

Life Expectancy in the Immune Recovery Era: The Evolving Scenario of the HIV Epidemic in Northern Italy

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Introduction: National cohort and intercohort studies have been set to describe the differences of life expectancy (LE) of HIV-infected individuals.

Objective: The aim of this study was to assess the impact of immune recovery (IR) on LE of patients with HIV undergoing combination antiretroviral therapy.

Methods: In this retrospective observational study, outcome measure was LE of patients with HIV compared with LE of northern Italian population. Group categorizations were as follows: patients with no immune recovery (nIR), patients with IR, patients who are immune maintained, and pre-highly active antiretroviral therapy (HAART) and post-HAART. Abridged life tables were constructed from age-specific mortality rates (per 1000 person years) to estimate LE from the age of 20–55 years.

Results: A total of 9671 patients, 71% men, were included. After 2005, we assisted to a rapid increase in the overall rate of patients attaining IR in the community coupled with a progressive decrease of AIDS death, but not of non-AIDS deaths. In a 40-year-old patient, LE was 38.10 years [standard error (SE) = 2.60], 30.08 years (SE = 0.98), and 22.9 (SE = 0.69) in the IR, post-HAART group and nIR, respectively, compared with 41.38 years of the general Italian population. An approximately 5-year gap in LE was observed in IR patients.

Discussion: We describe IR at a “community” level, related to calendar year and apparent 10 years after HAART introduction. HAART community IR is significantly influencing LE and is associated with the changing clinical picture of HIV disease. An increasing gradient of LE exists between nIR, post-HAART, and IR groups, with the latter, above the age of 40 years only, reaching LE of general population.

Key Words: life expectancy, immune recovery, immune recovery era, HAART era, mortality

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INTRODUCTION

Highly active antiretroviral therapy (HAART) for HIV infection has been a terrific medical success story: clinical AIDS is no longer the inevitable outcome of HIV infection in countries with good access to treatment and a disease that was previously associated with extremely high mortality rates is now generally thought of as a chronic condition.^{1–11}

This evolving scenario signaled a profound change in the epidemiological approach to HIV epidemic. The classification of HIV history in pre- and post-HAART eras, initially introduced to describe the reduction in mortality observed in antiretroviral treated patients, nowadays shows an increase of life expectancy (LE)¹² in people living with HIV.

In recent years, both national cohorts,¹³ and intercohort studies⁸ have described the improvements in LE of HIV positive individuals. However, given the diverse ages at which LE is reported, and the different populations under study (which have variable LEs), it is extremely difficult to compare the results from these studies.

Estimates of LE among adults with HIV infection are not usually quoted from birth, but from an exact age (often 20 or 25 years) in specific subpopulations, such as people experiencing seroconversion, or at the time of AIDS diagnosis, entry into care or HAART initiation. Recently, the Collaboration of Observational HIV Epidemiological Research in Europe group identified the circumstances under which treated HIV-infected individuals would be expected to experience similar mortality rates to those of the general population. More than 80,000 HAART-experienced individuals were included in the study. Death rates among men, but not women, reached those of the matched general population when individuals had attained (and maintained) a CD4 count of >500 cells per cubic millimeter on HAART for at least 3 years.¹⁴

Despite the differences between the studies, it is noteworthy that all studies that have described LE in this population have noted the strong association between increased LE and the immune recovery (IR) induced by HAART.

Immunological improvement has not been defined consistently in the HIV literature, but it is usually dependent on 2 measurements of the CD4 cell count: the individual's

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lowest CD4 count measured before starting HAART (the “nadir” CD4 count, a reflection of where the patient has come from) and the individual’s latest CD4 count on HAART (reflecting the person’s current status); the former is often categorized as above or below 350 cells per cubic millimeter, whereas the latter is more commonly categorized as above or below 500 cells per cubic millimeter.^{15,16}

Our study aimed to estimate LE in people living with HIV receiving HAART compared with that of the general population living in the same country, for example, northern Italy, and to assess the impact of IR, defined as a current CD4 count of ≥ 500 cells per cubic millimeter after HAART initiation among individuals with a CD4 count nadir before HAART of ≤ 350 cells per cubic millimeter on LE.

METHODS

The Italian Collaborative HIV Aging Cohort (ICHAC) is an ongoing network of 4 large reference centers for HIV care (S. Paolo Hospital-Milan-SPID Cohort-, S. Raffaele Hospital-Milan, Policlinico of Modena, National Cancer Institute-Aviano) in Northern Italy sharing epidemiological and health data, with a focus on aging.

A retrospective data set was created that included all HIV-infected patients aged older than 18 years receiving antiretroviral therapy (ART) from June 1985 to June 2011. No immunological exclusion criteria were present. Patient follow-up was right-censored at the time of death, at last visit, or at June 30, 2011.

Immunological and clinical data, including date and cause of death, are routinely collected in electronic database in the participating centers of ICHAC.

We estimated LE for patients with HIV on HAART and compared this with LE for the northern Italian population derived from the Italian National Institute for Statistics.¹⁷

Current CD4 count was defined as the most recent CD4 count available.

The following subgroups were prespecified for the analysis:

- Pre-HAART era patients: patients who started ART before first January 1997 (HAART was not routinely available in Italy before this date) and
- Post-HAART era patients: patients who started ART on or after first January 1997.

Patients were then further categorized as follows:

- Patients with no immune recovery (nIR): patients who started ART in the post-HAART period with a nadir CD4 count of ≤ 350 cells per cubic millimeter who had not attained a confirmed CD4 count of ≥ 500 cells per cubic millimeter by the censoring date. Note that because of the excess mortality rate of patients who had started ART in the pre-HAART era and who did not experience IR, patients starting ART in the pre-HAART era were not considered for inclusion in this subgroup;
- Patients with IR: patients who started ART with a nadir CD4 count of ≤ 350 cells per cubic millimeter and who had

attained a CD4 count of ≥ 500 cells per cubic millimeter by the censoring date; and

- Patients who maintained a reasonable level of immunity (IM): patients who started ART with a nadir CD4 count of > 350 cells per cubic millimeter in either era, who maintained this level over follow-up.

Deaths were categorized as follows:

- AIDS death: those where the recorded underlying cause of death related to an AIDS-defining event and
- Non-AIDS death: those where the recorded underlying cause of death not related to an AIDS-defining event.

All classification categories were built at the end of the observation period.

Statistical Methods

Abridged life tables were constructed from age-specific mortality rates (per 1000 person years), computed in the relevant category of patients, and grouped in 5-year age groups from age 20–55 years. These tables describe the mortality of a hypothetical group of individuals throughout their lifetime. LE at any exact age is the average number of years of life remaining for persons who have attained that age. LE for each category of patients was compared with the LE of population from northern Italy available at <http://www.demo.istat.it/unitav2012/index.html?lingua=eng>.

Standard errors (SEs) for age-specific mortality rates and LEs, as well as statistical tests, were computed as described in Chiang.¹⁸ Initiation of ART was the start of follow-up for all groups. To avoid immortal time bias, the baseline for the estimation of mortality rates, and therefore of LEs, for the IR group was set at the IR time.¹⁹

Mortality rates for those aged 55 years and older could not be meaningfully estimated because of the small number of patients in this age group. For this reason, the rate of death of those aged 55 years and older was adjusted by using the ratio of the mortality rate in each category to the mortality rate of the northern Italian population. We assumed that the rate ratio of those aged 55 years and older was the same as the average rate ratio of the 45–49 and 50–54 year age groups.²⁰

The used rate adjustments were 1.15, 2.74, and 5.60 for IR, post-HAART and nIR patients, respectively. A rate adjustment equal to 1 amounts to assuming that in all groups the mortality rate of patients aged 55 years and older is the same as that of the general population. We investigated the sensitivity of estimates of LE to the adjustment used by setting the adjustment equal to 1 and verified that all significant differences reported below remained statistically significant also under this assumption.

Furthermore, to improve the statistical efficiency of the analysis, male and female patients were analysed jointly and their estimated LE was compared with the weighted average of the male and female LEs of the northern Italian population. The weights used were set to 0.7515 and 0.2485, the proportions of men and women, respectively, starting HAART in the post-HAART era.

The Kaplan–Meier method was used to estimate survival probabilities; comparisons between survival curves were performed using the log-rank test. To compare survival of the IR group with other groups, we used time-dependent cox proportional hazard models to account for immortal time bias. The 2-sided χ^2 test was used for categorical variables, and the Mann–Whitney test for continuous variables.

To construct the figure which shows proportion of patients reaching IR and AIDS and non-AIDS mortality rate (for 1000 person years), from 1999 to 2010 (Fig. 2) we took the following approach: for each year of interest, we considered a window that was centered on June 30th in that year (eg, for 2004, we considered the window period from first July 2003 to June 30, 2005); all values were then estimated with respect to that window period. The percentage of patients with IR was calculated as the proportion of IR patients among the average number of patients under care during the window period, as reported on the right-hand *y* axis. The death rates from AIDS and non-AIDS causes for the 2-year window period are reported on the left-hand *y* axis. As it may take several years for IR to occur after initiation of HAART, the calendar year for this figure is set at 1999.

The project received approval from the institutional ethics review committee.

Analyses were performed using the statistical software R version 2.14.0 (R Development Core Team, 2011).²¹

RESULTS

A total of 9671 patients, 73.5% men, were included. Reported mode of HIV acquisition was intravenous drug use (IVDU) in 26.4%, sex between men (men who have sex with men) in 47.1%, and sex between men and women in 26.4%. Table 1 shows the characteristics of patients in each group at the time of starting ART.

A total of 2736 (28.3%) patients initiated ART in the pre-HAART era, and 6935 (71.7%) initiated ART in the post-HAART era. Pre- and post-HAART patients differed in terms of gender, age, nadir, and current CD4 count. In particular, those initiating ART in the post-HAART era were generally younger, more likely to be men, and had both higher nadir and higher current CD4 counts.

Among the pre- and post-HAART groups, 1047 (38.1%) and 2556 (36.6%) patients, respectively, experienced IR ($P = 0.18$). In total, 2805 (29.0%), 3603 (37.3%), and 1625 (16.8%) patients met the criteria for nIR, IR, and IM, respectively, with 1638 (16.6%) patients remaining unclassifiable per protocol definition.

Compared with the nIR group, the IR group demonstrated a lower rate of all-cause and AIDS mortality, had a different age structure, was less likely to be men and to have a Center for Disease Control stage C event. The IR group had a higher median nadir CD4 count, and, as expected, a higher current CD4 count. In contrast, compared with the IM group, the IR group demonstrated a significantly higher rate of all-cause mortality, a different age structure, was less likely to be men and more likely to have a Center for Disease Control stage C event and a lower nadir CD4 count. Interestingly, the IR and IM groups did not differ significantly in terms of their current CD4 count.

The median time with a CD4 count of >500 cells per cubic millimeter was 3.02 years [interquartile range (IQR) = 4.67, mean = 4.19 years, SD = 5.34] in the pre-HAART group and 2.47 years (IQR = 3.82, mean = 3.21 years, SD = 4.23) in the post-HAART group. The median time with a CD4 count of >500 cells per cubic millimeter was 3.09 years (IQR = 3.01, mean = 3.94 years, SD = 4.25) in the IR group.

Deaths

Over a median follow-up period of 8.86 years, 943 patients died either of an AIDS ($n = 455$, 48.3%) or non-AIDS ($n = 488$, 51.7%) cause. There were 389 deaths (14.2% of patients in the group) in the pre-HAART group and 554 (8%) in the post-HAART group. In terms of immune response, there were 409 (14.6%) deaths in the nIR group, 126 (3.5%) in the IR group, and 63 (4.9%) in the IM group. Deaths from AIDS causes represented 36.5% of the deaths occurring in the IR group, 53.5% of the deaths in the nIR group, and 12.70% of the deaths in the IM group.

The overall mortality rate per 1000 person years was 7.55 (SE = 0.38) in the pre-HAART group and 7.13 (SE = 0.30) in the post-HAART group ($P = 0.40$). Mortality rates were 13.78 (SE = 0.68), 6.38 (SE = 0.66), and 3.25 (SE = 0.41) in the nIR, IR, and IM groups, respectively (Tables 1 and 2, for the P values of mortality rate comparisons).

Survival

Figure 1 shows the estimated survival probability of the cohort according to the HAART era (panel A) and IR group (panel B). As expected, survival probabilities were significantly higher in the post- versus pre-HAART group ($P < 0.001$) and in the IR versus nIR group ($P < 0.001$).

IR Population Analyses

Table 2 shows the characteristics of IR patients who started therapy in the pre- or post-HAART eras. Significant differences between the patient groups were found for gender, age group, and the nadir CD4 count, reflecting demographic changes between patient groups over time.

The estimated survival probabilities reached borderline significance between IR patients who started HAART in the pre- versus post-HAART period ($P = 0.051$) nor between men and women ($P = 0.81$).

Figure 2 explores the association between IR and mortality; we considered the prevalence of IR patients, and the rate of AIDS/non-AIDS deaths according to calendar year from 1999 to 2010. There was a rapid increase in the number of IR patients after 2005, which was coupled with a progressive decrease in the rate of deaths from AIDS, but not from non-AIDS causes. There was a similar increase in both IR and non-AIDS deaths in the previous year of observation.

LE

Figure 3A shows a comparison of the LE of the Italian population with LE of the IR, nIR, and post-HAART patient groups; Figure 3B shows the difference in the expected

TABLE 1. Characteristics of Patients at the End of Follow-up, Stratified by Category

	Pre-HAART	Post-HAART	<i>P</i> Between Pre- and Post-HAART	nIR*†	IR‡	<i>P</i> Between nIR and IR	IM§	<i>P</i> Between IM and IR
Average months of observation	180.11	81.40		70.46	129.75		100.28	
No. patients at follow-up (% of total population)	2736 (28.3)	6935 (71.7)		2805 (29.0)	3603 (37.3)		1625 (16.8)	
Age strata percentage								
<30 yrs	1.0	4.0	<0.001	3.9	2.6	<0.01	4.1	<0.001
30–39 yrs	6.7	21.6		21.3	15.9		22.3	
40–49 yrs	55.3	46.7		45.2	51.5		45.8	
50–59 yrs	28.1	19.3		20.0	22.3		19.0	
≥60 yrs	9.0	8.4		9.6	7.7		8.7	
Men: n, % (SE of %)	1895: 69.3 (0.88)	5184: 75.1 (0.52)	<0.001	2103: 75.0 (0.82)	2531: 70.3 (0.76)	<0.01	1272: 78.3 (1.02)	<0.001
CDC = C: n, % (SE of %)	984: 36.0 (0.92)	2459: 35.5 (0.57)	0.65	1189: 42.4 (0.93)	1193: 33.1 (0.78)	<0.001	293: 18.0 (0.95)	<0.001
CD4 cell count: median (Q1–Q3)	485.0 (280–678)	528.0 (344.7–711)	<0.001	317.0 (180–411)	671.4 (581–818)	<0.01	700.0 (551–904)	0.22
CD4 nadir: median (Q1–Q3)	152.0 (54–260)	216.0 (97.9–319)	<0.001	135.0 (54–226)	200.0 (99–272)	<0.01	442 (387.4–542)	<0.001
No. deaths	389	554		409	126		63	
Death for AIDS: n, % among deaths (SE of %)	180: 46.3 (2.53)	275: 49.6 (2.12)	0.34	219: 53.5 (1.85)	36.5 (4.29)	<0.001	8: 12.7 (4.19)	<0.01
Mortality rates per 1000 person-years (SE)	7.55 (0.38)	7.13 (0.30)	0.40	13.78 (0.68)	6.38 (0.66)	<0.001	3.25 (0.41)	<0.01
20–29	0.21 (0.15)	2.17 (0.41)		4.56 (0.93)	0 (NA)			
30–39	5.93 (0.54)	5.76 (0.43)		10.85 (0.96)	7.04 (1.32)			
40–49	11.99 (0.87)	9.62 (0.63)		18.89 (1.45)	6.72 (1.0)			
50–59	11.86 (1.67)	10.91 (1.26)		23.18 (3.0)	4.38 (1.46)			

* nIR group does not include pre-HAART patients.

† nIR, patients with no immune recovery.

‡ IR, patients with immune recovery.

§ IM, patients who maintained a reasonable level of immunity.

number of life years left between the general Italian population and the HIV patient groups.

LE in a 25-year-old patient was 50.59 years (SE = 2.64), 42.72 (SE = 0.96), and 34.32 (SE = 0.75) in the IR, post-HAART, and nIR groups, respectively. The IR group was the patient group that exhibited LE that was closest to

that seen in the northern Italian general population within the same age category (55.93 years). However, even in this group, LE remained 5 years below that of the general population (*P* = 0.02).

LE in a 40-year-old patient was 38.10 years (SE = 2.60), 30.08 (SE = 0.98), and 22.9 (SE = 0.69) in the IR,

FIGURE 1. Estimated survival probability of the cohort according to HAART era (A) and IR groups (B) using Kaplan–Meier curves (nIR group does not include pre-HAART patients).

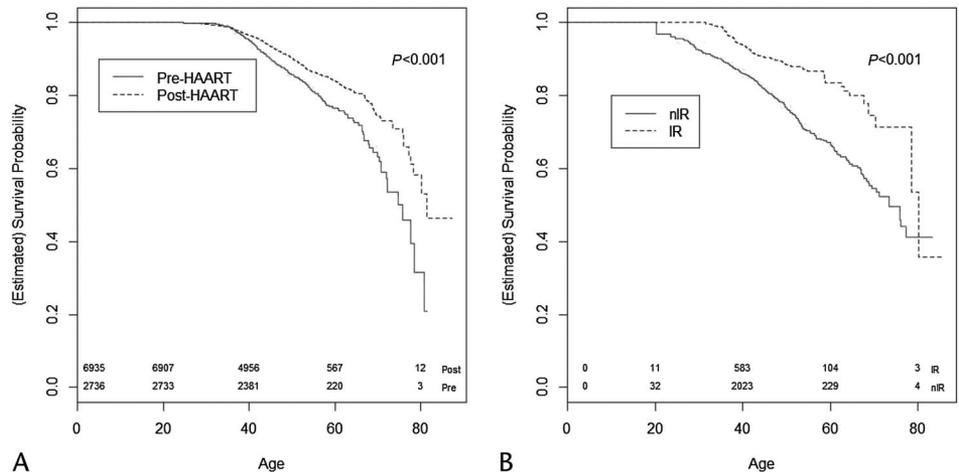


TABLE 2. IR Patients at the End of Follow-up, Stratified by HAART Era

	IR		P
	Pre-HAART	Post-HAART	
No. patients at follow-up (% of total population)	1047 (38.1)	2556 (36.6)	
Average months of observation	196.87	94.87	
Age strata percentage			
<30 yrs	0.5	3.5	<0.001
30–39 yrs	5.8	19.9	
40–49 yrs	57.5	49.1	
50–59 yrs	28.0	20.0	
≥60 yrs	8.1	7.5	
Men: n, % (SE of %)	674, 64.4 (1.48)	1856, 72.6 (0.89)	<0.001
CDC = C: n, % (SE of %)	339, 32.4 (1.45)	853, 33.4 (0.94)	0.56
CD4 cell count: median (Q1–Q3)	668.0 (578–816)	672.0 (581.8–819)	0.64
CD4 nadir: median (Q1–Q3)	175.0 (69–250)	209.0 (108–280)	<0.001
No. deaths	52	74	
Death for AIDS: n, % among deaths (SE of %)	17, 32.7 (6.51)	29, 39.2 (5.67)	0.58
Mortality rates per 1000 person years (SE)	8.34 (1.35)	5.47 (0.75)	0.07

post-HAART, and nIR groups, respectively. As with younger patients, the IR group was the patient group that exhibited LE that was closest to that in the general population within the same age category (41.38 years). In this case, LE is not significantly different from the corresponding value of the general population.

DISCUSSION

This is the first article to report LE in HAART-treated individuals with HIV in Italy and a comparison of LE with that seen in the general northern Italian population.

The improvement in LE may be explained by several factors: an upward trend in LE in the general population, changing demographics and risk factors of the HIV population, a decline in the transmission of drug-resistant virus strains, access to modern HAART regimens,²² and a good immune response of patients on HAART. These factors are, however, unlikely to contribute to improvements in LE homogeneously in different epidemiological settings. Therefore, information regarding LE in a given geographical area or country provides important epidemiological information; extrapolation of this information from large multinational intercohort studies is sometimes difficult.

It is noteworthy that the ICHAC cohort includes patients from 4 large reference centers that have a homogeneous and standardized practice in HIV management. In Italy, HAART is provided for free to any patients with HIV, and in the time frame of this study any HAART brought to the market was contemporary available in all the centers.

Notably no difference in proportion of patients experiencing IR was shown in the pre-and post-HAART groups suggesting that this immunological phenomenon is driven by a complex interplay of drugs, virus, and host factors.

It is known that Italian patients with HIV generally exhibit a higher level of risk behaviors (smoking and IVDU) and comorbidities (hepatitis C or B) than patients living in northern European countries or in the United States, and may experience a different pattern of emerging morbidities (eg, cardiovascular diseases). This may explain any differences between the findings from our study and those from other countries. In particular, Lohse et al included 3990 HIV-positive persons, treated and untreated, receiving care in Denmark and reported the LE of a 25-year-old HIV-positive person entering care. LE increased from 8 years in 1995–1996 to 23 years in 1997–1999 and 33 years in 2000–2005, but was still shorter than LE of HIV-negative control (aged 51 years).¹³ We therefore believe that the results obtained from our study provide important complementary information to the results recently published by other intercohort studies.

May et al were the first to focus the attention on CD4 >200 as a determinant of LE. In 17,661, United Kingdom HIV-infected patients LE at the exact age of 20 years increased from 30.0 to 45.8 years between 1996–99 and

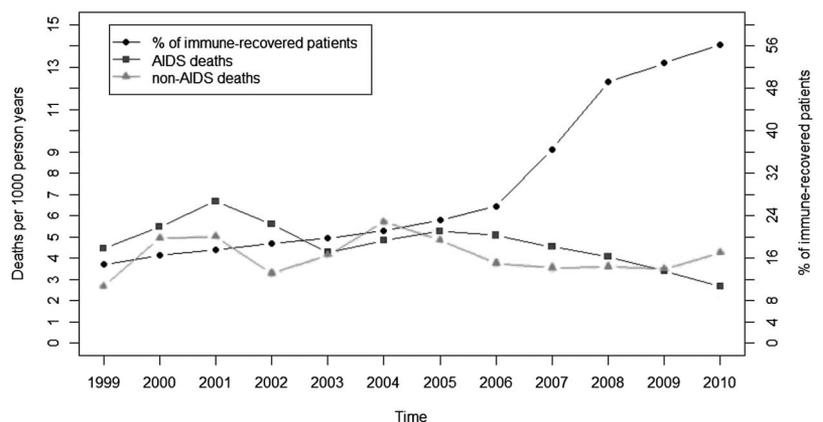
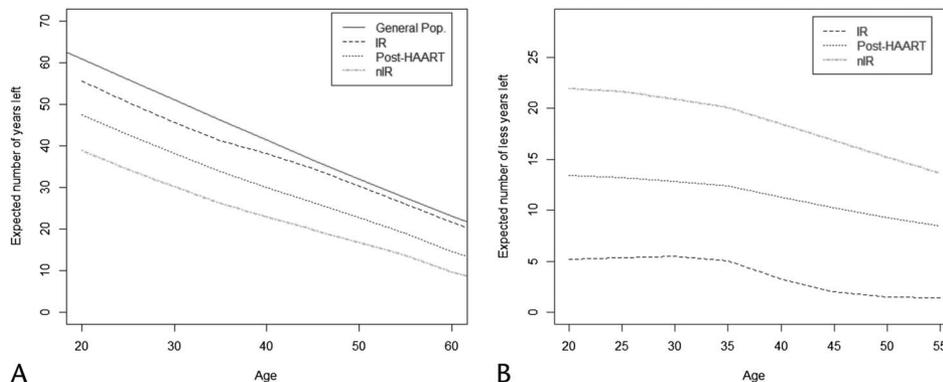


FIGURE 2. Proportion of patients reaching IR and AIDS and non-AIDS mortality rate (for 1000 person years), from 1999 to 2010.

FIGURE 3. Comparison of LE of the Italian population (Pop.) with LE of IR, nIR, and post-HAART patients group (A) and difference of expected numbers of less years left between Italian population and HIV patient groups (B). nIR group does not include pre-HAART patients.



2006–08. In this study, inclusion criteria was starting combination antiretroviral therapy with CD4 <350/ μ L, whereas exclusion criteria was injecting drug use. In this cohort LE was still about 13 years less than that of UK general population. A higher LE was observed in patients starting combination antiretroviral therapy with CD4 >200 and in women.²⁰

In our study, we bring forwards this idea concentrating in the IR phenomenon. We focused our analyses on a population of HAART-treated patients who had or had not experienced IR on treatment. Although categorization of IR is arbitrary, it comprises 2 immunological determinants: a measure of the persons' most advanced immunodeficiency and their current status. In future years, this categorization may become obsolete, if treatment guidelines move toward recommending initiation of ART at higher CD4 counts,²³ or even to all HIV-infected individuals regardless of their CD4 count.²⁴ However, under current clinical practice, this categorization remains clinically relevant, given the high number of HIV-infected people who are unaware of their HIV status and still represents the majority of individuals who will experience IR after initiation of HAART.

Although a CD4 increase from a low nadir does not fully guarantee restoration of health, this remains a good surrogate marker for mortality, and as described in Table 1, is a stronger predictor of subsequent mortality than a simple calendar period (pre-/post-HAART) classification.

As shown in Table 1, the mortality rate of the IM group is significantly lower than the mortality rate of the IR group, and seems to confirm current guideline indication on the “when to start” dilemma.²⁵ However, given the relatively small number of deaths in the IM group, we suggest some cautions in the interpretation of this finding.

The strength of our study is the description of IR as a phenomenon strictly related to calendar year, which characterized the changing clinical picture of HIV disease.

Analog to the recent definition of “community viral load,²⁶” we can define “HAART community IR,” the overall rate of patients undergoing HAART attaining IR.

HAART community IR was appreciable few years after HAART introduction (Fig. 2 from 1999) and apparently showed an increase in 2006. From this date, IR prevalence was associated with a significant reduction of AIDS-related death. We therefore suggest that this shifting pattern of HIV disease is better described by the HAART community IR

appreciable from 2006 rather than the start of HAART era in 1996.

As expected, the highest advantage to LE was observed at younger ages (25 years) in nIR groups. The gap of LE between the general population and the IR group, although statistically significant, was not highly significant ($P = 0.02$) and negligible from a clinical perspective.

Contrary to Athena cohort,¹ we were unable to detect any gender difference in survival in the IR group. This cohort is representative of both the epidemiology of HIV infection, and equal opportunities in access to care for men and women with HIV infection in Italy, resulting in similar outcomes.

We observed a parallel increase of IR and non-AIDS mortality in the year 2010. Given that this phenomenon was observed close to the censoring date, this could easily be a chance finding but it may suggest the need for future studies regarding the role of HIV and IR on chronic inflammation, which is known to be an independent risk factor for non-AIDS deaths.

The following limitations should be acknowledged: HIV-infected individuals were matched to the general population exclusively to age but no clinical data except mortality were available for the latter group.

Figure 3 allows us to compare LE in the general population, IR, post-HAART, and nIR groups. Unfortunately, the IM group could not be included in this model because of the small number of individuals in this group, limiting our ability to generate a reliable estimate of LE.

Moreover, IVDU was collected as a risk factor for HIV acquisition but ongoing drug use, and cocaine use in particular, was not reported in some cohorts making it impossible for us to analyze the specific role of ongoing IVDU as a predictor of mortality.

In conclusion, this study shows that within the HIV-infected population the proportion of subjects that has achieved a satisfactory IR has increased over time. As a consequence, a higher proportion of patients approaches LE of the general population.

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