Journal of
AIDS & Clinical Research
ISSN: 2155-6113

Keita et al., J AIDS Clinic Res 2012, 3:10
DOI: 10.4172/2155-6113.1000187

Research Article Open Access

Incidence and Risk Factors of First-Line HAART Discontinuation: Is it Worth Choosing Competing Risk or Standard Survival Approaches?

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Abstract

Objectives: To estimate the incidences of first-line HAART discontinuation (for intolerance, treatment failure or treatment simplification) and their risk factors by standard survival (1-KM, Cox model) or competing risk approach (CIF, Fine-Gray model) in HIV infected patients.

Methods: We studied 1136 patients receiving first-line Highly Active Antiretroviral Therapies (HAART), aged over 18 years, from the Dat'AIDS cohort, Toulouse, France, between January 2000 and June 2008. Cumulative incidence was estimated with 1-KM and CIF estimators and risk factors with Cox and Fine-Gray models.

Results: There were 265 discontinuations for intolerance, 136 simplifications, 101 treatment failure and 274 other reasons. One year incidences were 19.0% versus 16.8%, 8.0% versus 6.0%, 6.3% versus 4.8% and 20.0% versus 17.3%, with the estimators 1-KM and CIF, respectively. For intolerance, both models identified similar risk factors. For risk factors of simplification or treatment failure, results differed by the model.

Conclusions: As expected, the 1-KM overestimates the incidence of treatment discontinuation. For early and frequent events such as intolerance, the Cox and the Fine-Gray models appear to give similar results. For late and rare events, potentially exposed to competing risk, results differed. The common or specific nature of a factor may also play a role.

Keywords: First-line HAART discontinuation; Cumulative incidence; Cox model; Competing risks; Risk factors

Introduction

From 1996 onward, the advent of antiproteases and the introduction of Highly Active Antiretroviral Therapies (HAART) have enabled considerable progress in survival [1]. To achieve these aims, the success of first-line HAART has been shown to be of particular importance. Subsequent treatment regimens were less likely to be successful after a first-line HAART discontinuation [2]. Patients interrupting first-line HAART within two months after treatment initiation had poorer clinical results than those who had not stopped [3]. Discontinuation due to intolerance could reduce compliance with later regimens, and interruptions due to failure (clinical and/or immunological and virological) may raise the risk of development of resistant viral strains [4]. In clinical practice, premature discontinuations are frequent, ranging from 36% to 61% at 12 months [5-10]. Discontinuation due to intolerance has been reported to be the main cause in most cohorts, followed by discontinuation due to failure or to problems of compliance. The risk factors for discontinuation found in the literature can be grouped into three categories: (1) patient-related factors: age, sex, race, educational level, mode of HIV acquisition; (2) disease-related factors: CD4, plasma viral load (VL) at baseline or at discontinuation, AIDS stage; and (3) treatment-related factors: once or twice daily, pill burden, type of treatment.

These results were generally yielded by two main models (Logistic models or Poisson models) and in the vast majority of studies, the estimator of the cumulative incidence, the complement 1-KM [11] of Kaplan-Meier and Cox model [12] for risks factors were applied. This "standard" approach makes the assumption of non-informative censoring. Concerning first-line HAART discontinuations, this means that the occurrence, for example, of a discontinuation for intolerance does not affect the risk of observing another type of discontinuation (treatment failure, treatment simplification or other reasons). This assumption is questionable in a context of multiple events of interest such as first line HAART discontinuation. Indeed, the different types of discontinuations are in competition insofar as a patient who discontinued for any reason can no longer stop the treatment for another reason. By considering other events than the event of interest as censored observations, the standard approach could overestimate the incidence of the event of interest and bias the estimated effects of potential risk factor of discontinuation [11,13]. In the presence of competing risks, an alternative analysis of the cumulative incidence is based on the CIF estimator (Cumulative Incidence Function) [14] and Fine-Gray model for identifying the risk factors [15]. This "competing risk approach" considers the nature of informative censoring due to competing event, which is defined as an event whose occurrence alters the risk of occurrence of a main event under examination. Although competing risks may refer to events that are mutually non-exclusive [16], most calculation strategies are adapted to a follow-up which ends at the first event, thus (artificially) creating a competitive situation.

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Received October 31, 2012; **Accepted** November 28, 2012; **Published** November 30, 2012

Citation: Keita M, Chouquet C, Cuzin L, Cissé M, Lang T, et al. (2012) Incidence and Risk Factors of First-Line HAART Discontinuation: Is it Worth Choosing Competing Risk or Standard Survival Approaches? J AIDS Clinic Res 3:187. doi:10.4172/2155-6113.1000187

Our aim in this cohort study was thus, to compare results obtained with the standard approach (1-KM, Cox model) and the competing risk approach (CIF, Fine-Gray model) in the estimation of the incidence of first-line HAART discontinuation (for intolerance, treatment failure or treatment simplification) and their risk factors in HIV infected patients.

Methods

Originally called NADIS, Dat'AIDS is a multicenter cohort based on a computerized medical record that is used by clinicians in real time during their consultations. Overall follow-up is every three months, and the cohort was set up from 2000 onwards in six French teaching hospitals, including the Toulouse Teaching Hospital. The national Dat'AIDS database covers more than 10% of patients treated in French hospitals. Patients give their prior written informed consent to use their anonymous data for research and evaluation purposes. This tool has been described in detail by elsewhere [17].

Study population

The study population consisted of all HIV-positive patients who started first-line antiretroviral therapy (HAART) between January 1, 2000 and June 30, 2008 in the department of infectious and tropical diseases of Toulouse teaching hospital. Only HIV-1 positive, antiretroviral-naive patients older than 18 years were included in the study. Patients included in clinical trials or those with undetectable viral load at treatment initiation were excluded.

Prognosis variables and data collection

Disease-related variables were: mode of HIV acquisition, inclusion in a therapeutic education program during the three months before HAART initiation or within two weeks afterwards, AIDS-defining illness at treatment initiation, date of first HIV positive diagnosis, year of treatment initiation in four classes ([2000–2001], [2002–2003], [2004–2005] and [2006–2008]), type of first-line regimen coded as follows : two nucleoside reverse transcriptase inhibitors (2NRTI) with a boosted protease inhibitor or not (1PI/1PI$_b$); two nucleoside reverse transcriptase inhibitors (2NRTI) with one non-nucleoside reverse transcriptase inhibitor (1NNRTI); and other alternative combinations (one or two drugs, other three drugs combinations, or four drugs). CD4 measurements and viral load (VL) were collected at treatment initiation, within a maximum of three months for CD4 levels and one month for VL. The peripheral blood CD4 lymphocyte count was obtained by flow cytometry (Epics Profile, Coulter, Hialeah, Florida, USA). It was expressed as the number of cells per mm^3 and divided into three categories: <200 cells/mm^3 (reference), (200–350) and ≥ 350. VL was measured using the Amplicor HIV-1 Monitor technique (Laboratoire Roche-Diagnostic, Meylan, France). It was expressed in $\log_{10}$-copies/ml and divided into three categories: ([1.7-4.0] [$\log_{10}$ copies/ml] (reference), [4.0-5.0]) and ≥ 5.0. All these data were collected at or around treatment initiation.

Events of interest and data collection

A discontinuation was defined as a change or a cessation of one or more drugs of the initial regimen, as recorded by the physician. The date on which it occurred was recorded. Dose modifications were not accounted for. Four events of interest were considered: (1) the intolerance, defined as an adverse effect after taking at least one HAART drug and leading to discontinuation or change of the treatment regimen. (2) The treatment failure: clinical onset of symptoms of disease progression; absence of increase in CD4 count in spite of antiretroviral treatment, non-optimal decrease in VL at 6 months or occurrence of an increase in a previously undetectable VL. (3) The treatment simplification: a change in treatment intended to facilitate intake by the patient (once a day instead of twice, fewer pills at each time) and (4) the "other causes": mostly unknown or related to patient wish, problems of compliance, breast-feeding or pregnancy. When several events of interest were observed simultaneously in a given patient, data collection focused on the clinical event that the physician considered most relevant.

Statistical analysis

The first step concerned the estimation of incidence. Our survival analysis was based on estimation of the cumulative incidence for one of the multiple events of interest, in the presence of competing risks. Death was not a cause of censoring, as no death occurred during follow-up. We first used the non-parametric Kaplan-Meier method that estimates usually the overall survival probability of an event of interest, noted by KM. The cumulative incidence was deduced from the complement 1-KM [11] of this probability, which is the probability of having the event of interest at a given time. In this standard approach, the observed events other than this of interest are considered as non-informative censoring. Then, we estimated the cumulative incidence in the context of competing risks by CIF estimator, proposed by Kalbflesih and Prentice in 1980 [14]. CIF estimator became available on STATA in 2004 [18].

In a second step, risk factors were analyzed. Two approaches were used: the Cox model [12] and the Fine-Gray regression model [15]. Cox model is based on the cause-specific hazard function and takes into account patients who had the event of interest, the other patients being treated as censored. The method proposed by Fine and Gray, models the subdistribution hazard function to take into account competing risks, by introducing the probability of having a competing event before the event of interest. It gives the possibility to express effects of covariates directly on the cumulative incidence function.

For each event of interest, the variables identified in the literature as being associated with discontinuation of first-line treatment (sex, mode of HIV acquisition, type of treatment, age, and immunological and virological measurements at baseline) as well as variables that were significant at a p<0.20 level in bivariate analysis were included in each of Cox and Fine-Gray regressions models. Significance was assessed by using the overall p-value of all the indicators of each variable, using the Wald test for Cox and Fine-Gray models. In order to compare the results of the two models for each event of interest, we run models on the same population by excluding patients who had at least one missing item for one of the studied risk factors. A manual stepwise descending strategy, adapted from the method of Hosmer and Lemeshow was used to eliminate successively the factors with p>0.05. We then tested the interactions which were of clinical significance. To obtain the final model, we compared the model without interaction containing the variables with p<0.05, with the model with interaction using the Akaike Information Criterion (AIC). Risks proportionality assumption was checked by using, for the Cox model, the test proposed by Grambsch and Thernaud [19], and for the Fine-Gray model by testing the interaction between each variable and the logarithm of time. Lastly, we tested the robustness and goodness of fit of the model using Cox-Snell residuals for the Cox model and standardized score residuals for the Fine-Gray model. All analyses were carried out with STATA V11.2 software (Statacorp, College Station, TX).

Results

Population

Mean age (± standard deviation) at treatment initiation was 40 years

Baseline characteristics	Total (n = 1136)
Men/Women, n (%)	770 (67.8)/366 (32.2)
Age at HAART initiation (years)	
Mean (standard deviation)	40 (10.4)
[18–50[, n (%)	963 (84.8)
[50–82], n (%)	173 (15.2)
Mode of HIV acquisition, n (%)	
Heterosexual	552 (48.6)
Homosexual/Bisexual	389 (34.2)
Injection drug use	84 (7.4)
Other/Unknown	111 (9.8)
Year of first HAART, n (%)	
[2000–2001]	313 (27.6)
[2002–2003]	242 (21.3)
[2004–2005]	253 (22.3)
[2006–2008]	328 (28.8)
Therapeutic education, Yes, n (%)	226 (19.9)
First HAART regimen, n (%)	
2NRTI+1PI/1PI$_b$ ‡	406 (35.7)
2NRTI+1NNRTI	380 (33.5)
Other regimens	350 (30.8)
Death, Yes, n (%)	0 (0.0)
AIDS-defining illness at HAART initiation, n (%)	
Yes	151 (13.3)
Missing data	44 (3.9)
Duration HIV seropositivity (years)	
Mean (standard deviation)	4.7 (5.7)
CD4 cell count at HAART initiation (cells/mm^3)	
Mean (standard deviation)	264.9 (196.6)
Missing data, n (%)	210 (18.5)
Viral load at HAART initiation (log$_{10}$ copies/mm^3)	
Mean (standard deviation)	4.6 (1.1)
Missing data, n (%)	307(27.0)
‡ PI$_b$ = boosted protease inhibitor	

Table 1: Characteristics at treatment initiation of the 1136 participants receiving first-line HAART between January 1, 2000 and June 30, 2008 among patients treated at Toulouse Teaching Hospital.

(± 10 years) and 67.8% (N=770) were men. The most frequent mode of acquisition was heterosexual (48.6%, N=552), with homosexual and/or bisexual acquisition accounting for 34.2% (N=389) of infections. Nearly 71.2% (N=808) of patients started first-line HAART between 2000 and 2005 and one-fifth of patients had undergone a treatment education program. The first-line regimens consisted of 2NRTI +1PI/1PI$_b$ for 35.7% (N=406) of patients, 33.5% (N=380) received 2NRTI +1NNRTI, and 30.8% (N=350) received other treatment regimens. Half of the patients started treatment nearly two years after the diagnosis, and 13.3% (N=151) had AIDS-defining illnesses. CD4 counts ranged between 0 and 1341 cells/mm^3. VL ranged between 1.7 to 7.0 log$_{10}$ copies/mm^3. These data are summarized in table 1.

Causes of discontinuation of first-line treatment

As a whole, 776 of the 1136 patients discontinued first line regimen, including 265 for intolerance, 101 for treatment failure, 136 for treatment simplification, and 274 for other reasons. The estimated incidence was 34 (95% Confidence Interval, CI, [32–37]) per 1000 person-months. The cumulative incidence of discontinuation for all causes was 30.3% (27.6–31.6) at six months, 44.3% (41.3–47.3) at one year, 58.5% (55.4–61.6) at two years, 76.5% (73.5–79.5) at four years and 89.4% (85.5–92.6) at eight years. Median time to discontinuation, for any cause, was 15.3 months (InterQuartile Range, IQR, 4–45 months).

Cumulative incidence of discontinuation according to the 1-KM (Standard survival) and CIF (competing risk) estimators

With the 1–KM estimator, the median time to discontinuation for intolerance was 93.8 months. Median was not reached for treatment simplification or for treatment failure. With the CIF estimator, no cause reached the median. Figures 1 and 2 show the cumulative incidences estimated according to both approaches and using the CIF estimator respectively.

Whatever the approach used, the proportion of discontinuation because of intolerance was always greater than the proportions of the other causes of discontinuation. Using competing risk and standard

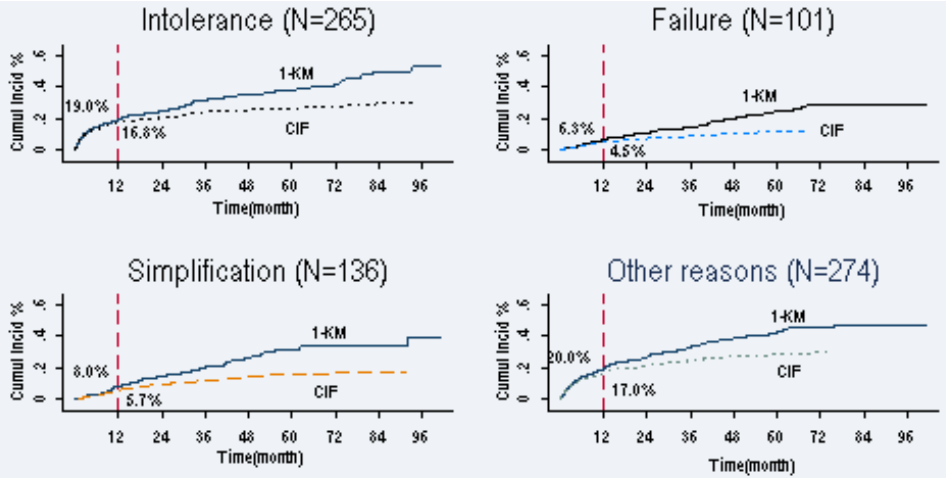

Figure 1: KM versus CIF, Cumulative incidence for types of first line HAART discontinuations in 1136 HIV infected patients

Cumulative incidences according to 1-KM (standard survival) and CIF (competing risk approach) for first-line HAART discontinuations due to intolerance, treatment failure, treatment simplification and other causes. For each of the four events, 1-KM over estimates cumulative incidence. The differences between the two approaches were larger as the duration of follow-up increased.

survival analysis, the estimations at one year were respectively 16.8% and 19.0% for intolerance, 4.5% and 6.3% for treatment failure, 5.7% and 8.0% for treatment simplification and, 17.3% versus (vs) 20.0% for other causes. The sum of specifics probabilities estimated by standard survival analysis was higher than the overall cumulative incidence (at one year, 53.3% vs 44.3%), which is not the case by using competing risk approach.

Analysis of factors associated with discontinuation of first-line treatment according to the Cox (Standard survival) and Fine-Gray (competing risk) Models

Multivariate analyses were applied for each model on the same population of 793 patients who had no missing data for all risk factors studied. For each cause of discontinuation, the interactions tested in the Cox or Fine-Gray model were not significant.

Risk factors of discontinuation of first-line treatment due to intolerance

Among the 793 patients, 191 discontinued treatment due to intolerance. The remaining 602 were considered as conventional right censoring by the Cox model and classified as 348 censorings of concurrent events and 254 conventional right censorings by the Fine-Gray model. Similar risk factors were identified by both models (Table 2). Participation in a therapeutic education program, age over 50 years and high viral load were the three factors associated with a higher risk of discontinuation for intolerance in the two adjusted models. The Cox model also detected a trend towards significance of AIDS-defining illness (p=0.0562), that was not identified as a risk factor by using competing risk approach.

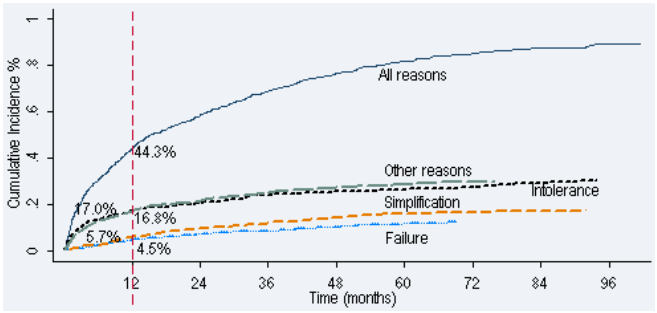

Figure 2: All reasons of first-line HAART discontinuations and the CIF estimation for types of discontinuations in 1136 HIV infected patients

Cumulative incidences of all reasons and the CIF estimation for types of first-line HAART discontinuations. The sum of specifics probabilities estimates by standard survival analysis (see also figure 1) was higher than the overall cumulative incidence which is not the case by using competing risk approach. By example, one year cumulative incidences were 53.3% versus 44.3%. Theses analysis also showed over estimation of 1-KM.

Risk factors of discontinuation of first-line treatment because of treatment failure

Among the 793 patients included, 64 discontinuations for treatment failure were observed. The 729 remaining cases were considered as conventional right censoring by the Cox model and classified as 475 censorings concurrent events and 254 conventional right censorings according to the Fine-Gray model. The type of first-line treatment and the duration of HIV infection were similarly identified as risk factors in both the Cox model and Fine-Gray model. AIDS-defining illness at treatment initiation increased the probability of discontinuation for treatment failure with the Cox model, but not with the Fine-Gray model (Table 3).

Risk factors of discontinuation of first-line treatment for treatment simplification

Discontinuation for treatment simplification occurred in 107 of the 793 patients. The 686 remaining patients were considered as conventional right-censored data with the Cox model and classified as 432 censorings of concurrent events and 254 conventional right censorings with the Fine-Gray model. Risk factors are shown in table 4. Mode of HIV acquisition and year of treatment initiation were identified as risk factors in both the Cox model and in the Fine-Gray model. In the Cox model but not in the Fine-Gray model, patients receiving a regimen combining 2NRTI+1NNRTI tended to have a lower risk of discontinuation for simplification than patients who had received 2NRTI+1PI/1PI$_b$. In the Cox model, the probability of discontinuation for treatment simplification was greater for patients with VL >5 $\log_{10}$ copies/mm^3 than for those with VL between (1.7-4) $\log_{10}$ copies/mm^3

			Bivariate analysis				Multivariate analysis, n =793			
	Occurrence		Cox		Fine-Gray		Cox		Fine-Gray	
Characteristics	n =1136	%	HR$^{\$}_{crude}$[80% CI]	P	SHR$^{¶}_{crude}$[80% CI]	P	HR$_{ajusted}$[95% CI]	P *	SHR$_{ajusted}$[95% CI]	P *
Age at Ti **(year)				0.0048		0.0013		0.0264		0.0058
[18 – 50]	210	21.81	1(Reference)		1(Reference)		1(Reference)		1(Reference)	
[50 – 82]	55	31.79	1.53 [1.26–1.86]		1.61 [1.33–1.95]		1.47 [1.04–2.07]		1.60 [1.14–2.25]	
Therapeutic education				<0.0001		<0.0001		0.0241		0.0341
No	202	22.20	1(Reference)		1(Reference)		1(Reference)		1(Reference)	
Yes	63	27.88	1.77 [1.47–2.14]		1.57 [1.30–1.90]		1.43 [1.04–1.97]		1.39 [1.02–1.89]	
AIDS-defining illness	N=1092	100%		0.0006		0.0129		0.0511		0.1605
No	209	22.21	1(Reference)		1(Reference)		1(Reference)		1(Reference)	
Yes	47	31.13	1.74 [1.41–2.14]		1.50 [1.21–1.86]		1.45 [0.99–2.10]		1.31 [0.89–1.92]	
VL ($\log_{10}$ copie/mm^3) Ti **	N=829	100%		0.0216		0.0173		0.0392		0.0308
[1.7– 4.0]	32	16.75	1(Reference)		1(Reference)		1(Reference)		1(Reference)	
[4.0– 5.0]	86	26.71	1.74 [1.33–2.27]		1.75 [1.35–2.28]		1.71 [1.12–2.60]		1.73 [1.15–2.60]	
≥ 5.0	79	25.00	1.66 [1.26–2.17]		1.66 [1.27–2.17]		1.41 [0.91–2.18]		1.48 [0.97–2.26]	

* P-value obtained by backward stepwise regression
** Ti : Time of HAART initiation
$ Hazard Ratio obtained by Cox model
¶ Subdistribution Hazards Ratio obtained by Fine-Gray model

Table 2: Baseline risk factors of first line HAART discontinuation for intolerance: Cox and Fine-Gray models.

			Bivariate analysis				Multivariate analysis, n = 793			
	Occurrence		Cox		Fine-Gray		Cox		Fine-Gray	
Characteristics	n = 1136	%	$HR^{\$}_{crude}$[80% CI]	P	$SHR^{¶}_{crude}$[80% CI]	P	$HR_{ajusted}$[95% CI]	P*	$SHR_{ajusted}$[95% CI]	P*
Year of first HAART				0.1448		0.0043		0.3461		0.0191
[2000–2001]	43	13.74	1(Reference)		1(Reference)		1(Reference)		1(Reference)	
[2002–2003]	32	13.22	1.18 [0.87–1.59]		1.02 [0.76–1.38]		1.09 [0.59–1.98]		0.97 [0.55–1.73]	
[2004– 2005]	16	6.32	0.72 [0.49–1.06]		0.50 [0.34–0.73]		0.53 [0.23–1.21]		0.36 [0.16–0.78]	
[2006– 2008]	10	3.05	0.55 [0.34–0.87]		0.38 [0.24–0.59]		0.68 [0.27–1.72]		0.43 [0.17–1.06]	
First HAART regimen				0.0001		0.0001		0.0060		0.0444
2NRTI + 1PI/$1PI_b$‡	19	4.68	1(Reference)		1(Reference)		1(Reference)		1(Reference)	
2NRTI + 1NNRTI	28	7.37	1.20 [0.82–1.77]		1.53 [1.04–2.24]		1.70 [0.79–3.67]		1.82 [0.84–3.94]	
Other regimens	54	15.43	2.66 [1.88–3.75]		2.86 [2.03–4.02]		2.94 [1.47–5.88]		2.38 [1.20–4.71]	
HIV seropositivity duration (years)				0.0032		0.0011		0.0094		0.0039
<0.169	28	9.89	1(Reference)		1(Reference)		1(Reference)		1(Reference)	
[0.16– 1.83]	13	4.56	0.45 [0.29–0.69]		0.49 [0.32–0.76]		0.64 [0.29–1.39]		0.68 [0.30–1.52]	
[1.83– 8.27]	18	6.34	0.56 [0.38–0.82]		0.65 [0.44–0.95]		0.80 [0.35–1.83]		0.68 [0.30–1.53]	
[8.27– 24.02]	42	14.79	1.19 [0.87–1.63]		1.45 [1.06–1.99]		1.92 [1.04–3.54]		1.94 [1.05–3.58]	
AIDS-defining illness	n=1092	100%		0.0059		0.1239		0.0311		0.1201
No	76	8.08	1(Ref)		1(Ref)		1(Ref)		1(Ref)	
Yes	18	11.92	2.06 [1.47–2.88]		1.50 [1.07–2.11]		2.05 [1.06–3.95]		1.74 [0.86–3.50]	

* P-value obtained by backward stepwise regression
** Ti =Time of HAART initiation
‡ PI_b = boosted protease inhibitor
$ Hazard Ratio obtained by Cox model
¶ Subdistribution Hazards Ratio obtained by Fine-Gray model

Table 3: Baseline risk factors of first line HAART discontinuation for treatment failure: Cox and Fine-Gray models.

			Bivariate analysis				Multivariate analysis, n = 793			
	Occurrence		Cox		Fine-Gray		Cox		Fine-Gray	
Characteristics	n = 1136	%	$HR^{\$}_{crude}$[80% CI]	P	$SHR^{¶}_{crude}$[80% CI]	P	$HR_{ajusted}$[95% CI]	P*	$SHR_{ajusted}$[95% CI]	P*
Mode of HIV acquisition				0.0255		0.0373		0.0290		0.0119
Heterosexual	67	12.14	1(Reference)		1(Reference)		1(Reference)		1(Reference)	
Homosexual /Bisexual	57	14.65	1.18 [0.94–1.49]		1.22 [0.97–1.53]		1.45 [0.97–2.16]		1.62 [1.09–2.41]	
Injection drug use	6	7.14	0.51 [0.29–0.88]		0.52 [0.30–0.90]		0.99 [0.38–2.52]		0.77 [0.30–1.94]	
Other/Unknown	6	5.41	0.40 [0.23–0.70]		0.45 [0.26–0.78]		0.30 [0.09–0.97]		0.39 [0.12–1.28]	
Year of first HAART				<0.0001		<0.0001		<0.0001		<0.0001
[2000–2001[	30	9.58	1(Reference)		1(Reference)		1(Reference)		1(Reference)	
[2002– 2003[	32	13.22	1.78 [1.28–2.48]		1.52 [1.10–2.10]		1.44 [0.80–2.59]		1.32 [0.75–2.31]	
[2004– 2005[	60	23.72	4.48 [3.30–6.08]		3.15 [2.38–4.17]		3.02 [1.72–5.29]		2.54 [1.56–4.13]	
[2006– 2008]	14	4.27	1.37 [0.88–2.13]		0.83 [0.55–1.25]		0.90 [0.41–1.96]		0.65 [0.32–1.32]	
First HAART regimen				0.0151		0.1588		0.0548		0.4172
2NRTI + 1PI/$1PI_b$ ‡	52	12.81	1(Reference)		1(Reference)		1(Reference)		1(Reference)	
2NRTI + 1NNRTI	35	9.21	0.53 [0.40–0.70]		0.66 [0.50–0.87]		0.56 [0.34–0.91]		0.73 [0.46–1.16]	
Other	49	14.00	0.85 [0.66–1.11]		0.89 [0.69–1.15]		0.89 [0.55–1.44]		0.89 [0.55–1.43]	
VL at Ti (log_{10} copies/mm^3)	N= 829	100%		0.0018		0.0046		0.0266		0.0537
[1.7 – 4.0]	20	10.47	1(Reference)		1(Reference)		1(Reference)		1(Reference)	
[4.0–5.0]	35	10.87	1.23 [0.85–1.76]		1.09 [0.76–1.56]		1.18 [0.65–2.13]		1.07 [0.60–1.90]	
≥ 5.0	57	18.04	2.21 [1.58–3.09]		1.95 [1.40–2.71]		1.90 [1.08–3.34]		1.69 [0.98–2.89]	

* P-value obtained by backward stepwise regression
** Ti : Time of HAART initiation
‡ PI_b = boosted protease inhibitor
$ Hazard Ratio obtained by Cox model
¶ Subdistribution Hazards Ratio obtained by Fine-Gray model

Table 4: Baseline risk factors of first line HAART discontinuation for treatment simplification: Cox and Fine-Gray models

(Hazard Ratio, HR=1.90, 95% CI 1.08-3.34). This difference was not strictly significant in the Fine-Gray model even though the relative risks did not greatly differ.

Discussion

Whatever the approaches used, (1-KM) or CIF, our results show that without "other causes", the incidence of discontinuation was in decreasing order of importance due to, intolerance, treatment simplification, and treatment failure. As expected, cumulative incidence was overestimated in standard survival (1-KM) compared with the CIF estimator of the competing risk approach. In contrast, regarding risk factors, our analyses showed that the identified risk factors could differ according to the statistical model (Cox or Fine-Gray) and the cause of discontinuation. Risk factors differed according to the statistical approach used, as observed for treatment failure and treatment

simplification. It was not the case for intolerance, where the same risk factors were identified by the Cox and Fine-Gray models.

Our study was limited to the population of one French center. However, the study has the merit of collecting data in real time of information, with a reasonably large sample and a prospective follow-up of eight years and a half, sufficient to achieve our objectives. Due to close monitoring during follow-up, few patients were lost to study.

With regard to estimated incidences, in our data, the differences between the two approaches were larger as the duration of follow-up increased. These differences could be explained by the way the "risk set" is calculated. The 1-KM complement considers that the population followed is exposed only to the risk of the event of interest, like in a context of independent concurrent events. Like subjects lost to follow-up, a subject who has undergone a concurrent event is no longer counted in the risk set. Conversely, by using the CIF approach, patients who have a competing event are considered in the calculation of overall survival, needed to estimate the cumulative incidence [20].

Regarding risk factors, our data showed that results are mixed according to the standard and competing risk approaches. They were the same for intolerance discontinuation but different regarding treatment failure and simplification. The time of occurrence and the frequency of an event of interest might explain these results. Intolerance is in fact frequent and occurred earlier, whereas treatment failure and simplification are less frequent, occurred later and thus are more exposed to competing risks. Wolbers et al. [21] indicated that when concurrent events are rare, the Cox model is equally appropriate as the competing risk model, which is what we found for discontinuation due to intolerance because it was not too much exposed to competing events. Conversely, discontinuations for simplification or failure were much more exposed to competing risk (discontinuation for intolerance) and consequently Cox model and Fine-Gray models gave different results. The "common" or "specific" nature of a given risk factor could also explain in part the difference observed between the two approaches. The Cox model would be more able to detect a risk factor common to different events and the Fine-Gray model would be more able to detect risk factors specific to a given event of interest. As an example, when considering discontinuations for intolerance or failure, in contrast with the Fine-Gray model, the Cox model identified AIDS-defining illness as a risk factor. One reason could be that this risk factor is a common cause of discontinuation, which is not specific to a type of discontinuation.

In conclusion, according to these results, recommendations have to make a clear distinction between estimation of incidence and identification of risk factors. As expected, 1-KM estimator overestimates the incidence of first-line HAART discontinuation, suggesting that the CIF estimator should be used in a situation where competing events are involved. With regard to identifying risk factors, use of the Cox model or the Fine-Gray model appears much more complex according to the research question. For early and frequent events, such as discontinuation due to intolerance in our example, the two models yielded similar results. Conversely, for later and rarer causes, more exposed to competing risk, the two models produced different results. The common or specific nature of a given factor might also play a role. To our knowledge, it is difficult to decide how these two models should be used in a context of multiple events, as shown in our example of treatment discontinuation. Further work is needed in order to clarify this question, probably through testing on simulated datasets. It should be emphasized that both models do not explore the same research question.

Acknowledgments

The authors wish to thank all the clinicians, patients, data managers, research nurses and clinical research workers who assisted in data collection. This work is one of three carried out as part of a thesis in clinical epidemiology. It was funded by the Dat'AIDS scientific committee (2010 grant). The opinions expressed in this paper are those of the researchers and are not necessarily those of the Dat'AIDS scientific board.

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