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Risk of clinical progression among patients re-entering in care after being lost

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Background

To fully benefit from antiretroviral therapy (ART), HIV infected individuals must be aware of their infection, link to and consistently engage in care, and receive and adhere to HIV treatment. Retention in HIV care is a critical step in this process, it is associated with improved survival, decreases HIV-related complications, and reduces HIV transmission to others. Also, retention in care may reduce aggregate healthcare costs by minimizing acute health service utilization.
In the context of HIV management as a chronic disease, evaluating the dynamic nature of retention in care over the longer term is of the utmost importance. Retention is a dynamic process and the treatment cascade is not unidirectional since a non negligible proportion of patients with HIV may re-engage in care after being lost at different steps of the cascade of care.
Identifying those most at risk for loss to care and a the clinical consequences of gaps in care is needed.

Objectives

We therefore studied those lost-to-care (LTC), and those who re-engage care (REC) over a 17-year period in the ICONA cohort.
The aim was to address several scientific questions:
1. What were the rates of lost-to-care?
2. What factors predicted lost-to-care and re-engagements?
3. Which is the risk of clinical progression of patients re-engaging in care?

Methods

Study population

HIV-1-infected patients from the Icona Foundation Study enrolled during the period 1997-2014.
Patients were considered lost-to-care (LTC) if they had no clinical visit for at least 12 months; a patient was considered re-engaging care (REC) if, after being lost-to-care, he/she had a clinical visit. Patients that became incarcerated or institutionalized or transferred out to other clinical center were not considered in this analysis, since we supposed that they were still be receiving care.

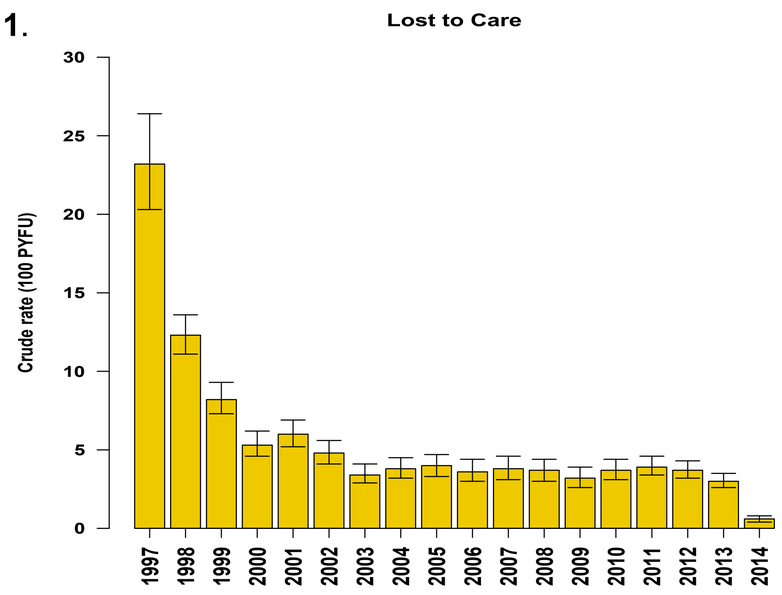
Statistical Methods

The incidence rate of LTC by study year was calculated as the number of patients LTC divided by PYFU and expressed as rate per 100 PYFU, with 95% confidence intervals (CI).
Since our primary interest was identifying patients with inconsistent engagement with longitudinal HIV care, we focused our analysis on characterizing patients who were lost-to-care, and contextualizing the factors (socio-demographic or clinical) that may inform those loss. Thus, a Poisson regression analysis was used to examine socio-demographic and clinical factors associated with the risk of being lost-to-care. Socio-demographic covariates included gender, age, nationality (an immigrant patient was considered a patient born outside Italy), education level, HIV risk category; clinical covariates included presentation with AIDS or low CD4 level (<350), HCV co-infection, CD4 count, HIV-RNA, ART therapy. The same analysis was also conducted for patients re-engaging care with respect to those who did not. Both analyses were adjusted for calendar year.
For those re-entering the cohort after a gap in care (GIC), CD4-cell count and HIVRNA before and after the gap in care were evaluated by paired t-test or by Mc Nemar's test.
A Poisson regression analysis was used to investigate the association between having a gap in care and the risk of clinical progression in terms of clinical events after re-engagement in care, by calculation of unadjusted and adjusted relative rates. To this aim a covariate called gap-in-care (GIC) was created; for those re-entering care, we assumed that GIC=1 for the first 6 months after the re-engagement in care and then GIC=0 again. Patients who were continuously engaged in care had GIC=0.
The clinical events we considered in the analysis were the following: occurrence of AIDS-related opportunistic infection or neoplasm (as defined by the CDC 1993 classification), serious non-AIDS events, (e.g. malignancies, severe infections, end stage kidney disease, end-stage liver disease, cardiovascular events) hospitalization or death.

Results

2,728 (21.5%) out of 12,693 patients were lost to care; the incidence rate of LTC ranged from 23.2 in 1997 to <1 per 100 PYFU in 2014, (p<0.001, test for linear trend, Figure 1). The mean time to the first gap in care, after the retention period, was 3.4 yrs (IQR: 0.96–4.71) (median=2.3). 480 patients (17.6%) re-engaged in care after a mean gap in care of 2.2 yrs (IQR: 0.76–2.78) (median=1.7).
At last visit before being LTC, median CD4-count were 471 cells (IQR: 298–510); 46% had a CD4-count>500; 33% had a viral load <= 400 copies/mL.
In a multivariable Poisson regression model, after adjusting for calendar year, gender, age, nationality, job status, education level, being on ART, current CD4 count, current viral load, current HCV-coinfection, are strongly associated with the risk of being LTC (Table 1). In particular, ART use, absence of HCV coinfection, higher CD4-count, suppressed viral load, older age, a stable working condition and not being IDU, were associated with a significant reduction of the risk of being LTC.

Figure 1.



In a logistic regression model, after adjusting for calendar year, the only protective predictor of re-entering care, was a suppressed viral load at last visit before gap (Table 1).
For those re-entering care, median CD4 were 551+/-322 cells/uL at last visit before being LTC, while after re-entering care this value decreased to 444+/-359 (p<0.001). The proportion of patients having CD4-cell count<200 increased from 10.7% before to 25% after re-entering in care (p<0.001). An increase was observed in median HIVRNA (4,103 before vs 11,030 copies/mL after); also the proportion of patients with>100000 copies/mL doubled after re-entering in care (8.8% vs 15.2%, p=0.028).
Clinical events occurred in 100 patients (21%) within 6 months after re-entering in care: 9 (2%) died, 22 (5%) developed AIDS, 21 (5%) a serious non-AIDS event and 48 (11%) had an hospitalization.
In a multivariable model adjusted for gender, risk factors, late presentation, HCV-coinfection, current CD4-cells count and calendar year, patients with a gap in care had an increased risk of clinical events (RR=2.36, 95%CI: 2.06-2.71, p<0.001).

Table 1. Risk ratio for Lost-to-care and odds ratio Re-engagings-care from fitting Poisson regression model and logistic regression model, respectively; both models were adjusted for calendar year.

		Poisson regression for LTC RR (95% CI)	Logistic regression for REC OR (95% CI)
Gender	F	ref	ref
	M	**1.16 (1.04-1.3)**	1.03 (0.79-1.38)
Risk	IDU	ref	ref
	Homosexual contacts	**0.86 (0.74-0.98)**	0.86 (0.61-1.23)
	Heterosexual	**0.75 (0.66-0.85)**	0.80 (0.58-1.09)
	Other/Unkown	**0.80 (0.65-0.98)**	0.65 (0.34-1.21)
Age	18-35	ref	ref
	36-50	**0.72 (0.65-0.79)**	1.01 (0.80-1.29)
	>50	**0.58 (0.49-0.68)**	1.29 (0.81-2.05)
Job	Unemployed	ref	ref
	Employed	**0.65 (0.58-0.72)**	1.18 (0.89-1.57)
	Self-employed	**0.75 (0.65-0.86)**	1.35 (0.95-1.93)
	Occasional	**0.82 (0.68-0.99)**	1.27 (0.79-2.05)
	Student	0.95 (0.70-1.29)	1.42 (0.49-2.64)
	Retired/Invalid/Housewife	**0.74 (0.61-0.90)**	0.87 (0.51-1.48)
	Other/Unknown	**0.59 (0.39-0.88)**	0.00
Education Level	University	ref	ref
	High School	**0.79 (0.64-0.99)**	2.00 (1.04-3.83)
	Primary/Secondary School	0.88 (0.71-1.09)	1.86 (0.99-3.60)
	Unknown	**1.83 (1.48-2.27)**	0.73 (0.38-1.41)
Nationality	Italian	ref	ref
	Other	**2.12 (1.86-2.42)**	1.05 (0.71-1.54)
Presentation with AIDS or CD4<350	No	ref	ref
	Yes	1.09 (0.97-1.22)	0.75 (0.55-1.01)
	Unknown	0.76 (0.45-1.29)	7.2 (2.19-22.6)
Current CD4-count	<200	ref	ref
	200-349	**0.76 (0.65-0.88)**	1.35 (0.88-2.07)
	350-500	**0.59 (0.50-0.69)**	1.36 (0.87-2.13)
	>500	**0.59 (0.50-0.68)**	1.41 (0.91-2.18)
Current HIV-RNA	>=400	ref	ref
	<400	**0.59 (0.53-0.66)**	**0.71 (0.54-0.94)**
HCV coinfection	No	ref	ref
	Yes	**1.20 (1.03-1.40)**	1.1 (0.72-1.63)
	Unknown	**0.88 (0.78-0.98)**	1.27 (0.92-1.76)
Currently on ART	No	ref	ref
	Yes	**0.49 (0.44-0.55)**	0.91 (0.71-1.17)

Conclusions

Among patients in ICONA cohort, gaps in care are associated with lower socioeconomic status and being born abroad and have become progressively less common during time.
Patients re-entering care after a gap of at least one year have an increased risk of presenting with a clinical event and viro-immunological deterioration and an increased potential for viral transmission linked to the increase in HIV viral load.
HIV clinical cohorts data may contribute to the monitoring of HIV continuum of care at national level. Nonetheless a series of possible limitations must be considered. In particular in our analysis we have assumed that patients were not receiving HIV care during gaps. However we have no information on the possibility that a patients attended clinical centers not belonging to the ICONA cohort, during the gaps and thus we may have overestimated this phenomenon. Further, we might assume that symptomatic patients have a higher probability of re-entering in care, and this may lead to an over estimation of the risk of clinical events associated with gap in care.

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