

Predictors of retention in care in HIV-infected patients in a large hospital cohort in Italy

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Original Paper

Cite this article: Prinapori R, Giannini B, Riccardi N, Bovis F, Giacomini M, Setti M, Viscoli C, Artioli S, Di Biagio A (2018). Predictors of retention in care in HIV-infected patients in a large hospital cohort in Italy. *Epidemiology and Infection* **146**, 606–611. <https://doi.org/10.1017/S0950268817003107>

Received: 3 August 2017
Revised: 17 November 2017
Accepted: 13 December 2017
First published online: 28 February 2018

Key words:

Antiretroviral therapy; continuum of care; HIV; migration; retention in care

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Abstract

Retention in care is a key feature of the cascade of continuum of care, playing an important role in achieving therapeutic success and being crucial for reduction of HIV transmission. The aim of this study was to evaluate the rate of retention in care in a large referral centre in the North of Italy and to identify predictors associated with failed retention. All new HIV-infected subjects were consecutive enrolled from 1 January 2008 to 31 December 2014. Demographics, immune-virological status, hepatitis co-infection and timing of initiation of combined antiretroviral therapy (cART) data were collected at baseline and at the time of last observation. Failed retention in care was defined as lack of laboratory data, clinical visits and drug dispensation for more than 6 months from the last visit. Cox regression analysis was used. Multivariate analysis of variables with $P < 0.05$ in univariate analysis was performed. We enrolled 269 patients (mean age 46.1 years). Males were 197 (73%), Italian 219 (81%) with mean length of disease of 5.1 years. cART was prescribed for 257 patients (95%). The rate of retention in care was 78.4% and the rate of virological suppression was 75%. Predictors of being loss to follow-up were foreign origin ($P = 0.048$), CD4+ count $< 200/\text{mmc}$ ($P = 0.001$) and not being treated for HIV infection ($P = 0.0004$). Predictors of cART efficacy were shorter duration of HIV infection and baseline HIV-RNA $< 100\,000$ copies/ml. These findings underline the necessity to improve retention in care by identifying groups at increased risk of being loss to follow-up. Retention in care of vulnerable population is crucial to reach 90-90-90 UNAIDS endpoint.

Introduction

Despite the intense efforts in preventing HIV-1 transmission, more than 2 million new infections were reported in 2014 worldwide [1]. However, thanks to the advances in care of people living with HIV-1, a drastic decrease in HIV-related morbidity and mortality was reported [2]. Retention in care of HIV-infected patients and adherence to the prescribed antiretroviral regimen are pivotal for obtaining virological suppression with the resulting long-term health benefits and the reduction in the risk of infection transmission, leading to a possible containment of HIV spread [3–5]. The continuum of care moves from HIV testing to linkage to care, retention in care, engagement in care with the prescription of combined antiretroviral therapy (cART) until achieving viral suppression and maintenance of status [6]. Monitoring of continuum of care is essential for maintaining virological success: it can be considered an important indicator of provided assistance quality level. Data from United States highlighted that approximately 77% of people diagnosed with HIV were linked to care, and 51% were retained in ongoing care; only an estimated 28% of all HIV-infected persons in the United States have a suppressed HIV-RNA [7]. In Italy, an estimation of continuum of care was developed in 2014 [8], extrapolating data from National Surveillance System for HIV and from ICONA cohort (*Italian Cohort of Antiretroviral-Naive Patients*) [9, 10]. An estimated 134 000 persons were living with HIV in Italy of whom 89% had been diagnosed [11]. Patient retained in ongoing care are approximately 102 000 [12]. Based on Italian cohort studies [10], cART was prescribed for an estimated 83% of patients linked in HIV care (74% of people living with HIV), and viral suppression (< 50 copies/ml) was achieved in 87% of treated patients, equal to 52% of HIV-infected Italian patients (69 680 of 134 000). It is evident that the impact of cART on HIV infection-related mortality and morbidity is only evaluable in a portion of the targeted population. Although national and international public health institutions emphasise the importance of population HIV testing and therapy as prevention, intermediate steps of the

cascade of care, and in particular the retention in care, are increasingly attractive tools in the fight against HIV infection [13, 14]. Notably, failed retention in care, with the resulting delayed start of cART, is associated with a worse outcome including virological failure and increased mortality [15–17]; nevertheless, few studies have paid attention to predictors associated with this endpoint, particularly in industrialised countries. The aim of this study is to evaluate the rate of retention in care for HIV-infected patients in a large University and Community Hospital, in Italy, and to identify predictors associated with failed retention in ongoing care. Virological success and predictors of failed cART efficacy are also evaluated as secondary endpoint.

Methods

The present study is a prospective, observational, cohort study involving all new HIV-1-infected patients diagnosed at the Clinic of Infectious Disease and at the Clinic of Immunology and Internal Medicine of Ospedale Policlinico San Martino of Genoa, a large city in the North West of Italy with nearly 600 000 inhabitants. Data collection began the 1st of January 2008 and ended the 31st of December 2014; all patients were consecutively enrolled in the study. All data were collected on the MedInfo online platform enclosed in the Ligurian HIV Network. The MedInfo platform (www.reteligurehiv.it) is an online database that allows anonymous and automatic data collection (laboratory test results and clinical information) for HIV-infected patients in the Ligurian region. Data are encrypted to ensure privacy but easily available to physician. The online database contains more than 2500 patients and allows the execution of multicentre clinical trials [18]. Key inclusion criteria were: age >18 years and documented HIV-1 infection. All participants were evaluated at baseline and demographic parameters (age, sex and nationality), plasma HIV-1-RNA levels, nadir lymphocyte T CD4+ (CD4+) cell count, HBV, HCV co-infection and CDC stage. cART regimens were registered at baseline and at scheduled follow-ups until 1 July 2015. The loss to follow-up was defined by the lack of outpatient physical examination and/or cART withdrawal and/or absence of laboratory tests for more than 6 consecutive months. Patients who died or moved during the study were considered lost to follow-up as well. In all patients actively on cART, virological suppression was defined as HIV-RNA <50 copies/ml after 6 months of therapy. The study was conducted according to the Declaration of Helsinki; on 21 October 2014, the protocol was reviewed and approved by the Liguria regional institutional review board/independent ethics committee (P.R. 353REG2014).

Statistical analysis

For clinical and demographic data, descriptive statistics were summarised in terms of medians with first and third quartiles (1st–3rd quarter) or in terms of absolute frequencies (percentage). Comparisons of disease characteristics between patient groups were performed by the χ^2 test (or by Fisher's exact test in case of expected frequencies <5) for categorical variables. For continuous variables, the comparison between patient groups was performed by Student's *t* test if reasonably normally distributed, otherwise Wilcoxon test was used. A *P* value of <0.05 was considered as statistically significant. The statistical package used was SAS 9.3 (Institute Inc., Cary, NC, USA).

Stepwise multivariate logistic regression analysis was performed, with loss to follow-up or efficacy after therapy as the dependent variable, and all variables with a significant univariate *P*-value as covariates. The final model was arrived at by means of a step-down procedure, based on the likelihood ratio test.

Results

In this study, 269 HIV-infected patients followed at Ospedale Policlinico San Martino of Genoa were enrolled and *linked in care*. Mean age was 46.1 years (38.6–54.1). Male were 197 (73%), Italian patients were 219 (81%). Mean length of disease was 5.1 years. One hundred and fifty-eight patients (59%) had a baseline lymphocyte T CD4+ cell count >200/mm³. Co-infection with hepatitis C and B virus was present in 32 (13%) and 7 (3%) patients, respectively. The rate of retention in care was 78.4% (211/269) after 6 months of follow-up. Among the patients who failed maintenance in care, 14 (24%) died and 10 (17.2%) moved to other medical centres. cART was overall prescribed for 257 patients (95%) and for 209 among retained patients (99%). Out of these subjects, 204 had HIV-RNA <50 copies/ml. The rate of virological success, considering the entire population of enrolled patients, was 75%. The cascade of continuum of care of HIV-infected patients is illustrated in Figure 1. In the univariate analysis being foreign-born patients, compared with Italian-native patients was statistically significant for failed retention in care as well as HBV co-infection, HIV-RNA >50 copies/ml at the last performed follow-up evaluation, absence of cART and low CD4+ cell count at the baseline. Demographic parameters of the population in the study and differences among patients linked to care and lost at the follow-up are shown in Table 1.

In the multivariate analysis, an association between failed retention in care and being migrants (*P* = 0.048), lack of cART prescription (*P* = 0.0004) and lower lymphocyte T CD4+ cell count at last observation (*P* = 0.001) was confirmed as illustrated in Table 2.

In Figures 2–4, Kaplan–Meier estimates of failed maintenance in HIV care for statistically significant variant were reported.

Lastly, predictors of cART efficacy (HIV-RNA <50 copies/ml at last observation) were considered: patients for whom cART was not prescribed were excluded by the analysis (*n* = 12). In the multivariate analysis, efficacy was lower in the presence of longer HIV disease duration (*P* < 0.0001) and of baseline HIV-RNA >100 000 copies/ml (*P* = 0.015) as showed in Table 3.

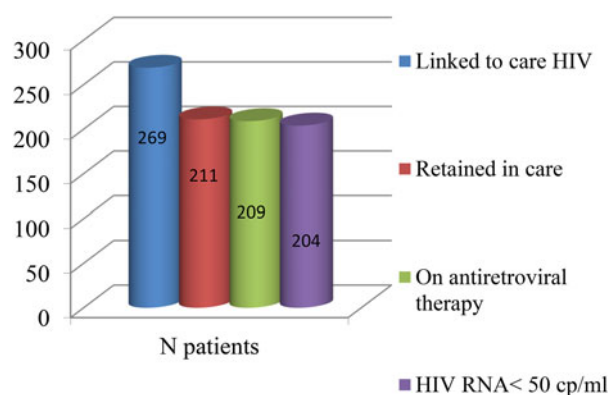


Fig. 1. The cascade of continuum of care.

Table 1. Demographics data and difference between retained and not retained in care patients

	Total (n = 269) n (%)	Retained in care (n = 211) n (%)	Not retained in care (n = 58) n (%)	P-value
Gender				0.238
Males	197 (73%)	151 (72%)	46 (79%)	
Females	72 (27%)	60 (28%)	12 (21%)	
Nationality				0.006
Italian	219 (81%)	179 (85%)	40 (69%)	
Foreign	50 (19%)	32 (15%)	18 (31%)	
HCV				0.765
Yes	32 (13%)	26 (14%)	6 (12%)	
No	209 (87%)	165 (86%)	44 (88%)	
HBV				0.029
Yes	7 (3%)	3 (2%)	4 (9%)	
No	218 (97%)	178 (98%)	40 (91%)	
Last CD4+ cell count				<0.0001
<200 N/mm ³	21 (8%)	9 (4%)	12 (21%)	
>200 N/mm ³	248 (92%)	202 (96%)	46 (79%)	
Basal CD4				0.03
<200 N/mm ³	111 (41%)	80 (38%)	31 (53%)	
>200 N/mm ³	158 (59%)	131 (62%)	27 (47%)	
Last HIV-RNA				<0.0001
<50 copies/ml	239 (89%)	203 (96%)	36 (62%)	
>50 copies/ml	30 (11%)	8 (4%)	22 (38%)	
Basal HIV-RNA				0.987
<100 000 copies/ml	176 (65%)	138 (65%)	38 (66%)	
>100 000 copies/ml	93 (35%)	73 (35%)	20 (34%)	
Cart				<0.0001
Yes	257 (95%)	209 (99%)	48 (83%)	
No	12 (5%)	2 (1%)	10 (17%)	
Median age (1st–3rd quartile)	46.1 (38.6–54.1)	46.4 (39.2–54.0)	44.3 (36.8–56.4)	0.104
Median years of disease duration (1st–3rd quartile)	5.1 (3.5–6.7)	4.8 (3.3–6.7)	5.8 (3.9–6.9)	0.06

cART, combined antiretroviral treatment.

Conclusions

The rate of retention in care of HIV-infected patients referring to the Ospedale Policlinico San Martino in Genoa is slightly lower compared with national estimation (78.5% vs. 85%); this is probably attributable to the fact that among the non-caregivers were also included the subjects transferred to other clinical centres within or outside the region.

However, the rate of virological success (rate of patients with HIV-RNA <50 copies/ml on the total of HIV diagnosed patients) was sharply higher (75.8% vs. 58%) [8]. On the whole, our data, as all Italian ones, resulted superior to estimation in the United States and several other developed countries [7].

In the analysis of predictors associated with failed retention in care, migrant patients were more frequently lost to follow-up

compared with Italian subjects. This finding is in agreement with different studies, supporting the concept that HIV-infected migrant subjects are more vulnerable patients due to linguistic, socio-cultural and educational barriers, as well as due to limited knowledge and information about HIV infection and its prevention [19]; they access later to treatment, with consequent higher rate of late HIV presentation [20]. Furthermore, foreign HIV-infected patients more frequently exhibit poor adherence to the prescribed care [21, 22] requiring proactive therapeutic simplifications [23]. In 2012, published data from Swiss Cohort demonstrated that there was a greater risk of failed maintenance in care among migrant patients with a rate of 8.10/100 person-years for sub-Saharan African males with HIV infection (adjusted risk ratio 2.82, $P < 0.0001$) [24]. Similarly to migrant patients, subjects diagnosed with more advanced disease, particularly with

Table 2. Predictors of failed retention in care

	HR (95% CI) univariate	P-value	HR (95% CI) multivariate	P-value
Gender (male)	1.5 (0.8–2.9)	0.191		
Nationality (Italian)	0.4 (0.2–0.7)	0.002	0.5 (0.2–1.0)	0.048
HCV	0.6 (0.3–1.5)	0.325		
HBV	3.4 (1.2–9.5)	0.02		
Last CD4 <200/mm ³	5.7 (3.0–10.8)	<0.0001	4.2 (1.8–9.6)	0.001
Basal CD4 <200/mm ³	1.7 (1.0–2.8)	0.05		
Last HIV-RNA <50 cp/ml	0.1 (0.1–0.2)	<0.0001		
Basal HIV-RNA <100 000 cp/ml	1.0 (0.6–1.7)	0.98		
Therapy (yes)	0.1 (0.04–0.2)	<0.0001	0.1 (0.04–0.4)	0.0004
Age	1.0 (1.0–1.0)	0.735		
Disease duration (years)	0.8 (0.7–1.0)	0.05		

CD4+ cell count <200/mm³ (*advanced naives*) [25], were more likely to be lost to follow-up. In our analysis, this result was due to died subjects included in the not retained in care group: notably, the mortality associated with HIV infection is related to

the degree of immunosuppression [26]; the risk of developing an AIDS-defining condition increases exponentially with the fall of CD4+, particularly below the 200/mm³ threshold [27]. This hypothesis was supported by the trend shown by the Kaplan–Meier curve (Fig. 4) where the scissors expanded immediately, demonstrating that, for the group of patients with low CD4+ cell count, failed retention in care suddenly occurred. Another predictor of high retention in care was the prescription of cART, thus supporting the now-assimilated concepts of ‘*test and treat*’ and of ‘*Therapy as Prevention*’. START and Temprano studies [28, 29] indicated that cART was associated with a clinical benefit on progression to AIDS or death even in subjects with CD4+ >500 cells/mm³. Moreover, cART prescription played a role in the reduction of HIV transmission, in the containment of the epidemic [30] and, on the basis of our findings, was protective against the loss to follow-up. Regarding the analysis of cART efficacy predictors, it emerged that longer duration of disease was associated with failed virological suppression. This was probably justified by the fact that patients who have an older infection, more often have changed the therapeutic regimen over the years, resulting in a greater pill burden and in worse adherence.

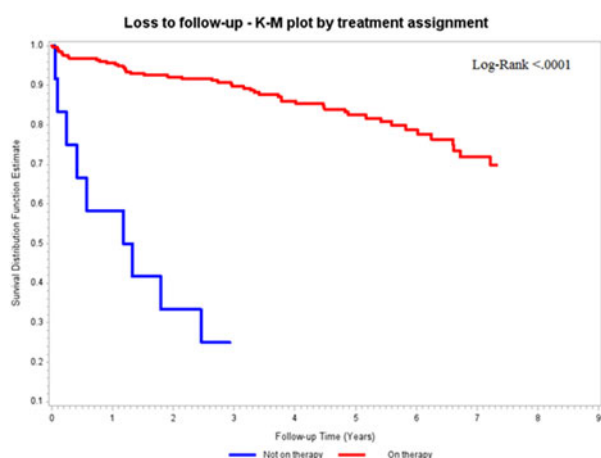
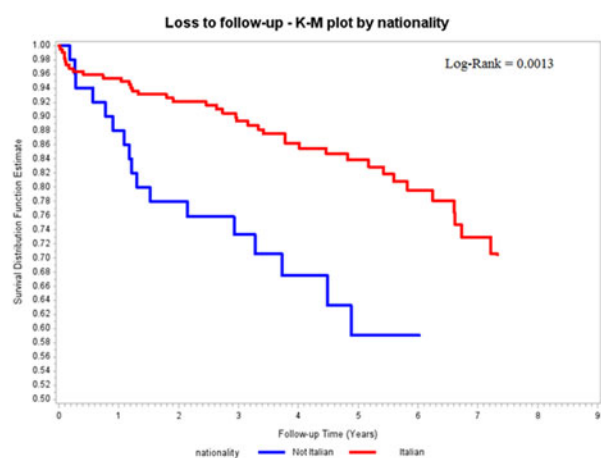
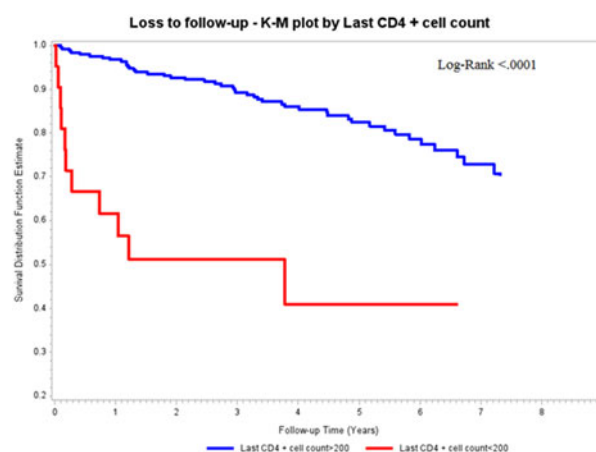
**Fig. 2.** Kaplan–Meier estimates of failed retention in care according to cART prescription.**Fig. 3.** Kaplan–Meier estimates of failed retention in care according to nationality.**Fig. 4.** Kaplan–Meier estimates of failed retention in care according to lymphocyte T CD4+ cell count at last observation.

Table 3. Predictors of failed cART efficacy

	HR (95% CI) univariate	P-value	HR (95% CI) multivariate	P-value
Gender (male)	1.1 (0.8–1.5)	0.469		
Nationality (Italian)	0.9 (0.7–1.3)	0.688		
HCV	0.6 (0.4–0.8)	0.006		
HBV	0.6 (0.2–1.6)	0.308		
Last CD4+ cell count <200 N/mm ³	1.1 (0.6–2.0)	0.155		
Basal CD4 <200 N/mm ³	0.7 (0.6–0.9)	0.016		
Basal HIV-RNA <100 000 copies/ml	1.5 (1.1–1.9)	0.004	1.4 (1.1–2.0)	0.015
Loss to follow-up	1.4 (1.0–2.1)	0.05		
Age	1.0 (1.0–1.0)	0.09		
Disease duration (years)	0.4 (0.3–0.4)	<0.0001	0.4 (0.3–0.4)	<0.0001

A correlation between failed cART efficacy and higher HIV-RNA load at baseline was observed: in the literature is well described that pre-treatment HIV-RNA >100 000 copies/ml is associated with an higher risk of clinical progression and poor response to treatment [31], suggesting that the choice of first-line regimen in the presence of high baseline viral load should be directed towards the use of more potent drugs [32]. In conclusion, our results, in agreement with national ones, are still far from the target of 90-90-90 identified by UNAIDS in 2014, in which it is supposed that diagnosing 90% of HIV-infected patients, treating 90% of them and obtaining 90% of virological suppression by 2020 will result in a reduction of 70–80% of new infections and deaths by 2030 [33, 34]. However, identifying categories of patients at greater risk of not being retained in care, such as migrants and advance naïve patients, and intensifying test and treat strategies could facilitate the achievement of the UNAIDS goal [35].

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