International Journal of Infectious Diseases 163 (2026) 108200

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

HIV infection among adolescents and young adults in Italy: Epidemiology, viro-immunological and treatment outcomes

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ARTICLE INFO

Article history:
Received 14 September 2025
Revised 5 November 2025
Accepted 7 November 2025

Keywords:
Adolescent and young adults
HIV infection
Antiretroviral therapy
Virological failure
Treatment discontinuation
Loss to follow-up

ABSTRACT

Objectives: No previous study described adolescents and young adults (AYAs) with HIV in Italy. Aims were to investigate the temporal trend of AYAs enrolment in the ICONA cohort over 2014-2023, and to compare their baseline characteristics and antiretroviral therapy (ART) outcomes with adults.
Methods: All subjects enrolled in ICONA, the Italian cohort enrolling HIV-1 positive individuals from ART-naïve, over 2014-2023 were grouped into: AYAs (18-24 years old) and adults (≥25). Study outcomes were: time to first ART start, time to treatment discontinuation (TD) of first-line regimen, cause-specific TD, virologic failure, and loss-to-follow-up (LTFU).
Results: Overall, 9519 participants: 653 AYAs (6.9%) and 8,866 adults (93.1%). Excluding the decline recorded in 2020, the percentage of AYAs enrolled showed a similar trend before- and after-COVID. Compared with adults, AYAs had a milder clinical presentation, a better viro-immunological status, a higher mean change of cluster of differentiation 4 count over 24 months and, after adjusting, a higher risk of TD for patient's choice/adherence-related issues and LTFU.
Conclusions: The less advanced clinical presentation and more robust immune recovery of AYAs, might depend upon more recent HIV infection, better thymic function, and lower immune activation. The higher risk of TD due to patient's choice/adherence-related issues and LTFU among AYAs is a major concern and suggests the need to create ad hoc clinical care pathways.

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https://doi.org/10.1016/j.ijid.2025.108200

Introduction

In Europe, age-specific rates of new HIV diagnoses declined from 2014 to 2020, remained stable between 2020 and 2021, and increased from 2022 across most age groups [1]. Similarly, in Italy, according to the most recent report of the national surveillance system [2], after the overall decrease in the number of new HIV diagnoses observed from 2012 to 2020, a reversal of the trend has been described in the last 3 years, and, in particular, the proportion of elderly people (>50 years) is gradually increasing. Despite this, a part of new diagnoses still occurs among adolescents and young adults (AYAs). According to the Centers for Disease Control and Prevention, adolescents (aged 13-19 years) and young adults (aged 20-24 years) accounted for 20% of the 31,800 HIV diagnoses in the United States in 2022 [3]. In Europe, between 2022 and 2023, the only groups that continued to see an increase in new HIV diagnoses were women aged 15 to 24 years, with a 15.8% increase, and men aged 15 to 19 years, where the rate increased by 20.6% [1] In Italy, about 7% of new HIV diagnoses occurs in people under the age of 25 years [2].

Data from literature suggest that this population has some common characteristics [4–10]: AYAs are less likely to report currently taking antiretroviral therapy (ART) and to being adherent to ART, have a higher rate of loss-to-follow-up (LTFU) and are more likely to have a treatment interruption. Consequently, AYAs as a population could have lower levels of viral suppression compared to older patients. Moreover, most people who acquire HIV during adolescence and young adulthood get it through sexual transmission and AYAs have peculiar lifestyle behaviors, an active sexual life, inconsistent use of condoms, and frequent alcohol or drug use. Finally, high rates of sexually transmitted infections (STIs) among young people may increase the risk of getting or spreading HIV [11]. Consequently, in this population, the overmentioned gaps in HIV care may significantly contribute to disease transmission. These behavioral aspects, together with social and psychological vulnerability, contribute to make HIV infection a real challenge, both for the patient and the treating physician.

Most of the available data come from studies conducted, many of them not so recently, in the United States and Africa, where social determinants and models of access to healthcare services may differ from Europe. Few data are available about this population in Europe, and no studies of AYAs with HIV infection have ever been conducted in Italy.

Herein, we plan to give a real-life picture of AYAs who acquired HIV infection in Italy in the last decade. Specifically, the present study is designed to: (i) investigate the trend over time of AYAs enrolment in the ICONA (Italian Cohort of Naïve to Antiretrovirals) cohort from 2014 to 2023; (ii) evaluate the epidemiological, socio-behavioral, clinical and viro-immunological profiles of AYAs at enrolment compared to the adult population; (iii) describe and compare ART treatment initiation, first-line ART discontinuation, and viro-immunological response in AYAs and adults; and (iv) assess and compare the risk of LTFU of AYAs and adults over the period of observation.

Methods

Study setting and ethical issues

Retrospective analysis of prospectively collected data from the ICONA cohort. The ICONA Foundation cohort is an Italian multicentric observational study, set up in 1997, of HIV-1 positive and antiretroviral-naïve subjects at the time of enrolment, aged ≥18 years. More than 21,500 people with HIV (PWH) were enrolled and prospectively followed in 62 Italian Infectious Diseases centers for adults. PWH enrolled in ICONA are representative of the Italian HIV population [12]. In the present study, all individuals newly enrolled in ICONA from January 2014 to December 2023 were included, after providing a written informed consent, to compare participants aged 18-24 years at enrolment (i.e., AYAs) with subjects aged >24 years (i.e., adults).

See supplementary materials for more details.

Statistical analysis

Demographic and clinical differences at ART initiation between the two groups were assessed using chi-square for categorical variables or non-parametric Kruskal-Wallis test for continuous variables. The proportion of AYA enrolment over total number of PWH included in ICONA per year has been evaluated. Moreover, to evaluate the temporal trends of the AYA proportion and to assess changes related to the COVID-19 pandemic, we performed an interrupted time series analysis (ITSA). The analysis was conducted using annual data from 2014 to 2023, with the year 2020 identified as the change point and comparing the trends in the two periods. Time to first ART regimen initiation from the date of HIV diagnosis was assessed using unadjusted and adjusted Cox regression models, including only subjects with HIV diagnosis after 2015, year of recommendation of universal ART start in Italy, and with at least one follow-up visit after enrolment or known ART initiation. Time to virologic failure (VF: two consecutive HIV-RNA ≥50 copies/ml after 6 months of the first ART regimen) from date of first ART start and time to treatment discontinuation (TD: discontinuation for any reason of at least one drug of the regimen or treatment intensification) were also analyzed using standard survival analysis (Kaplan-Meier curves and log-rank test) and unadjusted and adjusted Cox regression models. Survival analysis and unadjusted and adjusted Cox regression models were also used to assess cause-specific risks of first ART discontinuation: TD due to patient's choice or adherence issues, TD due to toxicity/intolerance (gastrointestinal intolerance, neuropsychiatric, renal, metabolic, and dermatologic adverse events, allergies, other toxicities) and TD for failure (virological, immunological, and/or clinical). For the ART discontinuation endpoints participants' follow-up accrued from the date of first ART start until discontinuation or to the last available clinical visit. For each cause-specific TD endpoint, subjects who discontinued for other reasons were truncated at the date of last clinical follow-up, assuming non-informative censoring. For the VF endpoint, censoring was applied at the date of participants' last available viral load measure. An intention-to-treat approach (which ignore any ART change) was used for the VF analysis.

Furthermore, we assessed time to LTFU through unadjusted and adjusted Cox regression models, considering as endpoint no follow-up visit for more than 12 months or with the last visit before January 2023 and excluding participants who died, or moved to another country or another hospital/center not included in the ICONA cohort network, those incarcerated, or PWH with voluntary withdrawn from the ICONA study within 12 months after the last visit. For this endpoint, we considered only the 16 ICONA centers with an active update of the follow-up visits over the period 2016-2023 with electronic import of laboratory and clinical visits data, to minimize possible bias due to missing data or delay in data reporting and to get a more accurate estimate for the overall rate of loss to care. Follow-up accrued at the date of enrolment until last available follow-up in the cohort. A second definition of definitive LTFU has also been used, considering only the subgroup of LTFU as previously defined that never returned to care.

Finally, immunological response has been investigated as cluster of differentiation 4 (CD4) changes from baseline (ART initiation) to 6 months (±2 months), 12 months (±3 months), and 24 months (±4 months), by means of adjusted linear mixed mod-

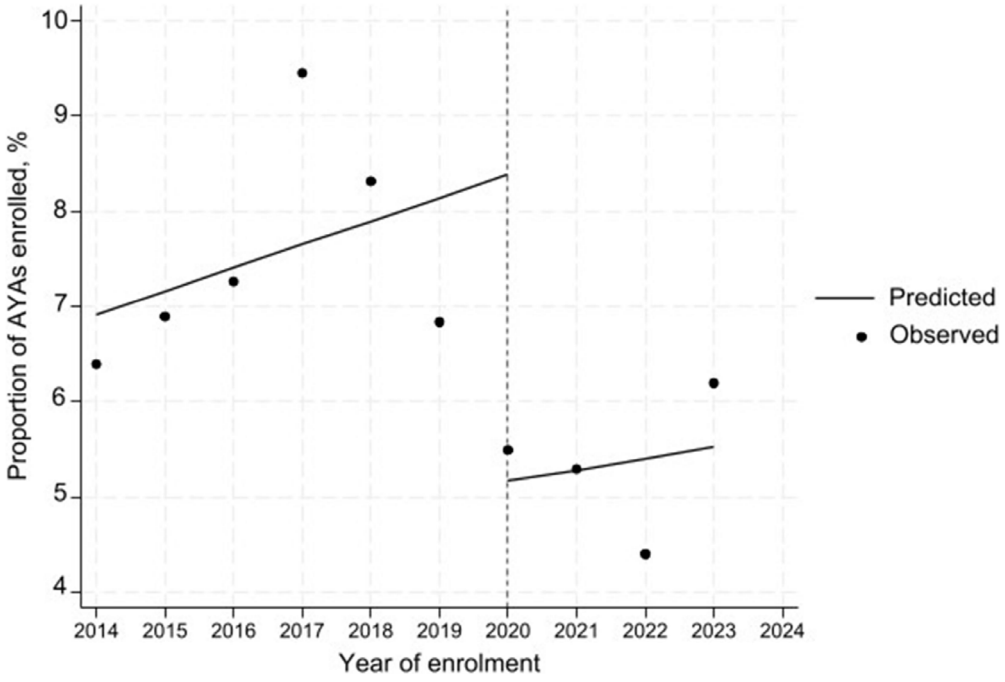

Figure 1. Proportion of AYAs enrolled in the ICONA cohort over the study period, from 2014 to 2023 (% of total enrollment), and predicted trend of AYAs enrollment estimated by interrupted time series analysis. The dashed vertical line marks the start of the post-COVID period (2020-2023).
AYA, adolescents and young adults.

els with random intercept and slopes per patient. Interaction terms (time × age group) were created to assess whether these changes differed significantly over time between AYAs and adults. We further tested whether there was an interaction between the class of the ART regimen on the first-line (integrase strand transfer inhibitors [INSTI] based vs non-INSTI based) and AYAs/adults on the CD4 count recovery on a 3-way interaction (time × age group × INSTI). The equality of all mean changes in the groups was tested by Wald test. All the models have been adjusted for pre-defined factors considered as confounders of the association between the exposure of interest (AYAs/adults) and each separate outcome. All statistical analyses were performed using STATA (v.18.0, StataCorp, USA) and RStudio (v 12.0). All *P*-values presented are two-sided and *P*-value <0.05 indicated conventional statistical significance.

Results

Descriptive analysis

Over the study period, 9519 individuals were included in ICONA: 653 AYAs (6.9%) and 8,866 adults (93.1%). From the beginning of the observation period until 2019, the trend of proportion of AYAs enrolled showed a small increase, although the confidence interval (CI) included zero (2014-2019 coefficient = +0.25%/year; 95% CI −0.42, +0.92; $P = 0.399$). In 2020, a steep drop of approximately 3.2% points was observed compared to the expected value based on the pre-2020 trend (level change coefficient = −3.23%; 95% CI −6.60, +0.15; $P = 0.058$). No evidence for a change was found in the trend after 2020 compared to the previous period (2014-2019) (change 2020/2023 coefficient - 2014/2019 coefficient = −0.13% year; 95% CI −1.15, +0.89; $P = 0.771$) (Figure 1).

In Table 1 socio-demographic, epidemiological, and clinical-therapeutic characteristics of AYAs are reported, as compared with adult participants, at enrolment. Briefly, AYAs were more frequently men-who-have-sex-with-men (MSM) and non-Italian and less frequently injective drug users (IDU). Time elapsed between HIV diagnosis and enrolment in ICONA cohort was similar between the two groups, but the clinical presentation was different: among AYAs, we observed a lower proportion of AIDS-related events and hospitalizations, higher CD4 counts and CD4/CD8 ratios, and lower HIV-RNA levels. A smaller proportion of AYAs had a positive hepatitis C virus (HCV) serostatus. Conversely, no differences were found in terms of acute HIV infection and concomitant diagnosis of Hepatitis B virus co-infection and STIs. The choice of the first ART regimen was similar between the two groups. Finally, the educational and job profiles were found to be different, with a higher percentage of AYAs who attended college and a lower percentage employed, as compared to adults.

Analysis of study outcomes

Antiretroviral therapy initiation

Among 9519 participants, 7453 received an HIV diagnosis as of 2015, when universal access to ART was included in Italian national guidelines, with at least one follow-up visit after enrolment or ART initiation. AYAs had a lower cumulative probability of ART start at 12-months (91.9% [91.9-96.0] for AYAs vs 96.3% [95.8-96.7] than adults, log-rank $P < 0.001$) (Supplemental Figure S1A). The Cox regression model confirms the lower crude risk of starting ART of AYAs than adults (hazard ratio [HR] = 0.83; 95% CI 0.73-0.88; $P < 0.001$), but we observed no evidence for differences between the two groups after adjusting for potential pre-defined confounders (adjusted HR [aHR] 0.98; 95% CI 0.68-1.08; $P = 0.68$) (Table 2).

Virological failure

Out of a total of 6,637 individuals who had at least two viral load assessments more than 6 months after starting ART, we observed 695 (10.5%) VF: 34 (7.9%) among 430 AYAs and 661 (10.6%) among 6,207 adults, defined as two consecutive HIV-RNA >50 copies/mL after 6 months of therapy. At the survival analysis, AYAs and adults had a similar cumulative probability of VF (at 1-year 3.1% [1.8-5.2] for AYAs *vs* 5.1% [4.6-5.7] for adults, log-rank $P = 0.082$) (Supplemental Figure S1B). Similarly, we found no

Table 1
Socio-demographic, epidemiological, and clinical-therapeutic characteristics of individuals enrolled in the ICONA cohort between 2014 and 2023, by age group (adolescents and young adults [AYAs] aged 18-24 years vs adults ≥25 years).

	Adults 8866 (93.1%)	AYAs 653 (6.9%)	Total 9519 (100.0%)	*P*
Age, median [IQR]	41 [33-50]	23 [21–24]	39 [31-49]	**<0.001**
Sex at birth, N (%)				
Female	1,628 (18.4%)	137 (21.0%)	1,765 (18.5%)	0.097
Male	7,238 (81.6%)	516 (79.0%)	7,754 (81.5%)	
Country of birth, N (%)				
Foreign-born	2,333 (26.3%)	277 (42.4%)	2,610 (27.4%)	**<0.001**
Italy-born	6,533 (73.7%)	376 (57.6%)	6,909 (72.6%)	
Risk factor for HIV acquisition, N (%)				
MSM contacts	4,256 (48.0%)	391 (59.9%)	4,647 (48.8%)	**<0.001**
Heterosexual contacts	3,502 (39.5%)	198 (30.3%)	3,700 (38.9%)	
IDU	490 (5.5%)	25 (3.8%)	515 (5.4%)	
Other/Unknown	618 (7.0%)	39 (6.0%)	657 (6.9%)	
Months from HIV diagnosis to enrollment, median [IQR]	0.4 [0.1-1.1]	0.5 [0.1-1.2]	0.5 [0.1-1.1]	0.591
Year of enrollment, median [IQR]	2018 [2015-2021]	2017 [2016-2019]	2017 [2015-2020]	**0.049**
Acute HIV infection, N (%)	154 (1.7%)	15 (2.3%)	169 (1.8%)	0.296
Italian geographic area, N (%)				
Central	3,101 (35.0%)	208 (31.9%)	3,309 (34.8%)	0.103
Northern	4,214 (47.5%)	312 (47.8%)	4,526 (47.5%)	
Southern/Islands	1,551 (17.5%)	133 (20.4%)	1,684 (17.7%)	
Job, N (%)				
Unemployed	1,143 (12.9%)	134 (20.5%)	1,277 (13.4%)	**<0.001**
Employed	5,674 (64.0%)	356 (54.5%)	6,030 (63.3%)	
Unknown	2,049 (23.1%)	163 (25.0%)	2,212 (23.2%)	
Education, N (%)				
College	2,306 (26.0%)	226 (34.6%)	2,532 (26.6%)	**<0.001**
Primary School	301 (3.4%)	26 (4.0%)	327 (3.4%)	
Secondary School	1,145 (12.9%)	65 (10.0%)	1,210 (12.7%)	
University	1,124 (12.7%)	84 (12.9%)	1,208 (12.7%)	
Unknown	3,990 (45.0%)	252 (38.6%)	4,242 (44.6%)	
Smoker, n (%)	3,329 (43.0%)	261 (45.6%)	3,590 (43.2%)	0.223
AIDS at diagnosis, N (%)	1,320 (14.9%)	28 (4.3%)	1,348 (14.2%)	**<0.001**
Hospitalization at enrollment, N (%)	1,404 (15.8%)	38 (5.8%)	1,442 (15.1%)	**<0.001**
HCV-Ab positive, N (%)	615 (7.7%)	31 (5.2%)	646 (7.5%)	**0.025**
HBsAg positive, N (%)	365 (4.6%)	21 (3.5%)	386 (4.5%)	0.242
STI at enrolment, N(%)	874 (9.9%)	56 (8.6%)	930 (9.8%)	0.549
CD4 at enrollment, cells/mm^3, median [IQR]	329 [121-527]	460 [311 -48]	339 [134-534]	**<0.001**
CD4 at enrollment, cells/mm^3, N (%)				**<0.001**
<200 CD4/mm^3	2,748 (33.9%)	62 (10.4%)	2,810 (32.3%)	
200-349 CD4/mm^3, N (%)	1,532 (18.9%)	126 (21.1%)	1,658 (19.0%)	
350-499 CD4/mm^3, N (%)	1,589 (19.6%)	142 (23.8%)	1,731 (19.9%)	
≥500 CD4/mm^3, N (%)	2,241 (27.6%)	266 (44.6%)	2,507 (28.8%)	
HIV-RNA at enrolment, log10 cps/ml, median [IQR]	4.9 [4.3-5.5]	4.7 [4.1-5.3]	4.9 [4.2-5.5]	**<0.001**
HIV-RNA at enrollment, log10 cps/ml, median [IQR]	4,433 (54.5%)	401 (66.6%)	4,834 (55.3%)	**<0.001**
<100.000 cps/mL				
100.000-500.000 cps/mL	2,162 (26.6%)	124 (20.6%)	2,286 (26.2%)	
>500.000 cps/mL	1,544 (19.0%)	77 (12.8%)	1,621 (18.5%)	
CD4/CD8 ratio at enrolment, median [IQR]	0.4 [0.2-0.6]	0.5 [0.3-0.8]	0.4 [0.2-0.6]	**<0.001**
First-line ART, N (%)				0.356
3DR-INSTI	5,245 (62.7%)	362 (60.1%)	5,607 (62.5%)	
3DR-NNRTI	1,150 (13.7%)	90 (15.0%)	1,240 (13.8%)	
3DR-PI	1,184 (14.1%)	78 (13.0%)	1,262 (14.1%)	
Others	67 (0.8%)	6 (1.0%)	73 (0.8%)	
2DR	444 (5.3%)	39 (6.5%)	483 (5.4%)	
4DR	281 (3.4%)	27 (4.5%)	308 (3.4%)	

ART, antiretroviral treatment; AYAs, adolescents and young adults; CD, clusters of differentiations; HCV-Ab, antibodies anti-hepatitis C virus; IDU, injective drug users; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; MSM, men-who-have-sex-with-men; N, number of participants; NNRTI, non-NRTI; PI, protease inhibitor; STI, sexually transmitted infection; cps, copies; 3DR, 3 drugs regimen; 2DR, 2 drugs regimen; 4DR, 4 drugs regimen.

evidence for differences in the risk of VF between the two study groups at both unadjusted and adjusted analyses (HR 0.74; 95% CI 0.52-1.04, $P = 0.083$; aHR 0.97; 95% CI 0.68-1.39, $P = 0.886$) (Table 2).

TD

Overall, 4992 (52.4%) study participants (331 AYAs and 4661 adults) discontinued at least one drug of their first ART regimen for one of the following reasons: treatment simplification, drug toxicity/intolerance, failure, and patient's choice or adherence issues and unknown/other causes. The different distributions of the causes of TD in the two groups and the Kaplan-Meier curves showing the cumulative probabilities of TD: for any causes, for failure, for patient's choice/non-adherence, and for toxicity of AYAs vs adults, are reported in Supplemental Figures 1 and 2C-F. In particular, AYAs reported a higher proportion of TD for patient's

Table 2
HR and aHRs of the different study outcomes in adolescents and young adults vs adults enrolled in ICONA cohort in 2014-2023.

Outcomes[a]	N, (%)	HR (95% CI) (AYAs vs Adults)	*P*	aHR (95% CI) (AYAs vs Adults)	*P*
Time to ART starting	7453/7643 (97.5%)	0.83 (0.73-0.88)	<0.001	[b]0.98 (0.89-1.08)	0.680
Time to virological failure	695/6637 (10.5%)	0.74 (0.52-1.04)	0.083	[c]0.97 (0.68-1.39)	0.886
Time to TD for any reason	4992/8334 (59.9%)	1.03 (0.92-1.15)	0.569	[d]1.10 (0.98-1.23)	0.120
Time to TD for toxicity	794/8334 (9.5%)	0.81 (0.59-1.10)	0.175	[d]0.96 (0.70-1.12)	0.810
Time to TD for failure	246/8334 (3.0%)	0.55 (0.28-1.07)	0.565	[d]0.75 (0.37-1.53)	0.470
Time to TD for patient's choice/adherence issues	165/8334 (1.9%)	2.34 (1.51-3.64)	<0.001	[e]2.21 (1.40-3.49)	0.001
Time to LTFU	606/2266 (26.7%)	1.90 (1.48-2.43)	<0.001	[f]1.49 (1.15-1.92)	0.002
Time to Definitive LTFU	359/2266 (15.8%)	1.75 (1.27-2.42)	0.001	[f]1.38 (0.99-1.92)	0.055

aHR, adjusted HR; ART, antiretroviral treatment; AYAs, adolescents and young adults; CD, clusters of differentiations; CI, confidence interval; HR, hazard ratios; N, number of participants; TD, treatment discontinuation of at least one drug of the first regimen; LTFU, loss to follow-up.

[a] See the main text for outcomes' definitions.

[b] Adjusted for gender, mode of HIV transmission, Italian nation of birth, AIDS diagnosis, acute HIV infection diagnosis, HIV-RNA at enrolment, CD4 count at enrolment, calendar year of HIV diagnosis

[c] Adjusted for gender, mode of HIV transmission, Italian nation of birth, AIDS diagnosis, HIV-RNA at ART start, CD4 count at ART start, calendar year of ART start, first ART regimen, hepatitis C virus co-infection

[d] Adjusted for gender, mode of HIV transmission, Italian nation of birth, AIDS diagnosis, HIV-RNA at ART start, CD4 count at ART start, calendar year of ART start, first ART regimen

[e] Adjusted for gender, mode of HIV transmission, Italian nation of birth, AIDS diagnosis, HIV-RNA at ART start, CD4 count at ART start, calendar year of ART start, first ART regimen, job profile, schooling

[f] Adjusted for gender, mode of HIV transmission, Italian nation of birth, calendar year of enrollment in ICONA, job profile, schooling.

choice/non-adherence (6.9% vs 3%; P <0.001), and a lower proportion of TD for failure (2.7% *vs* 5.1%; $P = 0.044$), compared to adults. At the unadjusted and adjusted Cox regression analysis, the risk of TD for any causes was similar between the two study groups (HR 1.03, 95% CI 0.92-1.15, $P = 0.569$; aHR 1.10, 95% CI 0.98-1.23, $P = 0.120$), and the risk of TD for failure (HR 0.55; 95% CI 0.28-1.07, $P = 0.078$; aHR 0.75; 95% CI 0.37-1.53, $P = 0.426$); the risk for TD for patient's choice/non-adherence of AYAs was instead confirmed to be higher than in adults (HR 2.34; 95% CI 1.51-3.64, P <0.001; aHR 2.21; 95% CI 1.40-3.49, $P = 0.001$) (Table 2). Finally, we investigated the risk of discontinuation of the first ART line for toxicity and again there was no evidence for a difference between AYAs and adults (HR 0.81; 95% CI 0.59-1.10, $P = 0.175$; aHR 0.96; 95% CI 0.70-1.32, $P = 0.81$) (Table 2), even when analyzed according to the class of the first ART regimen (P-value interaction = 0.826).

LTFU

The risk of LTFU was assessed by restricting the data derived from 16 centers of the ICONA network with active update of follow-up visits over the period 2016-2023; a total of 2266 study participants was included for the analysis of this outcome. After applying the definition of being LTFU detailed in the method section, we observed a total of 606 (26.7%) LTFU, 71 among 162 AYAs (43.8%) and 535 LTFU among 2104 adults (25.4%) (P <0.001), mostly distributed in 2019 and 2022 (Supplemental Figures 3). At the survival analysis, AYAs had a higher cumulative probability of LTFU than adults (at 1-year 23.9% [17.7-31.7%] for AYAs vs 12.6% [7.8-10.4] for adults, log-rank P <0.001) (Supplemental Figure S1G). The higher risk of LTFU was observed among AYAs, even after controlling for several potential confounding factors (HR 1.90; 95% CI 1.48-2.43, P <0.001; aHR 1.49; 95% CI 1.15-1.92, $P = 0.002$) (Table 2). Restricting the definition of definitive LTFU to individuals with no other follow-up visit recorded since their last visit, we found a total of 359 (15.8%) definitive LTFU, 42 among 162 AYAs (25.9%) and 317 (15.1%) among 2104 adults ($P \leq 0.001$). Again, AYAs showed a higher cumulative probability of definitive LTFU than adults (at 1 year 15.7% [10.7-22.7] for AYAs vs 7.4% [6.3-8.7] for adults, log-rank P <0.001) (Supplemental Figure S1H) confirmed at the unadjusted analysis and, marginally, a 38% higher risk after adjusting for the same set of covariates (HR 1.75; 95% CI 1.27-2.42, P <0.001; aHR 1.38; 95% CI 0.99-1.92, $P = 0.055$) (Table 2).

Immunological response

A total of 6900 study participants had at least two CD4 count determinations, the first at baseline (ART starting) and the other during the following 24 months. The estimated mean change of CD4 count by the linear mixed model from baseline to each time point after starting ART was significantly higher among AYAs compared to adults, after controlling for gender, calendar year of ART starting and class of first ART regimen and the trends of CD4 recovery overtime ($P < 0.001$). The test for the 3-way interaction (age group × time × ART class) was statistically significant ($P = 0.008$), suggesting that the effect of age (AYAs vs adults) on CD4 recovery over time differed across the classes of first-line regimen (INSTI vs non-INSTI class). Indeed, a wider increase in CD4 count from baseline to the other three timepoints was observed comparing AYAs with adults of the INSTI group (Figure 2, Table 3).

Discussion

This study describes the epidemiological, socio-behavioral, clinical, and viro-immunological characteristics of AYAs (aged 18-24 years) enrolled in the Italian ICONA cohort in the period 2014-2023 and compares this population with adults. At the best of our knowledge, it represents the first wide-scale description of AYAs living with HIV in Italy.

The comparison among the two populations shows a higher number of MSM and foreign-born among AYAs, and a higher number of IDUs and HCV-antibody positive among adults, reflecting the demographic evolution occurring among PWH in Italy. Indeed, MSM have progressively become the most represented population over the recent years in Italy, especially among younger patients, while the number of IDUs among PWH has progressively decreased [2]. Moreover, the different rate of IDU may explain the difference in HCV *serostatus*, considering that the use of injective drugs is the most frequent mode of HCV transmission [13]. In the meanwhile, in recent years, an increasing number of foreign-born, mostly belonging to the younger age groups, settled in Italy, and this is also reflected in the Italian epidemiological scenario and in the ICONA cohort [2]. The other significant difference between the AYA and adult groups is the severity of the clinical picture at enrolment; it is less advanced among AYAs, with a lower rate of AIDS events and hospitalization, a higher CD4 count, and a lower level of HIV-RNA. These differences are probably due to the presumable shorter duration of infection, to the more preserved immune system among AYAs [14], and to the higher prevalence of the population with awareness about HIV risk, such as MSM, who undergoes more frequent HIV testing, thus favoring early detection of the disease. Interestingly, the physicians' choice of the first ART regimen was

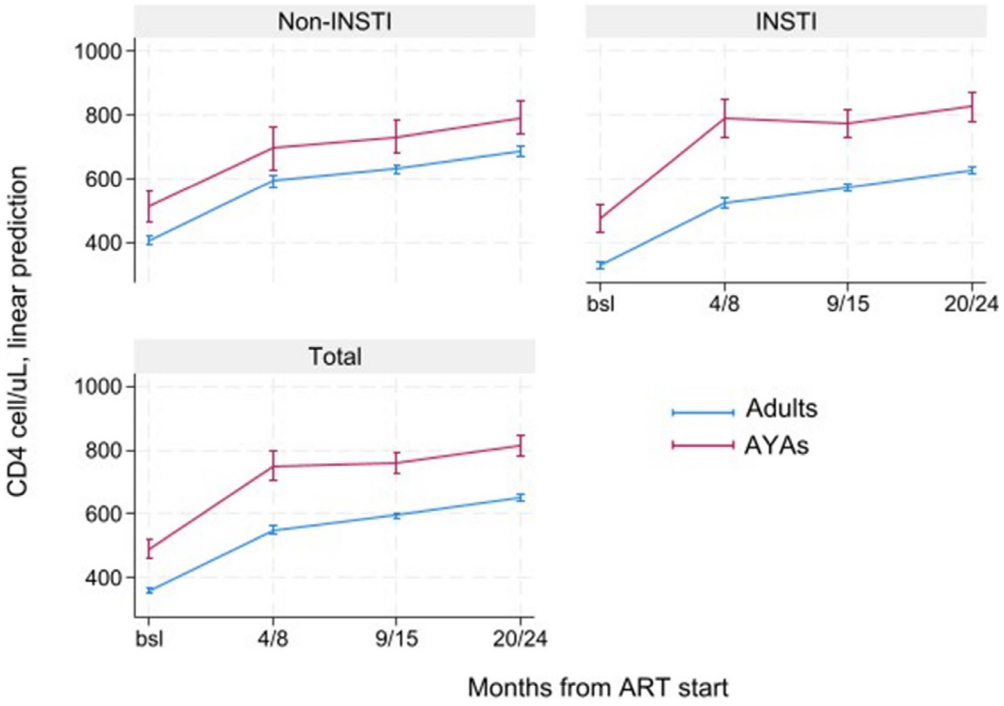

Figure 2. Immunological response in AYAs vs adults after initiation of the first-line ART—linear mixed model adjusted for gender, calendar year of ART starting, and class of first ART regimen INSTI vs non-INSTI class) with random intercept and slope per patient.
ART, antiretroviral therapy; AYAs, adolescents and young adults; CD, clusters of differentiations; INSTI, integrase strand transfer inhibitors.

Table 3
Mean CD4 change in AYAs vs adults after initiation of the first-line ART.

	Timepoint	Group	Mean CD4 change from ART start, cells/ul [95% CI]		Contrast, AYAs vs adults (change from ART start, cells/ul) [95% CI]		*P*-value
Overall	**6 months [±2]**	**Adults**	+191	[+180, +201]	+66	[+25, +108]	0.002
		AYAs	+257	[+217, +297]			
	12 months [±3]	**Adults**	+235	[+229, +242]	+29	[+3, +55]	0.031
		AYAs	+264	[+239, +289]			
	24 months [±4]	**Adults**	+291	[+284, +298]	+29	[+1, +56]	0.044
		AYAs	+320	[+293, +347]			
	Timepoint	Group	Mean CD4 change from ART start, cells/uL [95% CI]		Contrast, AYAs *vs* adults (change from ART start, cells/uL) [95% CI]		*P*-value
INSTI	**6 months [±2]**	**Adults**	+193	[+180, +206]	+120	[+65, +175]	<0.001
		AYAs	+313	[+259, +367]			
	12 months [±3]	**Adults**	+241	[+232, +249]	+57	[+22, +92]	0.001
		AYAs	+298	[+264, +332]			
	24 months [±4]	**Adults**	+297	[+288, +306]	+55	[+18, +92]	0.004
		AYAs	+351	[+316, +387]			
non-INSTI	**6 months [±2]**	**Adults**	+188	[+171, 204]	-4.5	[-67, +57]	0.885
		AYAs	+183	[+123, +243]			
	12 months [±3]	**Adults**	+226	[+215, +236]	-5	[-45, +35]	0.802
		AYAs	+221	[+182, +259]			
	24 months [±4]	**Adults**	+281	[+270, +393]	-1.5	[-43, +40]	0.941
		AYAs	+280	[+240, +320]			

ART, antiretroviral therapy; AYAs, adolescents and young adults; CD, clusters of differentiations; CI, confidence interval; INSTI, integrase strand transfer inhibitors.

similar between the two study groups, in accordance with current national and international guidelines.

Overall, the results on the proportion of AYAs enrolled in ICONA suggest a transient impact associated with the COVID-19 pandemic period, without significant modifications in the subsequent trend compared to pre-COVID years. There are no unequivocal reasons to explain this variation. The drop in the proportion of AYAs observed after the onset of the COVID-19 pandemic may be related to the pandemic itself. Indeed, during those years, access to HIV testing was significantly hampered for multiple reasons—including health system strain, lockdowns, and reduced outreach services—leading to a preferential diagnosis of more severe and symptomatic cases, which are more frequent among adult patients [15].

With regard to the first key outcome of the study, we found no differences between AYAs and adults, enrolled as of 2015, in the time to combination ART initiation, a result that reflects the universal recommendation to start combination ART as soon as possible after HIV diagnosis, regardless of CD4 cell count. Similarly, no

differences emerged in the time to VF and to first TD, but some differences occurred about reasons for TD: among AYAs, discontinuation were less frequent for VF and more frequent for patients' choice and/or adherence issues. The latter result may be due to disadvantaged social and economic situation among AYAs, and to a difficult access to care due to administrative and legal barriers, especially among foreign-born individuals, and these difficulties may contribute to their poor adherence to ART, as their main focus is not addressing health issues. Moreover, significant differences emerged about LTFU rates, with AYAs significantly at higher risk of being LTFU. This finding was confirmed independently by the definition used to measure LTFU rates. The higher mobility for educational and working reasons may justify this result among AYAs. In particular, young foreign-born individuals often change location or move to other countries during their migration project, looking for better opportunities, and the high presence of foreign-born among our AYAs population may have strongly contributed to this finding [16,17]. This reason may explain the lower rates of LTFU in 2020-2021, when lockdown was in force in Italy, such reflecting limitations in mobility. Finally, as the overmentioned baseline *status*, immunological response in AYAs after initiation of the first-line ART was stably and significantly higher at 6, 12, and 24 months in AYAs than in adults. This finding is more remarkable among those using INSTI. The presumable shorter duration of HIV infection, and a better thymic function, with a stable production of naïve T cells, a lower immune-activation and systemic inflammation comorbidity-driven, and the higher CD4 nadir may explain the faster and robust recovery of CD4 [18]. The more rapid virological suppression induced by INSTI may contribute to better immunological recovery among those using this drug class [19].

Most of the results from our analyses are consistent with similar studies performed elsewhere in the world. Although our study does not specifically measure adherence, the greater number of TD related to adherence problems is indicative of how common this issue is among AYAs and deserves special attention. A lower adherence and a higher risk of TD in AYAs have already been described in studies from the United States, Australia, and South Africa [4–7]. A large systematic review and meta-analysis including 50 studies found an overall suboptimal adherence to ART in AYAs, as low as 62.3% [20]. Similarly, and due to a likely common greater difficulty of retention in care, higher LTFU rates have been reported among AYAs in the United States, Australia, and Perù [4,6,7,9,21,22]. In contrast, overall, the continuum of care (CoC) among AYAs included in our population was good: time to ART initiation, total TD and rates of virological suppression were not significantly different in the two study groups. Consequently, the CoC is better preserved than those described in other similar studies: inconsistent care among AYAs, with lower rates of viral suppression, has been reported from Nigeria, USA, Canada, South Africa, and Perù [4–6,9,23,24]. Of note, some of these studies include patients perinatally infected, too. These patients, excluded from our cohort, which includes only ART-naïve PWH >18 years old, experienced the critical transition from pediatric to adult services, therefore their results about TD and LTFU rates cannot be entirely comparable with ours, since the populations are different. Similar barriers in adherence and retention have been documented in other chronic conditions affecting AYA, such as tuberculosis (TB), diabetes, and mental health disorders. In these settings, common critical points include the transition from family-supported to autonomous care, competing educational or social priorities, limited awareness of long-term health consequences, and stigma. Lessons from multidisciplinary and youth-friendly models developed in these areas—such as integrated TB/HIV services, peer-support programs, and community-based adherence support—may help in developing tailored strategies for AYAs living with HIV [25–28].

This study has some limitations, including the observational nature of the data source, which is prone to bias due to unmeasured confounders, and the incomplete information available about adherence and other factors such as comorbidities and/or concomitant medications. Moreover, we cannot know if those LTFU in our cohort are effectively lost or in care in another clinical center not included in the ICONA cohort.

Nonetheless, this study has a number of remarkable strengths. Firstly, it is the first description of the real-life situation of AYAs with HIV infection in Italy. Moreover, given the wide diffusion of centers participating to ICONA in Italy, the results of this study should be considered as representative of the Italian population of HIV-infected AYAs. In contrast, these results should not be generalized for other European countries, as many factors, including the differences among health systems and the proportion of foreign-born among AYAs, can strongly influence the study outcomes.

In conclusion, the results of this study highlight that AYAs with HIV have special needs, particularly regarding the adherence to ART and the risk of being LTFU. Less social and economic stability, and increased mobility for educational and working reasons, might contribute to these findings. Specific interventions, such as rapid linkage to care, immediate ART start, "ad hoc" clinical pathways and supportive care are essential to enhance awareness among AYAs about their health needs and increase retention in care, especially among those with higher risk of being LTFU and to experience VF, like young foreign-born AYAs.

Funding

No specific funding for this project. The ICONA Foundation is supported by unrestricted grants from Gilead Sciences, ViiV Healthcare, and Merck Sharpe & Dohme. The funders of the ICONA Foundation had no role in the study design, data collection, analysis, decision to publish, or preparation of this study. The research contribution of Mastrorosa I, Girardi E, and Antinori A was partially granted by the Ricerca Corrente of the Italian Ministry of Health, Linea 2-progetto 2 (INMI L. Spallanzani IRCCS).

Author contributions

Conception: FMF, IM, FV, and AT; Study Design: FMF, IM, FV, EG, AA, ADM, and AT; Accessing and verifying data: IM, AT; Statistical Analysis: AT; Acquisition of data: FMF, IM, FV, ACe, EQR, ACo, and ACi; Draft of the manuscript: FMF, IM, and AT; Patients' enrolment: FMF, IM, FV, ACe, AS, LC, EQR, MET, ACo, ACi, and AA; Review of the article and critical revision for important intellectual content: all the authors; Reading and final approval of the submitted version: all the authors.

Data availability statement

The datasets generated during the current study are not publicly available because they contain sensitive data that must be treated under data protection laws and regulations. An appropriate data sharing agreement can be arranged after a reasonable request to the corresponding author.

Ethics statement

All the enrolled subjects provided a written informed consent for study participation and processing of personal data. The ICONA Foundation study protocol and the informed consent were approved by the Institutional Review Board (IRB) of each participating center. The latest amendment of the ICONA Foundation Study

was approved centrally by the Lazio Area 4 Territorial Ethics Committee on 01 July 2024 (approval no. 83-2024). All procedures of the study were performed in accordance with the 1964 Declaration of Helsinki and its later amendments.

Declaration of competing interest

FMF received honoraria from ViiV Healthcare and Gilead Sciences for advisory board and support for travel and arrangement for congresses and meetings from ViiV Healthcare, GSK, Gilead Sciences, and MSD. IM reports payments to their institution from Gilead Sciences, speakers' honoraria/educational activities for ViiV Healthcare and Gilead Sciences and advisor for Gilead Sciences. EQR received travel grants from Gilead Sciences and ViiV Healthcare. Ace received consultant fees from ViiV Healthcare and Gilead Sciences. ACo received honoraria from Gilead Sciences for Advisory Board. ACi received funding for scientific advisory boards, travel, or speaker honoraria from Gilead Sciences, ViiV Healthcare, Janssen-Cilag, and MSD. EG received a research grant from Gilead Sciences and speaker fees from ViiV Healthcare and Gilead Science. AA served as a paid consultant to Astra Zeneca, Bavarian Nordic, Gilead Sciences, GSK, Janssen-Cilag, MSD, Moderna, Pfizer, and ViiV Healthcare and received institutional research grants from Astra Zeneca, Gilead Sciences, and ViiV Healthcare. FV, AS, LC, MET, AdM, and AT declare no competing interests.

Acknowledgments

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2025.108200.

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