Persistent poor clinical outcomes for AIDS presentation in Italy over the last decade

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on behalf of the Icona Foundation Study Cohort.

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0479

CROI Conference on Retroviruses and Opportunistic Infections

CROI 2020 Boston, March 8–11, 2020

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BACKGROUND:

- Despite the universal access to healthcare services, **advanced HIV presentation** (HIV-infected subjects presenting for care with CD4 count <200 cell/mL or with an AIDS-defining event [ADE])[1] and, particularly, **AIDS presentation are still an issue, even in high-income countries**.
- **Advanced HIV presentation** has been associated with **poor clinical and virologic outcomes** including: higher risk of mortality, particularly over the first year of diagnosis, even with a prompt ART initiation [2,3], reduced chance of viral suppression[4], increased risk of hospitalization and cost of care [5,6] and challenges in ART choice due to the higher risk for ART intolerance/toxicity and the more potential for drug-drug interactions.
- **Limited data on ART strategies, treatment responses and survival in this vulnerable population in more recent years**, after the availability of more effective and tolerable antiretroviral drugs, **are available**.

AIMS:

The aim of the study was to estimate **the impact of advanced presentation, and particularly of AIDS presentation, on mortality, virological failure and treatment discontinuation for toxicity** over the last decade (2009-2019) in a large Italian cohort.

STUDY DESIGN AND METHODS:

- **STUDY DESIGN AND POPULATION**:
  - ✓ **Prospective, observational study** analysing data from Icona Foundation Study Cohort.
  - ✓ All consecutive **HIV-infected ART-naïve patients,** enrolled in ICONA cohort from **January 2009 to December 2019**, who have received **first HIV diagnosis within 3 months prior to the enrolment**, were included in the analysis. Patients without at least 1 follow-up visit after enrolment were excluded.
  - ✓ Icona is a nation-wide cohort including more than 18.000 HIV-infected patients, naïve from ART at the enrollment, who are prospectively followed in 55 Italian centres.
  - ✓ Included patients were divided into three main groups, according to CD4 cell count and clinical presentation at the time of diagnosis:
    1. **AIDS PRESENTERS**: ART-naive patients with an **ADE at or within 3 months from HIV diagnosis,** regardless of CD4 cell count.
    2. **ASYMPTOMATICS CD4 ≤ 200:** ART-naïve patients **without ADE** and **with a CD4 cell count ≤200 cells/mm³** at HIV diagnosis.
    3. **ASYMPTOMATICS CD4 > 200:** ART-naïve patients **without ADE** and **with a CD4 cell count >200 cells/mm³** at HIV diagnosis.
- **DEFINITIONS:**
  - ✓ **Survival:** death due to any cause was considered.
  - ✓ **Virological Failure (VF):** confirmed HIVRNA≥200 cp/mL 6 months after ART start.
  - ✓ **Treatment Discontinuation (TD) due to toxicity:** discontinuation of at least 1 drug of the first antiretroviral regimen due to toxicity/intolerance.
- **STATISTICAL ANALYSIS:**
  - ✓ Baseline (BL) characteristics were compared among the three groups using Chi-square test and non parametric tests, as appropriate.
  - ✓ In the overall population, the **survival probability** was estimated by **Kaplan-Meier analysis** and compared among the groups in both the overall period and separately analyzing two consecutive time periods (2009-2013; 2014-2018).
  - ✓ In the subgroup of patients starting ART the **cumulative probability of VF and TD for toxicity** were estimated by **Kaplan-Meier analysis**
  - ✓ **Marginal regression models** including covariates and random effects from a priori knowledge of causal relations has been used to identify the **independent risks of death** in total population and the **independent risks for the main outcomes (death, VF and TD due to toxicity)** in the subgroup starting ART.
  - ✓ In the subgroup of AIDS presenters the **probabilities for the main outcomes** (survival, VF and TD for toxicity) according to the type of AIDS defining event was estimated by **Kaplan-Meier curves.**

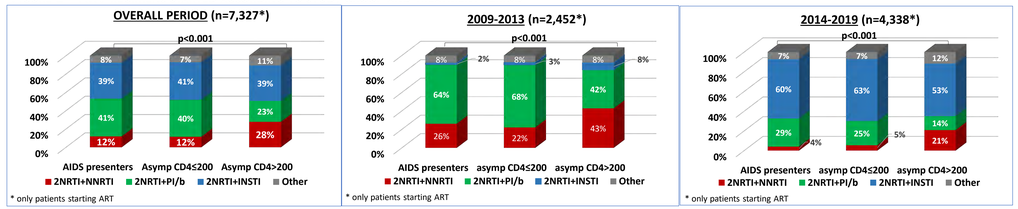
RESULTS:

- Overall, 7,851 patients were included: 1,086 AIDS presenters, 1,780 asymptomatic with CD4 count ≤200 and 4,985 asymptomatic with CD4 count >200.
- AIDS presenters were more likely to be female, older, migrant and heterosexual, other comparisons are shown in Table 1.
- ART was started in 7,327 pts of whom 96%, 97% and 92% in group 1, 2 and 3, respectively [Table 1].
- From 2009 to 2013, patients with advanced HIV presentation were significantly more likely to start PI/b-based regimens compared to asymptomatic CD4>200 (64% and 68% vs 42%,p=0.001). On the contrary, in the following period (2014-2019) INSTIs were the main third-drug started in all groups (60%, 63% and 53% for group 1, 2 and 3, respectively) [Fig 1].

TABLE 1 – BASELINE CHARACTERISTICS

Characteristic	TOTAL POPULATION (N=7,851) AIDS PRESENTERS (n=1,086, 13.8%)	ASYMPT CD4≤200 (n=1,780, 22.7%)	ASYMPT CD4>200 (n=4985, 63.5%)	p-value
Female gender, n (%)	269 (24.8)	366 (20.6)	882 (17.7)	**<0.001**
Age, years, median (IQR)	44 (36 - 53)	42 (34 - 51)	36 (28 - 45)	**<0.001**
Non-Italian Born, n (%)	335 (30.9)	499 (28.0)	1158 (23.2)	**<0.001**
Risk Factor for HIV, n (%)				**<0.001**
-Homosexual contacts	319 (29.4)	588 (33.0)	2,720 (54.6)	
- Heterosexual contacts	599 (55.2)	917 (51.5)	1,702 (34.1)	
-IDU	52 (4.8)	95 (5.3)	218 (4.4)	
HbsAg positive, n (%)	55 (5.1)	64 (3.6)	155 (3.1)	**<0.001**
HCVAb positive, n(%)	48 (4.4)	103 (5.8)	240 (4.8)	**<0.001**
Days from HIV diagnosis to enrolment, median (IQR)	8 (2-19)	12 (3-22)	16 (6-34)	**<0.001**
Calendar years of enrolment, n (%)				**0.009**
-2009-2013	392 (36.1)	639 (35.9)	1624 (32.6)	
- 2014-2018	694 (63.9)	1141 (64.1)	3361 (67.4)	
BL CD4 cells count, cell/mm³, median (IQR)	44 (20 - 116)	93 (41 - 147)	453 (327 - 617)	**<0.001**
BL HIV RNA, n (%)				**<0.001**
- < 100,000 cp/mL	247 (22.7)	562 (31.6)	3,277 (65.7)	
- ≥ 100,000 cp/mL	714(65.8)	1,114 (62.6)	1,422 (28.5)	
- missing	125 (11.5)	104 (5.8)	286 (5.7)	
ART initiation, n (%)	1,041 (95.9)	1,720 (96.7)	4,566 (91.6)	**<0.001**
Days from HIV diagnosis to ART start, median (IQR)	20 (11 -35)	21 (12 - 39)	47 (21 -102)	**<0.001**

FIGURE 1 – ARV REGIMENS STARTED ACCORDING TO STUDY GROUP AND TREATMENT PERIOD



* only patients starting ART

SURVIVAL:

FIGURE 2 – ESTIMATED PROBABILITY OF SURVIVAL IN THE OVERALL PERIOD (1A) AND IN THE TWO CONSECUTIVE TIME-PERIODS (1B,1C)

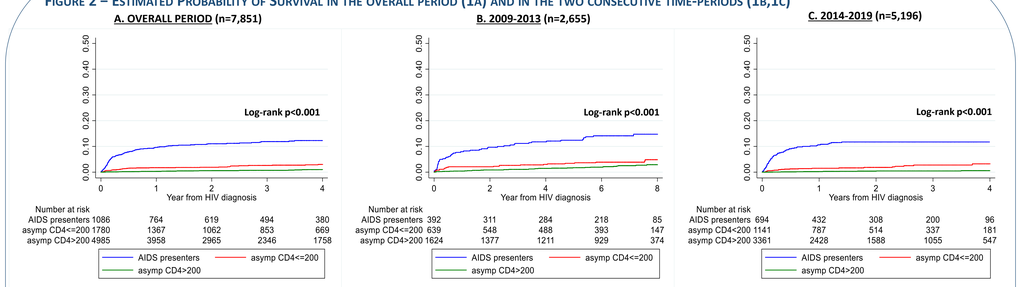
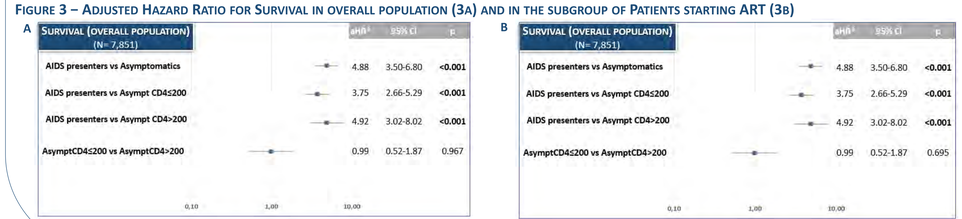


FIGURE 3 – ADJUSTED HAZARD RATIO FOR SURVIVAL IN OVERALL POPULATION (3A) AND IN THE SUBGROUP OF PATIENTS STARTING ART (3B)



* After adjusting for gender, age, nationality, HIV-RNA (time-dependent variable) and CD4 cell count (time-dependent variable)

- Over 26,300 PYFU, 219 (2.8%) patients died. The mortality rate was **34.7, 8.0 and 2.9 per 1000 PYFU** for AIDS presenters, asymptomatic CD4≤200 and asymptomatic CD4>200, respectively. At survival analysis**, AIDS presenters showed the lowest probability of survival among the groups** both in the overall period [Fig 2a] and in the two consecutive time-periods (2009-2013, 2014-2019) [Fig 2b and 2c]. After adjusting for the main confounders, **AIDS presenters confirmed to be a significantly higher risk of death** compared to other naïve patients, regardless of CD4 count[Fig 3a]. This data was confirmed also restricting the analysis to those who started ART [Fig 3b].
- At multivariable analysis, **AIDS presenters were also more likely to experienced VF** compared to **asymptomatic patients with CD4 ≤200 cell/mm³** and **maintained a trend toward a significant higher risk of VF compared to asymptomatic patients with CD4>200cell/mm³** [Fig5].
- On the contrary, after adjusting for confounders, **AIDS presentation was not associated with a greater risk of treatment-limiting toxicities** whereas, among non-AIDS presenters, **more severely immunocompromised patients seems to have higher risk of TD due to toxicity** [Fig7].
- After restricting the analysis to AIDS presenters, **patients presenting to care with either Non Hodgkin lymphoma or cerebral toxoplasmosis as ADE were associated with a higher risk of mortality** [Fig 8a]**.** On the contrary, no differences in the probability of VF or TD for toxicity according to the ADE were found [Fig 8b, 8c].

VIROLOGICAL FAILURE:

FIGURE 4 – ESTIMATED PROBABILITY OF VIROLOGICAL FAILURE

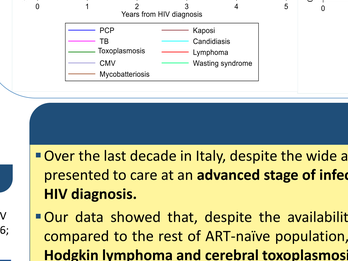
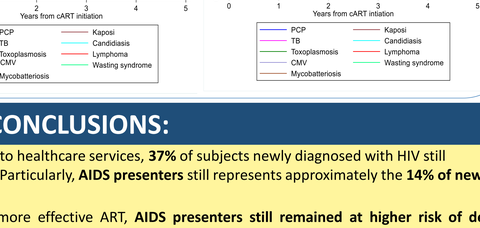


FIGURE 5 – ADJUSTED HAZARD RATIO FOR VIROLOGICAL FAILURE



* Patients with at least one viral load after 6 **months** from ART start.
** After adjusting for age, nationality, education level, antiretroviral regimen started (third durg) and CD4 (time-depenent variable)

TREATMENT DISCONTINUATION FOR TOXICITY:

FIGURE 6 – ESTIMATED PROBABILITY OF TREATMENT DISCONTINUATION FOR TOXICITY

FIGURE 7 – ADJUSTED HAZARD RATIO FOR TREATMENT DISCONTINUATION FOR TOXICITY

* Patients who started ART.
** After adjusting for gender, age, HIV transmission mode, antiretroviral regimen started (third durg) and CD4 (time-depenent variable)

AIDS PRESENTERS:

FIGURE 8 – ESTIMATED PROBABILITY OF SURVIVAL (8A), VIROLOGICAL FAILURE (8B) AND TREATMENT DISCONTINUATION FOR TOXICITY (8C) ACCORDING TO THE ADE

CONCLUSIONS:

- Over the last decade in Italy, despite the wide access to healthcare services, **37%** of subjects newly diagnosed with HIV still presented to care at an **advanced stage of infection.** Particularly, **AIDS presenters** still represents approximately the **14% of new HIV diagnosis.**
- Our data showed that, despite the availability of more effective ART, **AIDS presenters still remained at higher risk of death** compared to the rest of ART-naïve population, **event after starting ART and especially in the first year after HIV diagnosis. Non-Hodgkin lymphoma and cerebral toxoplasmosis** as AIDS defining event seems to be associated to the highest risk of mortality.
- Moreover, **AIDS presentation showed to be associated also to a poor response to ART in terms of virological control**.
- Public health strategies for emerging unknown infections and early treatment access are urgent to constrain the mortality gap of this vulnerable population.

Acknowledgments

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Funding

ICONA Foundation is supported by unrestricted grants from Gilead Sciences, Janssen, MSD and ViiV Healthcare