an informed consent to be included in observational studies. Access and data analyses of the CUSH data base are regulated by an institutional internal ethics committee and conform to Italian and European privacy legislations. The latest available updated version (up to January 2011) of the CUSH data base was used.

The baseline time was the start date of the anti-HIV antiretroviral therapy. The end-point of interest was the discontinuation date of the first-line anti-HIV antiretroviral therapy. Discontinuation was defined as stopping any antiretroviral drug for at least 2 weeks or switching (changing one or more drugs) to another regimen; the only exception was a substitution of lamivudine with emtricitabine or vice-versa, because it could simply reflect a shift to a fixed dose formulation of tenofovir-emtricitabine, abacavir-lamivudine or zidovudine-lamivudine. An adverse event was marked if the reason of discontinuation or switch (or eventually a concomitant death) was an event corresponding to toxicity or allergy; otherwise data were censored at that time point or at the latest available time point if the patient did not stop that therapy, following a cause-specific approach. All discontinuation causes were ascertained by electronic and clinical reports (see Table 1 for categories besides the adverse event definition). In case of a decease event without a prior therapy discontinuation date, data were censored as well. First-line anti-HIV antiretroviral therapies with a known stop date, but unknown reason of stop or decease, were not included in the study population.

Covariates of interest, contemporary or the closest previous to the baseline date, were: calendar year, patient's gender, age, nationality, risk group, first date of HIV-positive antibody test, CDC stage, viral subtype, anti-HIV antiretroviral therapy, HIV-RNA load, CD4⁺ T cell count, hepatitis C co-infection (HCVAb), hepatitis B co-infection (HBsAg), anti-HCV interferon/ribavirin treatment, anti-Mycobacterium Tuberculosis (TB) therapy, anti-Pneumocystis jirovecii pneumonia (PCP) therapy, other antibiotic treatments, other concomitant (prescription or over-the-counter) drugs exposure, total bilirubin, total cholesterol, hemoglobin, glucose, glutamate pyruvate transaminases (GPT), gamma-glutamyltransferase (gammaGT), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TGL), and glomerular filtration rate (GFR) estimated by modification of diet in renal disease (MDRD) formula. Chemistry parameters were classified as normal, high or low according to established cut-offs [13,14] (see Table 2 for cut-off values). The covariate list was consistent with other European cohort studies [15,16]. Baseline chemistry variables were registered in the database only for patients starting antiretroviral therapy after 1998; when not available, they were encoded as unknown.

The antiretroviral therapy was encoded in different ways: (i) as a combination therapy of 2 nucleoside reverse transcriptase inhibitors (NRTI) + 1 non-nucleoside reverse transcriptase inhibitor (NNRTI), 2 NRTI + 1 protease inhibitor (PI), 2 NRTI + 1 PI boosted with ritonavir (PI/r), and other combinations; (ii) as single compounds, i.e. emtricitabine, lamivudine, abacavir, zidovudine, stavudine, zalcitabine, didanosine, tenofovir, nevirapine, efavirenz, atazanavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir full or boosting dose, and saquinavir; (iii) as a combination therapy of different brand names, including those combinations with a
frequency of at least 10; (iv) as Truvada® + Sustiva®,
Atripla®, Reyataz®, Kaletra®, any other NRTI+PI, any
other NRTI+PI/r, any other NRTI+NNRTI, and other
combinations. Other compounds including enfuvirtide,
maraviroc, raltegravir, darunavir, and etravirine, were not
included due to their low frequency.

Statistical methods included descriptive summaries,
calculation of incidence ratios and confidence intervals,
Kaplan-Meier estimation for the probability of surviving
an adverse event, multivariable proportional-hazard hy-
pothesis testing, and multivariable Cox model fitting in
order to identify factors associated to an increased/
reduced hazard of an adverse event happening. Effect of
covariate interactions and nested model comparison via
ANOVA were also carried out. All statistical analyses
were carried out using R software (www.r-project.org).

Results
The total number of HIV-positive patients recorded in
the CUSH data base (up to January 2011) was 4,388.
Those with at least one anti-HIV therapy registered were
2,455, and 1,218 for which it was the actual first-line.
Of these, 1,096 had a documented reason of discontinuation
or did not stop the therapy and met the inclusion cri-
teria, starting their first-line anti-HIV therapy between
year 1988 and 2010 (median 2003, interquartile range
1998–2006). Of these patients, 317 started the first-line
anti-HIV therapy prior to 1999 (154 before 1997), whilst
779 afterwards (Figure 1). Tables 3 and 2 list patients’
demographic/clinical characteristics and chemical mar-
kers at the baseline date, concomitant to the first-line
anti-HIV therapy start date. Also, Additional file 1 shows
the distribution of patients under different first-line ther-
apy regimens per calendar year, using both encoding (i)
and (iv).

The observed number of therapy discontinuations for
adverse events (toxicity/allergy) was 302, over 1,861 per-
son years of follow up, corresponding to an incidence
(95% confidence intervals, CI) of 0.16 (0.14-0.18) per
person years of follow up (PYFU). Table 1 summarizes
in detail the causes of anti-HIV first-line therapy discon-
 tinuation. The most represented adverse events were
gastrointestinal symptoms (28.5%), hematological (13.2%)
or metabolic (lipid and glucose metabolism, lipodystrophy)
(11.3%) toxicities and hypersensitivity reactions (9.3%). By
a Kaplan-Meier estimation, the probabilities (95% CI) of
being free from an adverse event at 90 days, 180 days,
one year, two years, and five years were 0.88 (0.86-0.90),
0.85 (0.83-0.87), 0.79 (0.76-0.81), 0.70 (0.67-0.74), 0.55
(0.50-0.61), respectively. Figure 2 shows the Kaplan-
Meier curves overall and stratified for gender, risk group,
CDC stage at baseline. The test of proportional-hazard
assumption on the data set with the full set of covariates yielded global p-values of 0.3 and 0.8, using the anti-HIV antiretroviral therapy encoding (ii) and (iv), respectively. The proportional hazard hypothesis could not be rejected as well with the other therapy encodings. This allowed the subsequent fit of a main-effect multivariable Cox regression model.

Table 4 reports the relative hazards of the main-effects Cox models using the two different anti-HIV antiretroviral therapy encoding (ii) and (iv). These encodings were the only ones showing significantly different (defined with a p-value<0.05) hazards among such anti-HIV treatment categories, therefore encodings (i) and (iii) did not reveal differences among treatment strata.

Factors associated with an increased hazard of discontinuation for adverse events were: an older age, a CDC stage C vs. A, female gender, homo/bisexual risk group as compared to the heterosexual category, HBsAg positivity, zidovudine, stavudine, zalcitabine, didanosine, efavirenz, full dose ritonavir, or indinavir intake, any NRTI+PI/r intake (excluding Kaletra® and Reyataz®) compared to Truvada® + Sustiva®. The relative hazard (RH) of Atripla® compared to the Truvada® + Sustiva® category was 0.99, 95% CI 0.12-8.44, p=0.99. By changing the reference categories, we found that any NRTI+PI/r combination (excluding Kaletra® and Reyataz®) showed an increased risk of adverse events as compared to any other NRTI+NNRTI intake (not including Truvada®, Sustiva®, or Atripla®), with a RH of 2.49, 95% CI 1.22-5.06, p=0.012. In addition, any NRTI+PI/r combination vs. Kaletra® and Reyataz® yielded a RH of 3.10, 95% CI 1.57-6.09, p=0.001.

Also, in order to analyze the possible role of the introduction in Italy of tenofovir (November 2002), Truvada® (September 2005), and Atripla® (October 2008), the calendar year was stratified into: 1988–1996, 1997–1998, 1999–2002, 2003–2005, 2006–2008, and 2009–2010. However, this did not lead to any appreciable difference across time periods.

Of note, a trend toward an increased risk of adverse events was observed for HIV genotype F1 (when
Table 3 Characteristics of the study population (n=1,096)

| Factor/strata                                      | n    | %    |
|---------------------------------------------------|------|------|
| Female gender                                     | 372  | 33.9%|
| Non Italian nationality                           | 284  | 25.9%|
| Risk group                                        |      |      |
| Heterosexual                                      | 421  | 38.4%|
| Homo/bisexual                                     | 213  | 19.4%|
| IDU                                               | 199  | 18.2%|
| Other/unknown                                     | 263  | 24.0%|
| CDC stage                                         |      |      |
| A                                                  | 495  | 45.2%|
| B                                                  | 229  | 20.9%|
| C                                                  | 372  | 33.9%|
| HIV subtype                                       |      |      |
| B                                                  | 284  | 25.9%|
| 28_BF                                             | 84   | 7.7% |
| 17_BF                                             | 48   | 4.4% |
| F1                                                | 27   | 2.5% |
| Other                                             | 48   | 4.4% |
| Unknown                                           | 557  | 50.8%|
| First-line anti-HIV therapy (encoding i)          |      |      |
| 2NRTI+1NNRTI                                      | 227  | 20.7%|
| 2NRTI+1PI                                        | 214  | 19.5%|
| 2NRTI+1PI/r                                      | 426  | 38.9%|
| Other combination                                 | 229  | 20.9%|
| First-line anti-HIV therapy (encoding iv)         |      |      |
| Truvada* + Sustiva*                               | 47   | 4.3% |
| Atripla*                                          | 14   | 1.2% |
| Reyataz* + ritonavir + backbone                   | 22   | 2.0% |
| Kaletra* + backbone                               | 389  | 35.5%|
| Any other NRTI+NNRTI                              | 165  | 15.0%|
| Any other NRTI+PI                                 | 221  | 20.2%|
| Any other NRTI+PI/r                               | 18   | 1.6% |
| Other combinations                                | 220  | 20.1%|
| Non-anti-HIV therapies (concomitant)              |      |      |
| anti-TB                                           | 140  | 12.8%|
| anti-PCP                                          | 425  | 38.8%|
| anti-HCV                                          | 14   | 1.3% |
| other antibiotics                                 | 194  | 17.7%|
| other drugs                                       | 238  | 21.7%|
| HBsAg                                             |      |      |
| negative                                          | 978  | 89.2%|
| positive                                          | 56   | 5.1% |
| unknown                                           | 62   | 5.7% |
| HCVAb                                             |      |      |
| negative                                          | 771  | 70.3%|
| positive                                          | 247  | 22.5%|
| unknown                                           | 78   | 7.1% |
| Discontinuation/switch for adverse events         | 302  | 27.5%|
| Discontinuation/switch for other causes           | 618  | 56.4%|
| Non-discontinued first-line anti-HIV therapies    | 176  | 16.1%|
| Years                                             |      |      |
| 1988-1993                                         | 282.06 | 350.26 | 724.36 | 504.58 |
| 1994-1998                                         | 92   | 108  | 85  |
| 1999-2004                                         | 229  | 349  | 430  |
| 2005-2010                                         | 742  | 85  |

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http://www.biomedcentral.com/1471-2334/12/296
compared to genotype B). Moreover, unknown TGL showed a higher RH as compared to the corresponding “normal” (<150 mg/dL) category. We also formally tested for interactions between the calendar year and the efavirenz intake, using an ANOVA comparison on the nested models (i.e. with/without interaction), but the more complex model did not show a higher likelihood (p=0.5); the interaction term was not significant and the significant effect of efavirenz was canceled out.

In order to better assess the role of CD4+ T cell counts, different Cox regression models were fit with either the sole CD4+ or log(CD4+) cell/mm3 count or including the full covariate set with the exception of the CDC stage. Only for the univariable log(CD4+) regression there was a significant (p<0.05) decreased hazard of an adverse event per log(CD4+) higher (RH=0.88, 95% CI 0.79-0.99).

As a sensitivity analysis, we repeated the multivariable Cox regression using the subset of therapies posterior to 1998 (n=779, number of events=193, PYFU=1228.948, incidence of 0.16 with a 95% CI of 0.14-0.18), including only cART regimens (although 12/779, i.e. 1.5%, were not 2NRTI+1NNRTI or 2NRTI+1PI±r regimens). The described relative hazards did not change, and in addition there was a significant reduced hazard of an adverse event for any other/unknown risk group as compared to the heterosexual category (RH=0.62, 95% CI 0.40-0.95, p=0.03), and a trend of increased hazard for nevirapine (RH=4.42, 95% CI 0.92-21.12, p=0.06), fosamprenavir (RH=5.64, 95% CI 0.94-34.01, p=0.06), and nelﬁnavir (RH=4.42, 95% CI 0.97-20.22, p=0.05). Moreover, in this model a significant higher risk of discontinuation for adverse events was demonstrated for HIV genotype F1 (RH 2.63, 95% CI 1.22-5.67, p=0.013 when compared to genotype B), while a trend was observed for genotype C (RH 2.24, 95% CI 0.94-5.33, p=0.067).

**Discussion and conclusion**

Since adverse events are the most frequent reason for first-line antiretroviral therapy discontinuation or switch, investigation of variables associated with their occurrence in a routine clinical practice setting is of increasing interest. Such an understanding is crucial to tailor antiretroviral regimens on patients’ characteristics in order to increase the probability of cART tolerability.

In this study several demographic, clinical, laboratory and cART-related variables were investigated, providing useful information for the management of antiretroviral therapy. The prescribed antiretroviral drugs are main determinants of treatment discontinuation for toxicity. As expected, the use of older drugs such as zidovudine, stavudine, zalcitabine, didanosine and full-dose ritonavir was associated with increased risk of adverse events. However, these drugs are no longer recommended for first-line therapy because of their greater potential for toxicity [17]. When considering individual drugs currently recommended as preferred or alternative options in first-line regimens, an higher probability of treatment discontinuation for adverse events was observed for efavirenz (RH 2.4, 95% CI 1.2-5.1, p=0.02). Despite efavirenz has demonstrated high virologic efficacy, both neuropsychiatric and neurocognitive toxicity associated with this drug are not negligible [5,18]. In a recent study, it was shown that nearly 20% of patients discontinue efavirenz due to central nervous system adverse events [19]. Since similar rates of virological response have been observed for other recommended regimens, this observation should be taken into account at the time of prescription of first-line cART and close clinical monitoring should be warranted in efavirenz-treated patients. However, our analysis includes mainly patients treated with non-co-formulated efavirenz, since the single tablet regimen including efavirenz/tenofovir/emtricitabine is available in Italy from October 2008, and its availability seems to improve treatment convenience and related quality of life [20].

In this study, female patients showed a higher risk of treatment discontinuation for drug-related side effects, in accordance with previous results [3,21]. This might be due to peculiar gender-related pharmacokinetic characteristics which could influence drug exposure [21,22].

An interesting finding is the increased risk of discontinuation for adverse events observed in men who have sex with men. This could be ascribed to a different perception of side effects eventually related to sociocultural barriers, as described among vulnerable populations [23].
Unlike previous studies [2,3], in our population we did not observe a strong relation between discontinuation for toxicity and baseline CD4+ cells count or viral load.

Patients harboring HIV genotype F1 demonstrated an higher risk of treatment discontinuation for adverse events and a trend toward an association was observed for genotype C. F1 subtypes have been mostly detected in Latin America [24], where they were reported to be associated with faster HIV progression [25], and Central Africa [26]. F1-carrying patients in our sample were generally immigrants from poor resources countries often with non-steady residence in Italy. This may explain the higher, though non-significant, frequency of interruptions related to F1 subtypes (vs. B).

In agreement with previous studies [3], we confirmed the increased predisposition of older patients to discontinue antiretroviral therapy for side effects. This could be related to several factors, as an altered drug pharmacokinetic (e.g. modification of absorption, protein binding or distribution, impaired drug metabolism) and a potential for drug interactions with co-medications. Since our database does not include detailed data on co-medications other than drugs used for the treatment of opportunistic infections and co-infections, the potential role of drug-drug interactions as a major determinant of treatment discontinuation could not be assessed adequately.

Previous studies suggested that prescription of concomitant medications used for the treatment of opportunistic
### Table 4 Multivariable Cox model fit: relative hazards of adverse events, with two different antiretroviral therapy encodings (n=1,096)

| Factor | RH | 95% Cl | p-value |
|--------|----|--------|---------|
| calendar year (per more recent) | 1.01 | 0.96 | 1.07 | 0.6462 |
| gender M vs. F | 0.52 | 0.38 | 0.71 | <0.0001 |
| age per one year older | 1.04 | 1.02 | 1.05 | <0.0001 |
| nationality non-Italian vs. Italian | 0.82 | 0.57 | 1.17 | 0.2724 |
| nationality unknown vs. Italian | 1.08 | 0.62 | 1.87 | 0.7941 |
| risk homo/bisexual vs. heterosexual | 2.03 | 1.40 | 2.94 | 0.0002 |
| risk IDU vs heterosexual | 1.16 | 0.75 | 1.79 | 0.513 |
| risk other/unknown vs. heterosexual | 0.74 | 0.52 | 1.07 | 0.1090 |
| years from first positive test | 0.99 | 0.96 | 1.02 | 0.3804 |
| CDC stage B vs. A | 1.10 | 0.79 | 1.54 | 0.5716 |
| CDC stage C vs. A | 1.57 | 1.14 | 2.15 | 0.0051 |
| HBsAg positive vs. negative | 1.67 | 1.04 | 2.69 | 0.0356 |
| HBsAg unknown vs. negative | 1.11 | 0.54 | 2.28 | 0.7780 |
| HCVAb positive vs. negative | 1.02 | 0.69 | 1.52 | 0.9109 |
| HCVAb unknown vs. negative | 0.68 | 0.34 | 1.36 | 0.2766 |
| CD4+ per cell/mm³ higher | 1.00 | 1.00 | 1.00 | 0.8679 |
| HIV-RNA per Log₁₀ higher | 0.85 | 0.68 | 1.07 | 0.1761 |
| subtype 17 BF vs. B | 1.49 | 0.81 | 2.75 | 0.1973 |
| subtype 28 BF vs. B | 0.96 | 0.56 | 1.65 | 0.8714 |
| subtype 29 BF vs. B | 0.90 | 0.38 | 2.15 | 0.8113 |
| subtype C vs. B | 1.87 | 0.83 | 4.18 | 0.1289 |
| subtype F1 vs. B | 1.89 | 0.94 | 3.83 | 0.0747 |
| subtype other vs. B | 1.46 | 0.75 | 2.86 | 0.2691 |
| subtype unknown vs. B | 0.95 | 0.70 | 1.29 | 0.7441 |
| bilirubin high vs. normal | 1.02 | 0.46 | 2.26 | 0.9576 |
| bilirubin unknown vs. normal | 0.67 | 0.42 | 1.06 | 0.0845 |
| hemoglobin normal vs. low | 0.97 | 0.66 | 1.40 | 0.8525 |
| hemoglobin unknown vs. low | 0.91 | 0.47 | 1.87 | 0.7903 |
| gammaGT high vs. normal | 0.93 | 0.62 | 1.39 | 0.7125 |
| gammaGT unknown vs. normal | 1.12 | 0.77 | 1.64 | 0.5307 |
| glucose diabetes vs. normal | 1.55 | 0.80 | 3.01 | 0.1959 |
| glucose high vs. normal | 1.73 | 0.92 | 3.26 | 0.0888 |
| glucose unknown vs. normal | 1.04 | 0.55 | 1.96 | 0.9142 |
| GPT high vs. normal | 1.20 | 0.87 | 1.66 | 0.2757 |
| GPT unknown vs. normal | 0.70 | 0.37 | 1.32 | 0.2691 |
| HDL normal vs. low | 1.04 | 0.60 | 1.81 | 0.2891 |
| HDL unknown vs. low | 0.97 | 0.35 | 2.67 | 0.9476 |
| LDL high vs. normal | 1.51 | 0.56 | 4.03 | 0.4137 |
| LDL unknown vs. normal | 1.62 | 0.58 | 4.51 | 0.3551 |
| TGL high vs. normal | 0.95 | 0.63 | 1.42 | 0.8048 |
| TGL unknown vs. normal | 1.65 | 1.11 | 2.44 | 0.0125 |
| MDRD normal vs. low | 1.41 | 0.58 | 3.41 | 0.4430 |
| MDRD unknown vs. low | 1.94 | 0.69 | 5.45 | 0.2098 |

### Additional Notes

Infections could increase the risk of discontinuation owing to cumulative toxicities or drug interactions [3]. In our population we did not observe an increased risk of discontinuation for adverse events in patients treated for PCP, TB or HCV co-infection. However, patients with
AIDS-defining events were more likely to interrupt or switch cART for drug-related side effects.

Co-infection with HBV or HCV have been claimed as a predisposing factor for treatment discontinuation due to hepatic adverse events [9]; however, this association remain controversial [2,23]. In our population we did not observe a significant role of HCV co-infection, but HBsAg-positive patients showed an increased hazard of adverse events. The importance of co-infection with hepatitis viruses could be strictly related to the frequency of prescription of specific antiretroviral drugs, with older drugs bearing a higher risk of hepatotoxicity.

The calendar year was not showing an impact on the hazard of toxicity/allergy events. A similar observation has been previously described in other cohorts [2,27]. This could seem paradoxical since in recent years several drugs with better tolerability profile have been introduced in routine clinical practice. A possible explanation of this finding can rely on the increased number of alternative regimens that have become available in recent years; for this reason clinicians can be more prone to switch drugs also for less severe adverse events. Unfortunately, we could not verify this hypothesis since grading of clinical adverse events was not available in our database.

The potential association of treatment discontinuation for side effects and baseline chemical parameters has not been investigated in previous studies. Chemistry characteristic can represent important tools on the basis of which clinicians can choose the appropriate antiretroviral regimen in order to limit the occurrence of toxicities. In our population, we did not observe any association with the explored parameters; however, the relevant proportion of missing data could have influenced such finding masking the real effects in terms of increased/reduced hazard of adverse events occurrence. Moreover, only baseline markers were analyzed, while the effect of current markers may be crucial, for instance the raise levels of bilirubin during atazanavir-containing antiretroviral therapy [28]. We decided not to perform a time-dependent analysis given the high rate of missing information in the baseline variables. A few multi-centric HIV study cohorts in Italy, specifically the MASTER (www.mastercohort.it) and Icona (http://www.fondazioneicona.org) foundations, and in Europe, including the Copenhagen HIV Programme and EuroSIDA (http://www.cphiv.dk) record such detailed information for all patients, besides the standard HIV serologic markers [15,16].

Some limitations should be recognized when interpreting the results of our study. First, cART toxicity was analyzed considering only treatment modification, but clinical events or alterations in laboratory parameters not leading to treatment discontinuation were not investigated, thus leading to an underestimation of overall drug-related side effects. There might be a population bias, since the first-line anti-HIV therapies could have been tuned appositely on the patients’ background, basing on the guidelines available at that time. This can be truer for drug combinations circulating for a longer time, whose adverse effect have been deeply disclosed. Since this study is retrospective, the bias cannot be ruled out even using strong selection criteria and a patient cohort with a high level of detail and follow up.

Another possible limitation of this study is that we conducted a cause-specific analysis, ignoring the potential effects of competing events in the survival analysis; such events may drive the happening of adverse effects, and surely a design of a competing-risk analysis after this study is warranted.

Given the current, fair, rate of virologic and immunologic successes of first-line anti-HIV antiretroviral therapies in the European Union and other developed countries [29-32], along with the decrease of drug-resistance prevalence [33-39], the objective is now the prolongation of the therapy duration with the minimization of adverse events. Intolerance/toxicity still remains the major cause of drug discontinuation in Italy [40]. Therefore, an effort in gathering data from all available sources to assess more precisely prognostic factors and relative hazards of adverse events is warranted. Eventually, a personalized scoring system might be inferred, as it has been done with the prediction of virologic responses and time to virologic failure [41-44].

In conclusion, several predictors of treatment discontinuation for drug-related adverse events were investigated. These findings could help clinicians to identify individuals at higher risk of developing toxicity, thus allowing an improved prescription of antiretroviral regimens tailored on patients’ characteristics. Moreover, these results suggest the importance of anticipating the probability of occurrence of adverse events in order to ensure close clinical and laboratory monitoring and adequate management of side effects which could improve the durability of cART.

### Additional file

**Additional file 1:** Distribution of first-line anti-HIV therapies by calendar year.

### Abbreviations

cART: Combination antiretroviral therapy; CI: confidence intervals; CUSH: Catholic University of the Sacred Heart; gammaGT: gamma-glutamyltransferase; GPT: Glutamate pyruvate transaminases; GFR: Glomerular filtration rate; HDL: High-density Lipoprotein; LDL: Low-density Lipoprotein; MDRD: Modification of diet in renal disease formula; NNRTI: Non-nucleoside reverse transcriptase inhibitor; NRTI: Nucleoside reverse transcriptase inhibitors; PCP: Pneumocystis jirovecii pneumonia; PI: Protease inhibitor; PI/r: PI
boosted with ritonavir/PFVU. Person years of follow up; RH: Relative hazard; TB: Tuberculosis; TGL: Triglycerides; 95% CI: 95% Confidence Interval.

Competing interests
MF received speakers’ honoraria from Abbott Virology, Merck Sharp and Dohme and Janssen-Cilag. MZ received speakers’ honoraria from Abbott Virology, Merck Sharp and Dohme, Janssen-Cilag, Bristol-Myers Squibb and Gilead Science. MC was an employee of Bristol-Myers Squibb from May 2010 to February 2011 and resigned before starting the present work. RC was advisor for Gilead and Janssen-Cilag, received speakers’ honoraria from ViIV, Bristol-Myers Squibb, Merck Sharp and Dohme and Janssen-Cilag, and research support from “Fondazione Roma”. SDG received speakers’ honoraria from ViIV, Bristol-Myers Squibb, Merck Sharp and Dohme and Janssen-Cilag. All other authors: none to declare.

Authors’ contributions
MCFP contributed to study design, data analysis and interpretation, and article writing; MF and MZ contributed to interpretation of data and article writing; IF, MC, AM, ADA, AB contributed to data collection; RC and SDG coordinated the project and contributed to interpretation of data. All authors reviewed the manuscript during preparation, provided critical feedback and approved the final manuscript.

Acknowledgements
No specific fundings was received for this work.

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Received: 20 April 2012 Accepted: 1 November 2012
Published: 12 November 2012

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doi:10.1186/1471-2334-12-296

Cite this article as: Prosperi et al.: Predictors of first-line antiretroviral therapy discontinuation due to drug-related adverse events in HIV-infected patients: a retrospective cohort study. BMC Infectious Diseases 2012 12:296.

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