

## Virological response and retention in care according to time of starting ART in Italy: data from the Icona Foundation Study cohort

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**Objectives:** To describe: (i) factors associated with rapid and delayed ART initiation; (ii) rates of 12 week virological response; and (iii) virologically controlled retention in care by 1 year from ART initiation according to timing of start in a real-life setting.

**Methods:** All individuals in the Icona cohort diagnosed with HIV in 2016–17 who initiated ART were grouped according to the time between HIV diagnosis and ART initiation: Group 1, ≤7 days; Group 2, 8–14 days; Group 3, 15–30 days; Group 4, 31–120 days; and Group 5, >120 days. Multivariable logistic regression models were used to identify factors associated with: (i) the probability of rapid (Group 1) and very delayed (Group 5) ART initiation; (ii) the 12 week virological response (by a modified snapshot algorithm); and (iii) the probability of retention in care at 1 year (on ART with HIV-RNA <50 copies/mL).

**Results:** A total of 1247 individuals were included [82 (6.6%) in Group 1, 115 (9.2%) in Group 2, 267 (21.4%) in Group 3, 641 (51.4%) in Group 4 and 142 (11.4%) in Group 5]. Main predictors of rapid ART start (Group 1) were low CD4 cell count and high HIV-RNA at first contact with the infectious diseases centre. There was no association between probability of virological response and timing of ART initiation. Overall, 90% of individuals remained on ART after 1 year, 91% with undetectable HIV-RNA. Participants of Italian nationality, those with higher CD4 cell count and lower HIV-RNA at ART initiation were more likely to be retained in care after 1 year.

**Conclusions:** In our high-income observational setting, we did not observe differences in the 1 year rate of virological response and retention in care according to timing of ART initiation.

### Introduction

The initiation of ART is associated with both the control of HIV transmission, as undetectable virus means untransmittable virus,<sup>1</sup> and life expectancy and health state in people living with HIV (PLHIV); for these reasons, universal ART coverage is strongly needed.

In this context, although it was established that ART should be initiated in any person with HIV regardless of CD4 cell count,<sup>2,3</sup>

there is still debate on how quickly ART should be started after HIV diagnosis, particularly in chronic asymptomatic patients. Accelerated or even immediate, so-called 'same-day', initiation of ART has been advocated in order to reduce the probability of onward transmission of the infection and to address the issue of a possible disengagement from care occurring between HIV diagnosis and initiation of ART. On the other hand, starting treatment before the availability of laboratory test results may limit the

therapeutic options, mainly because of risk of transmitted drug resistance. Moreover, it requires substantial resources to ensure availability of counselling, clinical evaluation and drug provision in a very short time frame.<sup>2,3</sup>

A recent systematic review identified several randomized controlled trials that compared health outcomes of rapid initiation of ART within 14 days from HIV diagnosis with standard of care.<sup>4</sup> In all the studies,<sup>5–9</sup> other interventions designed to improve uptake and adherence to ART were offered alongside rapid ART and most individuals in control groups started ART several weeks after HIV diagnosis. These studies provide moderate evidence of greater viral suppression and better retention in care at 1 year from ART initiation.<sup>4</sup>

Similar results have been reported from observational studies in which accelerated ART initiation (same-day start or ART start within 7–14 days from HIV diagnosis) was compared with standard of care.<sup>10–14</sup> All these studies, however, included patients with primary HIV infection and pregnant women, two categories that need urgent treatment and are highly committed to treatment itself. Furthermore, they were generated in low- to middle-income countries. Therefore, results could not be directly transferred to high-income countries with free-of-charge access to care, where HIV is generally diagnosed in earlier stages, with relatively high CD4 cell count, and where health systems are more efficient and better organized.

Some evidence of the potential benefit of starting ART early in the setting of high-income countries comes from the RAPID study in San Francisco, an interventional study including patients with acute or recent infection or with CD4 cell count <200 cells/mm<sup>3</sup>, belonging to a population of vulnerable PLHIV.<sup>15,16</sup> Same-day ART initiation and intensive social and medical evaluation and support were provided within this programme. Compared with the historical standard-of-care control group, RAPID shortened the time from referral to viral suppression by 3 months, although during the first 18 months loss to follow-up was similar in the RAPID and the standard-of-care groups.

In general, there is no consensus on the definition of rapid ART (same-day or within 7 or 14 days from diagnosis) and WHO guidelines suggest using a cut-off of 7 days from the diagnosis.<sup>17</sup>

Taking these studies altogether, further evidence is needed in order to establish the optimal timing of ART initiation in routine clinical practice in asymptomatic subjects diagnosed with HIV in high-income countries. Moreover, a rapid approach to ART initiation may have different consequences in countries with healthcare reimbursement systems, as in Europe.

In this paper, we aim to analyse the rates and predictors of early and very delayed ART initiation in individuals from the Icona cohort recently diagnosed with HIV and initiating ART; we also aim to analyse the rates and predictors of 12 week virological response and of virologically controlled retention in care 1 year after ART initiation, according to the timing of ART initiation. We believe that these data are relevant to inform the design of future experimental studies addressing this question.

## Patients and methods

The present analysis was conducted on the data of a subset of the HIV-infected individuals enrolled in the Italian Cohort Naive Antiretrovirals (ICONA) Foundation Study, a multicentre, observational cohort study that

has recruited ART-naive PLHIV since 1997. The ICONA study has been approved by institutional review boards of all the participating centres. Data are collected prospectively from the date of entry in the cohort until the last available follow-up for all patients who agree to participate and sign consent forms, in accordance with the ethical standards of the Committee on Human Experimentation and the Helsinki Declaration. Demographic, clinical and laboratory data and information on therapies are prospectively collected and recorded in anonymous form. Details of the cohort are described elsewhere.<sup>18</sup>

Patients from the cohort were included in this analysis if: (i) they had been diagnosed with HIV between January 2016 (year of already-available universal treatment guidelines)<sup>2,3</sup> and December 2017 (to allow at least 1 year of follow-up after HIV diagnosis); and (ii) they had initiated ART. Pregnant women and patients with acute HIV infection and AIDS at HIV diagnosis were excluded because rapid ART is universally recommended for these subpopulations. Follow-up accrued from the date of HIV diagnosis [even if before the first contact with the infectious diseases (ID) centre] to the last clinical visit or death. The database was locked and data extracted on May 2019.

Patients were divided into five groups according to the time that had elapsed between HIV diagnosis and ART start: Group 1 (G1), ≤7 days; Group 2 (G2), 8–14 days; Group 3 (G3), 15–30 days; Group 4 (G4), 31–120 days; and Group 5 (G5), >120 days.

Prevalence of the five groups was calculated. The median (IQR) time from HIV diagnosis to first visit at the ID centre (i.e. enrolment in Icona) and from the date of enrolment to starting ART were calculated for the whole population being studied and according to the elapsed-time groups.

We defined the following outcomes: rapid initiation (within ≤7 days of HIV diagnosis); very delayed initiation (>120 days from HIV diagnosis); early virological response [defined as HIV-RNA <50 copies/mL within 12 (9–15) weeks of starting ART]; and retention in care with undetectable HIV-RNA (<50 copies/mL) 1 year from ART start.

Factors associated with rapid ART initiation (i.e. ≤7 days versus >7 days from the date of the first HIV-positive test) and very delayed ART initiation (>120 days versus ≤120 days) were identified in separate logistic regression models. Variables considered in the multivariable model were: age (30, 31–49 and ≥50 years), sex, Italian nationality, mode of HIV transmission, calendar year of HIV diagnosis, education, employment, CD4 cell count strata and HIV-RNA strata at first contact with the ID centre.

The early virological suppression outcome was defined using a modified FDA snapshot analysis,<sup>19</sup> with an 'ITT missing = failure' approach and a time window of 9–15 weeks. For those whose viral load in the window was missing, the definition uses viral load values measured before and after the window to classify participants as success or failure [see Table S1 (available as [Supplementary data](#) at JAC Online) for details].

In addition, we analysed the probability of being retained in care on ART, with HIV-RNA <50 copies/mL, 1 year from starting ART. This analysis was performed only in patients initiating ART by the end of 2017, so that everybody had the potential of being followed up for an entire year. Predictors of this endpoint were analysed by logistic regression according to an 'ITT missing = failure' principle. Variables considered in multivariable models for early virological suppression and virologically suppressed retention in care at 1 year outcomes were: age, sex, Italian nationality, mode of HIV transmission, calendar year of HIV diagnosis, ART regimen, CD4 cell count strata and HIV-RNA strata at first ID centre contact.

## Results

Out of a total of 1581 patients with an HIV diagnosis during 2016–17, 259 (16.5%) were excluded because of presentation with an AIDS-defining illness ( $n=157$ ) or with primary infection ( $n=102$ ) and 75 (4.8%) were excluded because they never initiated ART. The remaining 1247 PLHIV who satisfied the above-mentioned

criteria were included. The 75 PLHIV who never started ART, compared with the 1247 included patients, were younger [median (IQR) = 34 (27–45) versus 38 (29–47) years;  $P=0.048$ ], more frequently migrants (40% versus 27%;  $P=0.011$ ), with higher CD4 cell count at first ID centre contact [median (IQR) CD4 cell count = 572 (439–768) versus 367 (213–566) cells/mm<sup>3</sup>;  $P<0.001$ ] and with lower HIV viral load (>100 000 copies/mL: 16.7% versus 36.7%;  $P<0.001$ ).

Overall, the median (IQR) time from HIV diagnosis to ART initiation was 40 (21–73) days. In detail, 82 (6.6%) PLHIV were classified as G1; 115 (9.2%) as G2; 267 (21.4%) as G3; 641 (51.4%) as G4; and 142 (11.4%) as G5.

The baseline characteristics of the patients according to the timing of ART initiation are shown in Table 1. There were

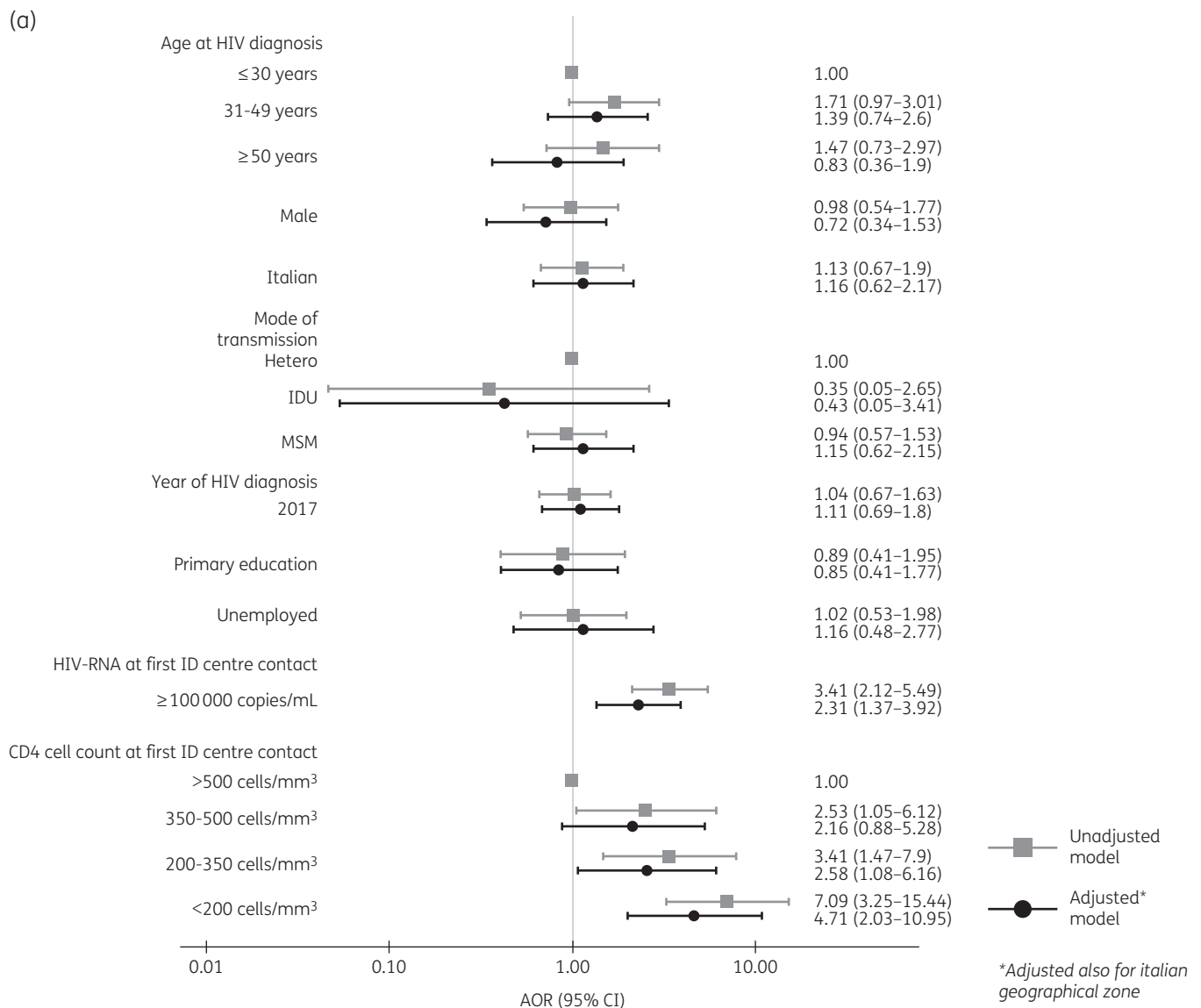
differences in demographics and clinical parameters according to the time of ART initiation. In particular, participants initiating within 7 days of HIV diagnosis were more often severely immunosuppressed (CD4 cell count <200 cells/mm<sup>3</sup>: 48% in G1; 45% in G2; 31% in G3; 17% in G4; and 9% in G5;  $P<0.001$ ) and highly viraemic (HIV-RNA >100 000 copies/mL: 65% in G1; 60% in G2; 42% in G3; 31% in G4; and 18% in G5;  $P<0.001$ ) than those initiating later.

We also disentangled the time from HIV diagnosis to ART start into two different time periods: time from HIV diagnosis to enrolment in Icona; and time from enrolment to ART start. These two periods were strictly related: subjects initiating ART earlier showed both a shorter time from HIV diagnosis to referral to the ID centre and a shorter time from referral to ART initiation than those initiating later (Table 1).

**Table 1.** Demographic and clinical characteristics of 1247 HIV-positive individuals grouped in relation to the time spent from HIV diagnosis to ART start

|  | G1: ≤7 days,<br>N=82 | G2: 8–14 days,<br>N=115 | G3: 15–30 days,<br>N=267 | G4: 31–120 days,<br>N=641 | G5: >120 days,<br>N=142 | P                | Total,<br>N=1247 |
|--|----------------------|-------------------------|--------------------------|---------------------------|-------------------------|------------------|------------------|
| Year of diagnosis, 2016, n (%)   | 42 (51.2)            | 61 (53)                 | 130 (48.7)               | 325 (50.7)                | 93 (65.5)               | 0.252            | 651 (52.1)       |
| Age at enrolment (years), median (IQR)   | 37 (32–48)           | 43 (32–52)              | 39 (31–50)               | 37 (29–46)                | 36 (28–44)              | <b>&lt;0.001</b> | 38 (29–47)       |
| Age strata at enrolment (years), n (%)   |                      |                         |                          |                           |                         | <b>&lt;0.001</b> |                  |
| ≤30  | 17 (20.7)            | 24 (20.9)               | 64 (24.0)                | 212 (33.1)                | 50 (35.2)               |                  | 367 (29.4)       |
| 31–49  | 49 (59.8)            | 56 (48.7)               | 136 (50.9)               | 323 (50.4)                | 76 (53.5)               |                  | 640 (51.3)       |
| ≥50  | 16 (19.5)            | 35 (30.4)               | 67 (25.1)                | 106 (16.5)                | 16 (11.3)               |                  | 240 (19.2)       |
| Gender, female, n (%)  | 14 (17.1)            | 27 (23.5)               | 45 (16.9)                | 101 (15.8)                | 22 (15.5)               | 0.360            | 209 (16.8)       |
| Nationality, Italian, n (%)  | 62 (75.6)            | 88 (76.5)               | 200 (74.9)               | 464 (72.4)                | 102 (71.8)              | 0.808            | 916 (73.5)       |
| Mode of HIV transmission, MSM, n (%)   | 43 (52.44)           | 54 (46.96)              | 144 (53.93)              | 373 (58.19)               | 90 (63.38)              | <b>0.002</b>     | 704 (56.46)      |
| Education, primary, n (%)  | 3 (3.7)              | 2 (1.7)                 | 2 (0.8)                  | 17 (2.7)                  | 6 (4.2)                 | <b>0.031</b>     | 30 (2.4)         |
| Unemployed, n (%)  | 8 (9.8)              | 10 (8.7)                | 27 (10.1)                | 78 (12.2)                 | 31 (21.8)               | <b>0.021</b>     | 154 (12.4)       |
| CD4 cell count at first ID centre contact (cells/mm <sup>3</sup> ), median (IQR) | 208 (50–390)         | 237 (76–389)            | 300 (151–502)            | 396 (264–557)             | 576 (346–770)           | <b>&lt;0.001</b> | 367 (213–566)    |
| CD4 cell count <200 cells/mm <sup>3</sup> , n (%)                                | 38 (48.1)            | 50 (44.6)               | 83 (31.2)                | 108 (16.9)                | 13 (9.2)                |                  | 292 (23.6)       |
| HIV-RNA at first ID centre contact (log <sub>10</sub> copies/mL), median (IQR)   | 5.1 (4.7–5.7)        | 5.2 (4.5–5.6)           | 4.8 (4.3–5.5)            | 4.6 (4.1–5.1)             | 4.3 (3.5–4.8)           | <b>&lt;0.001</b> | 4.7 (4.1–5.3)    |
| HIV-RNA >100 000 copies/mL, n (%)  | 51 (64.6)            | 69 (60.0)               | 112 (42.4)               | 198 (30.9)                | 25 (17.7)               | <b>&lt;0.001</b> | 455 (36.7)       |
| Positive for hepatitis C antibody, n (%)   | 3 (3.7)              | 7 (6.1)                 | 12 (4.5)                 | 34 (5.3)                  | 11 (7.8)                | 0.353            | 67 (5.4)         |
| Positive for hepatitis B surface antigen, n (%)                                  | 6 (7.3)              | 7 (6.1)                 | 13 (4.9)                 | 25 (3.9)                  | 6 (4.2)                 | 0.331            | 57 (4.6)         |
| First-line combination ART, n (%)  |                      |                         |                          |                           |                         |                  |                  |
| 2NRTIs + bPI   | 15 (18.3)            | 32 (27.8)               | 45 (17)                  | 66 (10.4)                 | 9 (6.3)                 | <b>&lt;0.001</b> | 167 (13.5)       |
| 2NRTIs + INSTI   | 66 (80.5)            | 74 (64.4)               | 163 (61.5)               | 441 (69.7)                | 91 (64.1)               |                  | 835 (67.5)       |
| 2NRTIs + NNRTI   | 1 (1.2)              | 5 (4.4)                 | 49 (18.5)                | 112 (17.7)                | 32 (22.5)               |                  | 199 (16.1)       |
| other (dual, four drugs)   | 0 (0)                | 4 (3.5)                 | 8 (3)                    | 14 (2.2)                  | 10 (7)                  |                  | 36 (2.9)         |
| Italian area, n (%)  |                      |                         |                          |                           |                         | <b>0.002</b>     |                  |
| central  | 44 (53.7)            | 50 (43.5)               | 155 (58.1)               | 261 (40.7)                | 48 (33.8)               |                  | 558 (44.8)       |
| northern   | 26 (31.71)           | 40 (34.8)               | 83 (31.1)                | 291 (45.4)                | 60 (42.3)               |                  | 500 (40.1)       |
| southern   | 12 (14.6)            | 25 (21.7)               | 29 (10.9)                | 89 (13.9)                 | 34 (23.9)               |                  | 189 (15.2)       |
| Days from HIV diagnosis to start of combination ART, median (IQR)                | 5 (3–6)              | 12 (9–13)               | 22 (19–27)               | 54 (40–75)                | 183 (143–311)           | <b>&lt;0.001</b> | 40 (21–73)       |
| Days from HIV diagnosis to first ID centre contact, median (IQR)                 | 0 (0–3)              | 4 (0–8)                 | 7 (0–12)                 | 16 (6–30)                 | 34 (10–120)             | <b>&lt;0.001</b> | 10 (1–23)        |
| Days from first ID centre contact to start of combination ART, median (IQR)      | 2 (0–5)              | 7 (2–10)                | 15 (9–20)                | 33 (22–51)                | 127 (49–220)            | <b>&lt;0.001</b> | 23 (9–44)        |

Statistically significant  $P$  values (<0.05) are indicated in bold.



**Figure 1.** Crude OR and AOR of association between different clinical and demographic baseline characteristics and starting ART, (a) ≤7 days from HIV diagnosis and (b) >120 days from HIV diagnosis. Hetero, heterosexual contacts; IDU, intravenous drug user.

In those who have started ART, lower CD4 cell count and higher HIV-RNA at the first ID centre contact were associated with a more rapid time of initiation. After adjusting for age, sex, risk factors for HIV, calendar year of HIV diagnosis, Italian nationality, employment status, education and Italian geographical region, compared with PLHIV having a CD4 cell count >500 cells/mm<sup>3</sup>, those with a CD4 cell count <200 cells/mm<sup>3</sup> had a 4.71-fold (95% CI=2.03-10.95) higher probability, those with a CD4 cell count 200-350 cells/mm<sup>3</sup> had a 2.58-fold (95% CI=1.08-6.16) higher probability and those with a CD4 cell count 350-500 cells/mm<sup>3</sup> had a 2.16-fold (95% CI=0.88-5.28) higher probability of initiating ART within 7 days of HIV diagnosis rather than later than 7 days. Also, PLHIV with HIV-RNA ≥100 000 copies/mL had a 2.31-fold higher probability (95% CI=1.37-3.92) of initiating ART within 7 days than PLHIV with HIV-RNA <100 000 copies/mL (Figure 1a).

CD4 cell count and viral load were also independent predictors of very late ART initiation (i.e. >120 days since the first HIV-positive test). In addition, being unemployed was independently associated with a 2.32-fold higher risk of starting ART >120 days after HIV diagnosis (95% CI=1.34-4.02) (Figure 1b).

The 12 week virological response (i.e. snapshot endpoint HIV-RNA ≤50 copies/mL) occurred overall in 747/1247 (59.9%) PLHIV: 45/82 (54.9%) of G1; 63/115 (54.8%) of G2; 149/267 (55.8%) of G3; 403/641 (62.9%) of G4; and 87/142 (61.3%) of G5 (P=0.168). The time elapsed from HIV diagnosis to ART start was not associated with the probability of 12 week virological response; independent predictors of this outcome were Italian nationality [1.39-fold higher probability (95% CI=1.04-1.87) versus migrants] and having started ART with integrase inhibitor (INSTI)-containing regimens: both PLHIV initiating boosted PI (bPI)-containing regimens and PLHIV initiating NNRTI-containing regimens had a lower

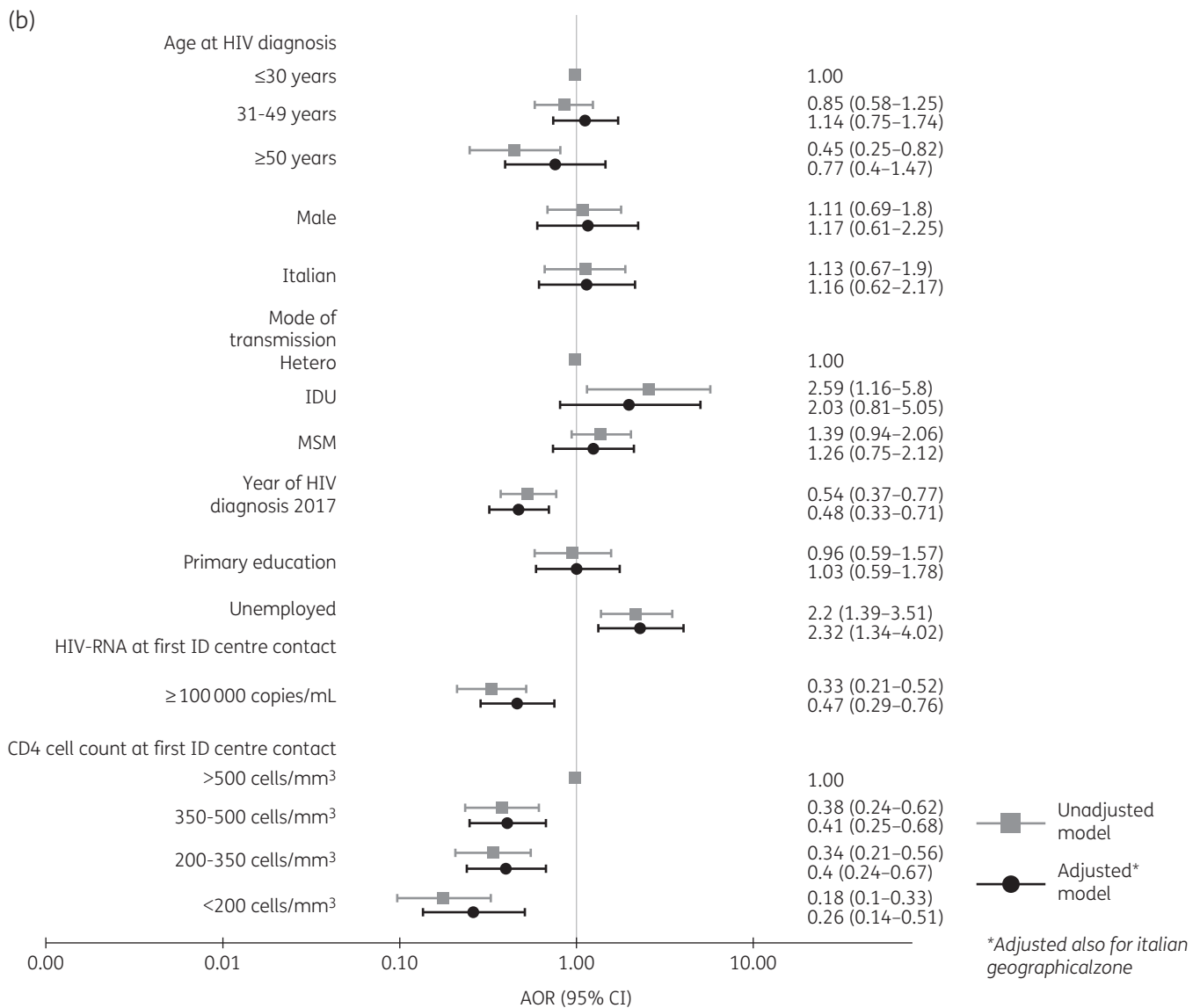


Figure 1. Continued

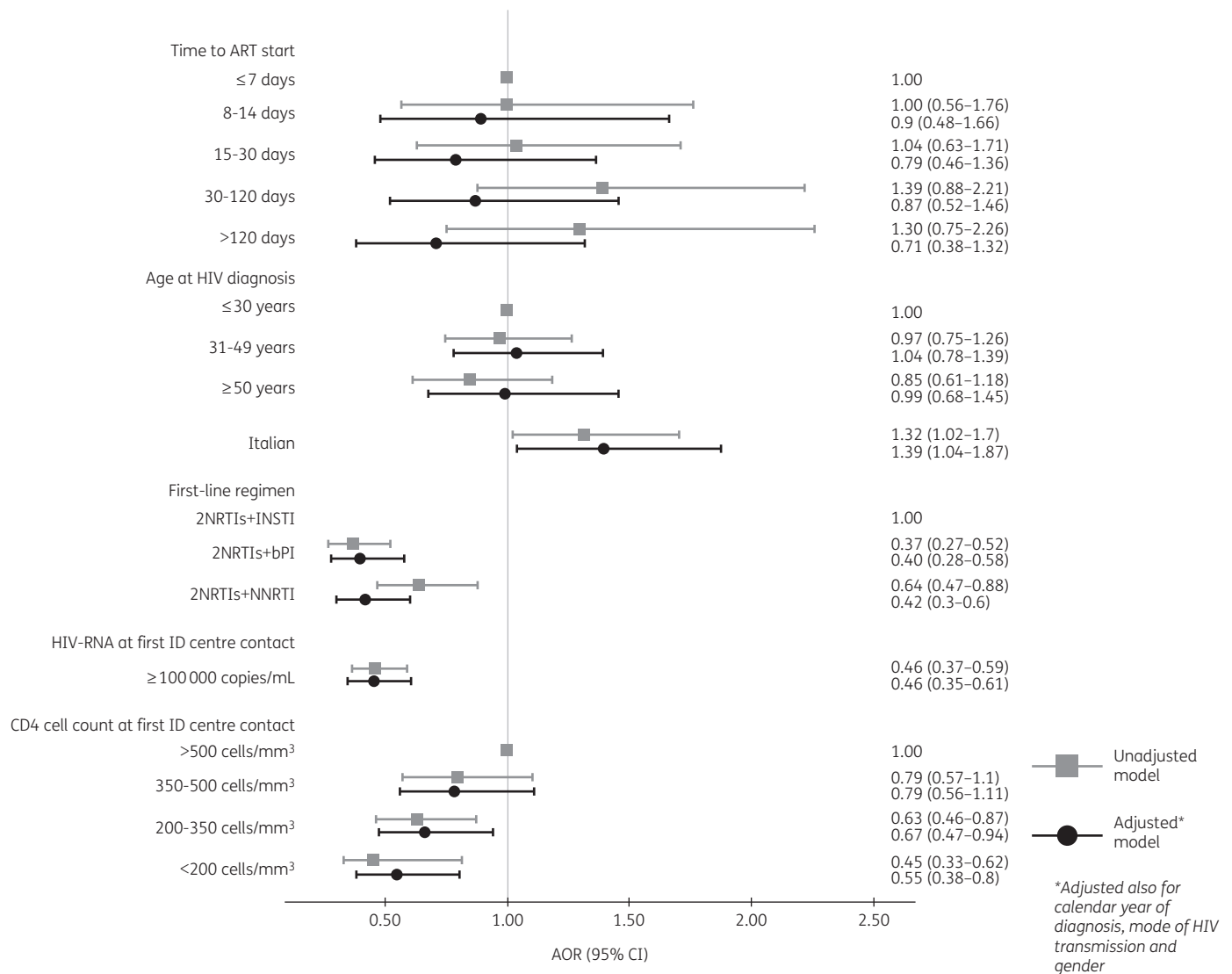
probability [bPI: adjusted OR (AOR)=0.40 (95% CI=0.28-0.58); NNRTI: AOR=0.42 (95% CI=0.30-0.60)] of obtaining virological success after 12 weeks of ART as compared with PLHIV initiating INSTI-containing regimens, after adjusting for demographic and viro-immunological variables. Moreover, as expected, both CD4 cell count and HIV-RNA at the first ID centre contact were independent predictors of achieving 12 week virological success (Figure 2).

Finally, we analysed the percentage of PLHIV still attending the ID centre, on ART and with a viral load <50 copies/mL after 1 year of therapy, according to the elapsed-time groups. This analysis included only the 1164 patients starting ART by the end of 2017, who had the potential for being followed up for an entire year. Overall, 90% of PLHIV were on therapy after 1 year and 91% of these had an HIV-RNA value <50 copies/mL. Twelve patients (1.0%) died during the first year of ART and 100 (8.5%) were no longer in care in Icona after 1 year. Of these individuals, 75 (6.4%)

were lost to clinical follow-up and 25 (2.1%) moved to another country or another clinical centre in Italy outside of the Icona cohort network.

A total of 957/1164 (82.2%) PLHIV were retained in care with a viral load <50 copies/mL after 1 year with no differences according to G1-G5: 63/81 (77.8%) of G1; 89/115 (77.4%) of G2; 219/259 (84.6%) of G3; 494/600 (82.3%) of G4; and 92/109 (84.4%) of G5 (P=0.373). The main independent predictor of retention in care with a viral load of <50 copies/mL was again Italian nationality [versus migrants, AOR=2.02 (95% CI=1.39-2.93)], while lower CD4 cell count at the first ID centre contact [<200 versus >500 cells/mm<sup>3</sup>, AOR=0.56 (95% CI=0.35-0.91)], higher HIV-RNA at the first ID centre contact [≥100 000 versus <100 000 copies/mL, AOR=0.68 (95% CI=0.48-0.98)] and first-line ART with bPI-based regimens [versus INSTI-based, AOR=0.62 (95% CI=0.40-0.95)] were associated with a lower probability of retention in care with HIV-RNA <50 copies/mL 1 year after the start of ART (Figure 3).





**Figure 2.** Crude OR and AOR of association between time from HIV diagnosis to ART start and 12 week virological success (i.e. HIV-RNA <50 copies/mL) using a modified snapshot analysis from fitting a logistic regression.

The results were confirmed by running two case-control analyses with unmatched and matched HIV-RNA, using G1 and G4 (data not shown).

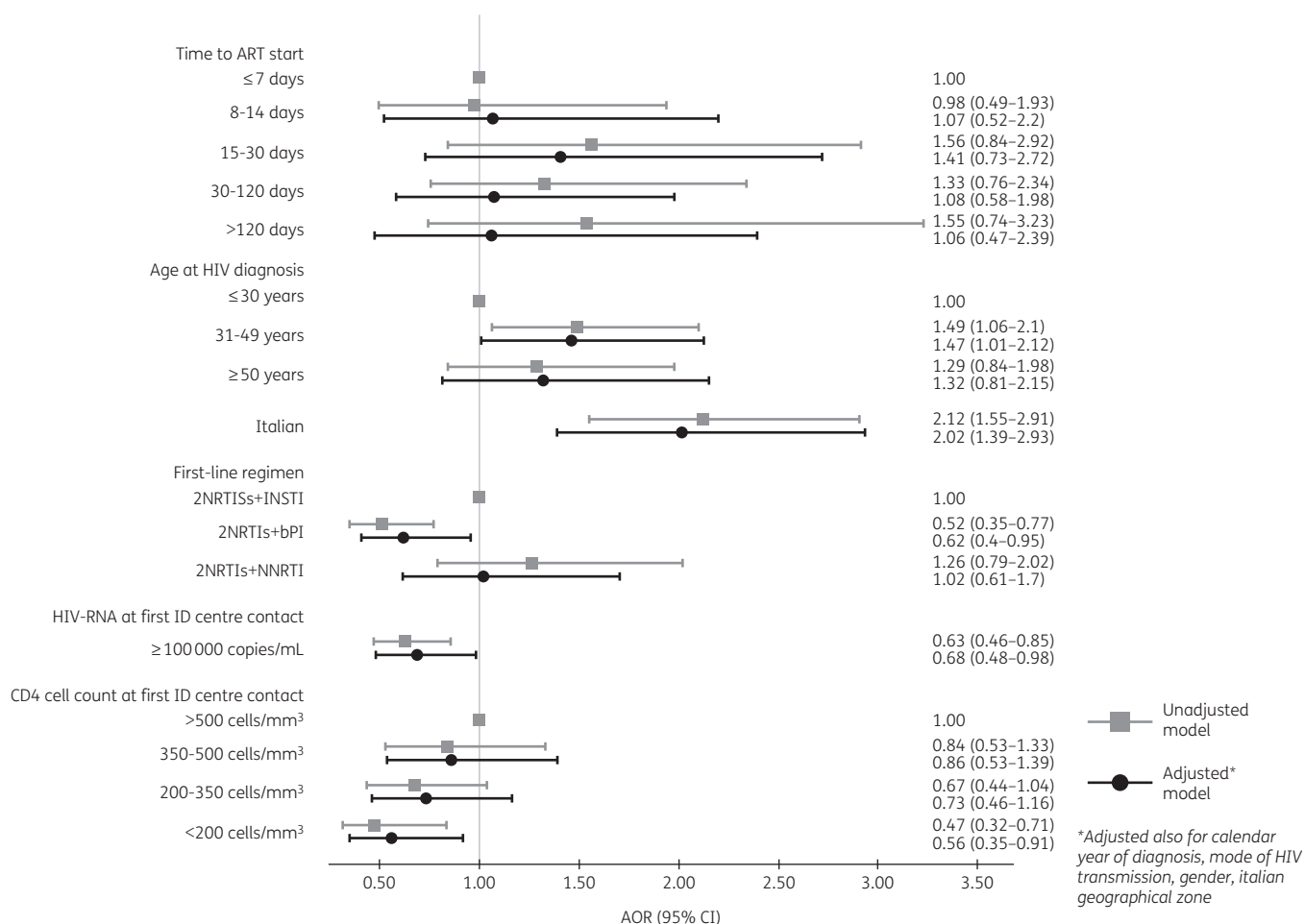
### Discussion

Our analysis of observational data, including more than one thousand PLHIV seen for care in a setting of free access to medical care who all initiated ART, failed to show clear benefit of rapid ART initiation in terms of virological success and retention in care 1 year from ART start in chronic asymptomatic PLHIV.

In our cohort, only 16% of the PLHIV initiated ART within 14 days of HIV diagnosis and only 37% initiated ART within 30 days. It has to be underlined that the lag time from HIV diagnosis to referral to a clinical centre contributed, at least partially, to the time spent waiting for ART and this does not relate to the ID centre policy or organization. Particularly in metropolitan areas,

there are many testing points outside hospital settings, such as outpatient laboratories, in which HIV testing is offered and once the subject is found to be HIV positive (it may take several days for the response to arrive) he/she is referred to the ID centre and the whole process takes time. A bit different is the setting of community-based checkpoints, in which the response is immediate and, after counselling, the subjects are immediately referred to one ID centre for a confirmatory test and for care; unfortunately, only two cities in Italy, Bologna and Milan, have this community-based facility to date.

Our analysis shows that Italian clinicians tend to initiate ART more quickly in the most immunosuppressed asymptomatic PLHIV, as they follow all guidelines that recommend ART initiation independently from CD4 cell count and HIV load,<sup>2,3</sup> but with a greater urgency for subjects with low CD4 cell count. Indeed, the group of PLHIV who started within 7 days of HIV diagnosis showed lower CD4 cell count and higher HIV-RNA levels. Interestingly, the



**Figure 3.** Crude OR and AOR of association between time from HIV diagnosis to ART start and being in care with virological suppression 1 year after starting ART.

group of people who started very late (i.e. >120 days from HIV test) had the highest proportion of persons who declared to be unemployed. Considering that Italy has universal healthcare coverage, this indicator underlines the importance of reaching more fragile strata of the population that can contribute to the spread of HIV infection. In this regard, the San Francisco RAPID programme, for vulnerable subjects, might constitute a valid example of intervention.<sup>16</sup>

The fact that ART was started more quickly in participants with advanced disease could have introduced a bias in our analysis and may limit the generalizability of our results. We have tried to control for imbalances in key common causes of timing of ART initiation and chance of retention in care but residual confounding cannot be ruled out and this could explain the discrepancies between our results and those shown by randomized comparisons.

On the other hand, because of the differential rate of access to care and level of care provided in the two settings, it is possible that the effect of early ART initiation has a genuinely lower impact on the probability of retention in resource-rich countries (e.g. Italy) than that seen in the setting of the randomized trials (mainly conducted in Africa).

Our analysis also aimed to evaluate the correlation between timing of initiation and short-term probability of achieving an

HIV-RNA of <50 copies/mL once ART was started, as this condition relates to absence of HIV transmission.<sup>1</sup> A total of 747 out of 1247 (60%) PLHIV achieved <50 copies/mL HIV load after 12 weeks of ART; as expected, both CD4 cell count and HIV-RNA at baseline were associated with the probability of achieving this outcome. Use of INSTI-based regimens was also associated with a higher probability of achieving HIV-RNA suppression, consistent with the results of randomized trials.<sup>20-22</sup> People of Italian nationality also had a higher chance of achieving this outcome; this might be due to the fact that migrants are often in poor and unstable socioeconomic situations, potentially leading to no adherence to therapies or to change of residence.

Looking at 1 year retention in care, our data show that once HIV-positive individuals are referred to clinical centres, the large majority are retained in care and 90% of them have HIV-RNA <50 copies/mL by 1 year. People who appeared to be no longer retained in care after 1 year of ART were more likely to be those with an advanced stage of HIV infection, migrants and those starting a bPI regimen. Migrants are often moving from one city to another or going back to their own country and this more fragile population should be better followed in order to guarantee continuum of care. More difficult to explain is the higher risk of

poor retention in care of PLHIV initiating bPI-containing regimens. It might be the result of bias by indication, as clinicians could have offered these regimens more frequently to patients who are perceived to be less adherent, due to the high genetic barrier of PIs.<sup>23</sup>

Our study has several limitations. First, the analysis is restricted to individuals who have initiated ART. In order to evaluate whether the strategy of initiation of ART <7 days from HIV diagnosis, as opposed to other strategies in the observational context, more sophisticated methods involving the simulation of a hypothetical trial, such as RAPID for example, as well as the use of counterfactuals are needed. Although only 75 people who did not start ART were excluded from this analysis, the consequences of this selection bias on the final results are difficult to predict. In addition, time-dependent confounding due to censoring of people deviating from the various timings of initiation strategies under examination have not been properly accounted for. Finally, we considered only asymptomatic patients and cannot extend our conclusions to symptomatic/AIDS patients who, according to WHO, need urgent ART initiation.<sup>17</sup> Finally, because of the observational nature of the study, we cannot rule out that all sources of potential confounders have been taken into account.

In conclusion, our data show that approximately 7% of recently diagnosed, asymptomatic, HIV-infected individuals in Italy initiated ART within 7 days of HIV diagnosis, and 16% within 14 days, and would fit with a strategy defined as rapid ART initiation. Furthermore, in this large series of PLHIV cared for in a free-access setting, we found no evidence that the timing of ART initiation was associated with the probability of virological success and 1 year retention in care. Of course, a randomized study conducted in a resource-rich setting, to evaluate the possible benefits of this rapid initiation strategy versus a less rapid start in asymptomatic HIV-positive individuals, is urgently needed. The data shown in this work should be useful to better inform the design of such future studies.

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## Transparency declarations

None to declare.

## Supplementary data

Table S1 is available as [Supplementary data](#) at JAC Online.

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