Durability of different initial regimens in HIV-infected patients starting antiretroviral therapy with CD4+ counts <200 cells/mm^3 and HIV-RNA >5 log$_{10}$ copies/mL.

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Abstract

Objective.

To investigate the durability of different initial regimens in patients starting ART with CD4+ <200 cells/mm^3 and HIV-RNA >5 $\log_{10}$ copies/mL.

Methods.

Retrospective study of HIV-infected patients prospectively followed in ICONA cohort. Those who started ART with boosted protease inhibitors (bPI), or non-nucleoside reverse transcriptase inhibitors (NNRTI) or integrase strand transfer inhibitors (InSTI), CD4+ <200 cells/mm^3 and HIV-RNA >5 $\log_{10}$ copies/mL, were included in this analysis.

Primary endpoint: treatment failure (TF), a composite endpoint defined as virological failure (VF, first of two consecutive HIV-RNA >50 copies/mL after six months of treatment) or discontinuation of class of the anchor drug or death.

Independent associations were investigated by Poisson regression analysis, in a model including age, gender, mode of HIV transmission, CDC stage, hepatitis C virus (HCV) and hepatitis B virus (HBV) co-infection, pre-treatment HIV-RNA, CD4+ count and CD4/CD8, ongoing opportunistic disease, FIB-4, eGRF, hemoglobin, platelets, neutrophils, calendar year of ART initiation, anchor drug class (treatment group) and nucleos(t)ide backbone.

Results.

One thousand one hundred ninety-five patients fulfilled the inclusion criteria: 696 started ART with a bPI, 315 with an InSTI and 184 with a NNRTI.

During 2759 PYFU, 642 patients experienced TF.

Starting ART with bPIs (adjusted incidence rate ratio - aIRR [95% CI]: 1.62 [1.29-2.03] versus starting with NNRTIs; p<0.001) and starting ART with InSTIs (aIRR [95% CI]: 0.68 [0.48-0.96] versus starting with NNRTIs; p=0.03) were independently associated with TF.

Conclusions

In patients starting ART with <200 CD4+ cells/mm^3 and >5 log_{10} HIV-RNA copies/mL, the durability of regimens based on InSTIs was longer than that of NNRTI- and bPI-based regimens.

Introduction

Current guidelines recommend starting ART regardless of CD4+ cell counts.[1-5] While this should lead to early ART start (i.e. in presence high CD4+ cell counts), many patients are diagnosed as HIV-infected with still less than 200 CD4+ cells/mm^3, especially in low-income countries,[6, 7] but also in high income countries, including Italy.[8]

The results of many studies suggested that starting ART when CD4+ cell counts are less than 200/mm^3 may be associated with worse treatment outcomes. Some randomized controlled trials (RCTs) in HIV-infected ART-naïve subjects have suggested that when ART is started when CD4+ cell counts are less than 200/mm^3, virological success rates may be lower.[9-13] Observational studies have also pointed out that having lower baseline CD4+ cell counts is a risk factor for incomplete CD4+ recovery[14] and for selecting drug-resistant variants at virological failure.[15]

Furthermore, in a large observational study, starting ART with CD4+ cell count less than 200 cells/mm^3 was associated with a 20% greater risk of regimen modification.[16]

A poorer virological success while receiving some first-line regimens has been often observed also in patients who had a baseline viral load of more than 5 $\log_{10}$ HIV-RNA copies/mL.[17-22]

Low pre-ART CD4+ cell counts and high pre-ART viral load are often overlapping features of HIV-infected patients. For instance, in a study in which having less than 100 CD4+ cells/mm^3 at screening was an inclusion criterion, 72% of patients had also more than 5 $\log_{10}$ HIV-RNA copies/mL at enrollment.[23] However, patients with active opportunistic diseases, or with less than 200 CD4+ cells/mm^3 and more than 5 $\log_{10}$ HIV-RNA copies/mL, at ART start are largely underrepresented in clinical trials. In the pooled analysis of two of the more recent registration trials in naïve patients initiating ART, only 5% of the enrolled patients had these baseline characteristics;[24] in the NEAT001/ANRS143 trial, only 77 out of 805 (<10%) patients enrolled had both CD4+ counts of less than 200 cells/mm^3 and viral load greater than 5 $\log_{10}$ HIV-RNA copies/mL at enrollment.[11]

Furthermore, the way the results of RCTs are presented seldom allow evaluating with precision the outcome of people starting ART with both CD4+ counts of less than 200 cells/mm^3 and viral load greater than 5 log_{10} HIV-RNA copies/mL. Indeed, in the NEAT001/ANRS143 trial, the treatment outcome was worse in patients with both CD4+ counts of less than 200 cells/mm^3 and viral load greater than 5 log_{10} HIV-RNA copies/mL at ART start, compared to those without these baseline characteristics.[11] However, the virological outcome is usually presented by baseline viral load and CD4+ strata separately (i.e. by HIV-RNA greater than or not greater than 5 log_{10} HIV-RNA copies/mL or by CD4+ counts of less than or not less than 200 cells/mm^3), but not for the stratum of patients who started ART with both CD4+ counts of less than 200 cells/mm^3 and viral load greater than 5 log_{10} HIV-RNA copies/mL compared to the stratum of those who started ART with neither of these characteristics.[13, 24] Thus, data from large observational studies may help bridging this knowledge gap.

The aim of this study was to investigate the durability of different initial regimens in patients starting ART in the worst viro-immunological status, i.e. with CD4+ cell counts less than 200 cells/mm^3 and HIV-RNA greater than 5 log_{10} copies/mL.

Patients and methods

ICONA Foundation Study is a multi-centre prospective observational study of HIV-infected patients, which was set up in 1997. Eligible patients are those starting ART when they are naive to antiretrovirals, regardless of the reason for which they had never been previously treated and of the stage of their disease. The ICONA Foundation study has been approved by Institutional Review Boards (IRBs) of all the participating centers; sensitive data from patients are seen only in aggregate form. All patients sign a consent form to participate in ICONA, in accordance with the ethical standards of the committee on human experimentation and the Helsinki Declaration (last amendment October 2013). Demographic, clinical and laboratory data and information on therapy are collected for all participants and recorded using electronic data collection [www.icona.org].

Patients are followed-up prospectively at each of the clinical sites participating in the study and HIV viral load monitoring in cohort participants is performed at least twice yearly, according to study protocol and to Italian guidelines.[5] Dates of start and stop of each antiretroviral are collected together with the main reason for discontinuing as reported by the treating physician.

Study population and outcomes

The database for this analysis has been put together retrospectively selecting only subjects who started ART between 2004 and 2017 with one anchor drug (ritonavir or cobicistat-boosted protease inhibitor [bPI], or NNRTI or integrase strand transfer inhibitor [InSTI]) plus tenofovir/emtricitabine or abacavir/lamivudine, CD4+ $\leq$200 cells/mm^3 and HIV-RNA $\geq$5 $\log_{10}$ copies/mL, and at least 1 HIV-RNA assessed both before and after the start of ART.

Viral load was assessed in each centre according to local procedures, using an assay with a sensitivity of at least 50 HIV-RNA copies/mL (Biomerieux NucliSENS EasyQ HIV-1 v.2.0, Siemens VERSANT HIV-1 RNA 1.5 Assay kPCR, Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 Test or v.2.0, Abbott RealTime HIV-1).

Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI)[25] and the liver fibrosis FIB-4 index was calculated as described.[26]

The response to the initial regimens was compared according to the specific anchor drug class started with respect of a number of end-points.

The primary study endpoint was treatment failure (TF), a composite endpoint defined as virological failure (VF, first of two consecutive HIV-RNA >50 copies/mL after six months of treatment) or discontinuation of class of the anchor drug for any reason (e.g switching from lopinavir/ritonavir to darunavir/ritonavir was not considered as discontinuation, while a switch from lopinavir/ritonavir to efavirenz was considered discontinuation) or death.

Secondary study endpoints were: i) TF in the stratum of patients starting ART with >500,000 HIV-RNA copies/mL, ii) the pure VF, iii) changes in CD4+ cell counts during follow-up and iv) treatment discontinuations due to intolerance or toxicity.

Statistical analysis

The comparison of baseline characteristics among the three groups were made by Chi-square or Kruskal-Wallis test for categorical or continuous variable respectively.

Cumulative probability of TF and VF according to drug class was assessed by Kaplan Meier method and compared by log-rank test. Incidence rate of each endpoint was calculated as number of events over person-years follow-up (PYFU). Independent associations were investigated by Poisson regression analysis, in a model including variables associated with the outcome at a p-value <0.1 at univariable analysis. The models were adjusted also for nucleos(t)ide backbone and year of cART initiation, as it was considered essential to adjust the analysis also for these variables. At univariable level all the following time-fixed covariates at cART initiation were assessed: age, gender, mode of HIV transmission, CDC stage, HCV and HBV coinfection, pre-treatment HIV-RNA, CD4+ cell count and CD4/CD8 ratio, ongoing opportunistic disease, FIB-4, eGRF (estimated by CKD-EPI formula) hemoglobin, platelets, neutrophils, calendar year of ART initiation, anchor drug class (treatment group) and nucleos(t)ide backbone.

For the analysis, the follow-up accrued from ART start to the outcome/last observation (including death), discontinuations of the NRTI backbones have been ignored.

In a subset of the study population with complete CD4 count data, median CD4 change from baseline to 12 and 24 months of observation were also compared according to the anchor drug class, by Kruskal-Wallis. test.

Results

One thousand one hundred ninety-five patients fulfilled the inclusion criteria: 696 started ART with a bPI (331 [48%] darunavir/ritonavir, 201 [29%] atazanavir/ritonavir, 140 [20%] lopinavir/ritonavir, 16 [2%] fosamprenavir/ritonavir, 8 [1%] darunavir/cobicistat), 315 with an InSTI (157 [50%] dolutegravir, 81 [26%]

elvitegravir/cobicistat, 77 [24%] raltegravir) and 184 with a NNRTI (173 [94%] efavirenz, 5 [3%] rilpivirine, 4 [2%] nevirapine, 2 [1%] etravirine). Patients' characteristics at ART start are described in detail in table 1. Groups differed for several baseline characteristics: in general, patients who started ART with NNRTIs had less advanced disease (as testified by CD4+ cell counts and CD4+/CD8+ ratio) and were more frequently co-infected with HCV; those who started ART with InSTIs did this in more recent years and more frequently with abacavir and lamivudine as backbone.

During a total of 2759 person-years of follow-up (PYFU, 585 for the NNRTI group, 1676 for the bPI group and 498 for the InSTI group), 642 patients experienced TF (96, 470 and 73 in the NNRTI, in the bPI and in the InSTI group, respectively); the overall incidence rate (95%CI) of TF was 23.2 (21.4-25.0) per 100 PYFU (16.4 [13.4-20.0], 28.0 [25.6-30.7], and 14.7 [11.7-18.5] per 100 PYFU in the NNRTI, in the bPI and in the InSTI group, respectively).

The cumulative probability of TF is illustrated in Figure 1 and was significantly different between groups ($p<0.001$). The one- and two-year probability (95%CI) of TF was 28.4% (22.4-35.5) and 40.3% (33.5-48.0) in the NNRTI, 32.8% (29.5-36.5) and 48.0% (44.2-51.9) in the bPI, 18.5% (14.6-23.4) and 23.1% (18.5-28.7) in the InSTI group.

During 3846 person-years of follow-up, VF occurred in 254 patients: 40 , 187 and 27 in the NNRTI, in the bPI and in the InSTI group. The overall incidence rate (95%CI) of VF was 6.6 (5.8-7.5) per 100 PYFU: 5.1 (3.8-7.0), 7.5 (6.5-8.6) and 4.8 (3.3-7.1) per 100 PYFU in the NNRTI, in the bPI and in the InSTI group.

The one- and two-year probability (95%CI) of VF was 12.6% (8.6-18.4) and 18.6% (13.6-25.2), 17.2% (14.5-20.2) and 22.4% (19.4-25.7) and 7.9% (5.3-11.6) and 9.3% (6.4-13.4) in those who started ART with NNRTIs, bPIs and InSTIs, respectively. The cumulative probability of VF was significantly different between groups ($p<0.001$, Figure 2).

The one- and two-year probability (95%CI) of discontinuation due to intolerance or toxicity was 13.8% (9.4-19.9) and 16.1% (11.3-22.7), 13.2% (10.8-16.2) and 19.5% (16.4-23.1), 4.3 % (2.5-7.3) and 5.1 % (3.0-8.6) in those who started ART with NNRTIs, bPIs and InSTIs, respectively. The cumulative probability of discontinuation due to intolerance or toxicity was significantly different between groups (p=0.005, Figure 3).

At univariable analysis (Table 2), variables associated with TF were age (p=0.006), presence of anti HCV antibodies (p=0.072), baseline HIV-RNA (p<0.001), baseline CD4+ cell counts (p=0.015), hemoglobin (p=0.077) and the type of ART regimen started (p<0.001). After adjustment for HCV coinfection, baseline CD4 count, hemoglobin, FIB-4, eGFR, NRTI backbone and calendar year of cART initiation, a baseline HIV-RNA >500,000 copies/mL (adjusted IRR [95% CI]: 1.26 [1.07-1.48] compared with baseline values between 100,000 and 500,000 copies/mL; p=0.006), starting ART with a bPI (adjusted IRR [95% CI]: 1.62 [1.29-2.03] compared with starting ART with a NNRTI; p<0.001) and starting ART with an InSTI (adjusted IRR [95% CI]: 0.68 [0.48-0.96] compared with starting ART with a NNRTI; p=0.03) remained independently associated with TF. Using the bPI group as reference group, both starting ART with NNRTIs (adjusted IRR [95% CI]: 0.62 [0.49-0.78]; p<0.001) and starting ART with InSTIs (adjusted IRR [95% CI]: 0.42 [0.32-0.56]; p<0.001) were independently protective from TF (Table 2).

In a sensitivity analysis limited to the 424 patients who started ART with baseline HIV-RNA >500,000 copies/mL, the use of NNRTIs and InSTIs as anchor drug class was still independently associated with lower probability of TF (compared to the bPI group, adjusted IRR [95% CI]: 0.65 [0.44-0.97], p=0.035, for the NNRTI group and adjusted IRR [95% CI]: 0.47 [0.31-0.71), p<0.001, for the InSTI group). The PI group showed higher risk of TF if compared to the NNRTI group: adjusted IRR (95% CI): 1.54 (1.03-2.29); p=0.035.

The type of anchor drug class was independently associated with VF only for individuals who started cART with HIVRNA between 100,000 and 500,000 cp/mL (adjusted IRR [95% CI] for the NNRTI group compared to the bPI group: 0.64 [0.41-1.00]; p=0.048; adjusted IRR [95% CI] for the InSTI group compared to the bPI

group: 0.30 (0.14-0.66); p=0.002). VF was not associated with the anchor drug class if the baseline HIV-RNA was >500,000 copies/mL: using bPI group as reference, the adjusted IRR (95% CI) for the NNRTI group was 0.79 (0.45-1.39); p=0.421; the adjusted IRR (95% CI) for the InSTI group was 1.01 (0.61-1.65); p=0.978. P-value at interaction test between baseline HIVRNA and the anchor drug class was 0.30.

After one and two years of follow-up, we observed a similar increase in CD4+ cell counts across treatment groups (Figure 4). The median increase at 12 months was 190 (IQR 123-305) cell/mm^3 for NNRTI group, 201 (129-296) for bPI, 211 (138-322) for InSTI, (p=0.324); at 24 months, CD4+ counts increased by 288 (189-396), 291 (202-416) and 308 (214-389) cells/mm^3 in the NNRTI, bPI and InSTI group (p=0.853), respectively.

Discussion

This study showed that in patients with advanced HIV infection, the type of regimen was independently associated with treatment failure. The type of initial regimens was also independently associated with virological failure in the stratum of patients who started ART with a VL between 100,000 and 500,000 copies HIV-RNA/mL. By contrast, the CD4+ cells gain during follow-up was optimal with any regimen and comparable among types of regimen. It must be underlined that more than 95% of patients who started ART with a NNRTI-based regimen received efavirenz: thus, our results should be read keeping in mind this feature.

The results of this study can inform physician caring for a consistent proportion of treatment naïve patients who are going to start their first-line ART with both CD4+ cell counts less than 200/mm^3 and HIV-RNA greater than 5 $\log_{10}$ copies/mL; these two clinical characteristics are often associated at HIV diagnosis[23] and specific studies in this patient population are lacking. The design of our study was unique and so, it is not easy to make direct comparisons with other studies. Some direct comparisons is possible only with the NEAT001/ANRS143 trial: in this study, 77 out of 805 (<10%) patients enrolled had both CD4+ counts of less than 200 cells/mm^3 and viral load greater than 5 $\log_{10}$ HIV-RNA copies/mL at ART start: the composite primary outcome (change of randomized treatment before week 32 because of insufficient virological

response, no virological response by week 32, HIV-1 RNA concentration 50 copies per mL or higher at any time after week 32; death from any cause; any new or recurrent AIDS event; or any serious non-AIDS event) was met by 60.1% and by 29.9% of those who started ART with darunavir/ritonavir plus raltegravir and with darunavir/ritonavir plus emtricitabine/tenofovir disoproxil fumarate, respectively.[11] In our study, the two-year probability of TF was 47.2% in the in the bPI group, 39.2% in the NNRTI group and 22.2% in the InSTI group, with bPI-based and NNRTI-based regimens independently associated with a higher risk of treatment failure. Despite different endpoints, both studies confirm the difficulty of obtaining an optimal clinical outcome and the difficulty of maintaining in the long-term the initial regimen in HIV-infected patients with advanced disease; this is particularly true in those who start ART with a bPI- or a NNRTI-based regimen.

Our results seem also consistent with other previous studies,[22, 27, 28] even if the very low number of patients enrolled in randomized controlled trials with baseline CD4+ cell counts less than 200/mm^3 and HIV-RNA greater than 5 $\log_{10}$ copies/mL makes any comparison very difficult. It could be possible that in patients with very high viral load and very low CD4+ cell counts at ART start both the efficacy and the tolerability of InSTI-based, NNRTI-based and bPI-based regimen are not similar. This is suggested not only by our findings, but also, in part, by the results of another large observational study: patients who received a PI-based ART (but not those who received a NNRTI-based ART) were significantly more likely to have regimen modifications, compared with those who received an InSTI-based ART.[16] The authors of this study did not perform secondary analyses on the subgroup of patients with both CD4+ cell counts less than 200/mm^3 and HIV-RNA greater than 5 $\log_{10}$ copies/mL at ART start: hence, a more direct comparison with our findings is not possible.

A randomized controlled trial was specifically performed in severely immunosuppressed adults and children in Africa.[23] All patients had less than 100 cells/μL and 72% of them had greater than 5 $\log_{10}$ HIV-RNA copies/mL at ART start the 24-week mortality (the primary study end point) was not reduced by a raltegravir-intensified four-drug regimen; there was also no difference in the virological outcomes, with 83% and 80% of patients attaining less than 50 HIV-RNA copies/mL at week 48 in two arms. Despite different populations, socio-economic context and endpoints, also these results seem consistent with the main finding of our study.

In our study, differences between regimens were evident with regard to both virological efficacy and tolerability, with InSTI-based regimens emerging as the more potent and more tolerable anchor drug class: InSTI-based regimens showed the lowest risks of both virological failure and treatment interruption due to intolerance or toxicity. Indeed, in many randomized controlled trials, InSTI-based regimens resulted superior to a variety of comparators belonging both to the NNRTI class and to the PI class; this superiority was driven by differences in treatment interruptions for adverse events more than by differences in the rates of pure virological failure.[22, 27-30]

We sought to investigate also the association between type of initial regimen and treatment failure or virological failure in patients starting ART with greater than 500,000 HIV-RNA copies/mL: in this case, we were not able to confirm such association, likely because of the smaller sample size.

The only other factor independently associated with treatment failure was a baseline viral load greater than 500,000 HIV-RNA copies/mL. Again, our study has a unique design as included only patients with greater than 5 $\log_{10}$ copies/mL at ART start. However, our results are consistent with those from randomized[18-22] and observational studies,[31, 32] which showed a worse virological outcome in patients starting ART with these characteristics.

In our study, the type of initial ART was independently associated with virological failure if baseline viral load was between 100,000 and 500,000 HIV-RNA copies/mL. This is consistent with the results of the aforementioned studies and, in particular, with those which investigated specifically the role of very high baseline viral loads on the virological outcome.[31, 32] By contrast, the type of initial regimen was not independently associated with the risk of virological failure in patients who started ART with >500,000 HIV-RNA copies/mL; this suggests that the greater risk of virological failure associated with a very high baseline viral load leads cannot be significantly attenuated by starting ART with a regimen rather than another.

In another observational study in which only patients starting ART with greater than 500,000 HIV-RNA copies/mL were analyzed, those treated with a PI-based regimen showed the lowest probability of virological suppression (PI group: 72.4%; NNRTI group: 75.5%; PI plus InSTI group: 81.0%); accordingly, patients who received an initial regimen based on a PI plus an InSTIs and those who received NNRTI-based

initial regimens showed a significantly higher adjusted hazard ratio of virological suppression compared to those treated with PI-based regimens.[33] In the study of Santoro and coll., also patients with primary HIV infection and high CD4+ cell counts were included in the analysis; we limited our analysis to patients with less than 200 CD4+ cells/mm^3. Furthermore, we did not consider regimens based on more than three drugs because they are not recommended by current guidelines. Despite different population characteristics, the two-year probability (95%CI) of virological failure in patients who started ART an InSTI-based regimen in our study was 9.3% (6.4-13.4), i.e. lower than that observed in patients who started ART with a four-drug regimen in the study of Santoro and coll.; this suggest that in patients with very high viral load at ART start a three-drug regimen based on InSTIs could be as effective as a four-drug regimen based on the association of PIs and InSTIs as anchor drugs.

The main strength of this study is the relevant number of patients included in the analysis: to the best of our knowledge, this is the largest study of patients stating ART with both CD4+ cell counts less than 200/mm^3 and HIV-RNA greater than 5 $\log_{10}$ copies/mL.

The main limitation of this study was the lack of randomization; however, although statistically significant, baseline differences between groups were not clinically relevant. Nevertheless, it is possible that residual confounding by indication is present and it must be also acknowledged that we were able to adjust the analyses only for known possible confounders: for instance, we cannot exclude some differences between regimens in adherence to treatment due to both pill burden and twice daily dosing, especially in the bPI group.

Another possible limitation of our statistical approach is that we cannot completely exclude that we have missed some association, as we included in our models mainly variables associated with the outcome with p-value <0.1 at univariable analysis. However, we believe that all really relevant possible confounders have been considered in the multivariable analysis.

Finally, a further limitation is the different follow-up in the different treatment groups; however, the follow-up was adequate to estimate regimen durability also in the InSTI group.

Conclusions

In patients starting ART with less than 200 CD4+ cells/mm^3 and greater than 5 log_{10} HIV-RNA copies/mL, the durability of regimens based on InSTIs was longer than that of NNRTI- and bPI-based regimens. In these patients, InSTI-based regimens were also associated to lower probabilities of virological failure and of discontinuation because of intolerance or toxicity.

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Transparency declaration

Nicola Gianotti: advisor for Gilead Sciences, AbbVie and Janssen-Cilag and speakers' honoraria from Gilead Sciences, ViiV, Bristol-Myers Squibb, Merck Sharp and Dohme, Roche, AbbVie, Boehringer Ingelheim, and Janssen-Cilag.

Andrea De Luca: board membership for Gilead and ViiV, consultancies for Abbvie, Merck, Teva and Janssen, grants from ViiV and Merck, service in speakers's bureau for Gilead and travel grants from ViiV and Janssen.

Giordano Madeddu has received consultancy and/or speakers' fees from Gilead Sciences, Janssen, Merck Sharp & Dohme and ViiV.

Cristina Mussini: member of boards for Gilead, BMS, ViiV, Abbvie, MSD and have been member of speaker's bureau for Gilead.

Andrea Antinori: consultancies for Bristol-Myers Squibb, ViiV, Gilead, Abbvie, Merck Sharp and Dohme and Janssen-Cilag, grants from Gilead Sciences, Janssen-Cilag and Bristol-Myers Squibb and travel grants from Abbvie.

Antonella d'Arminio: member of boards for Abbvie, BMS, Gilead, Janssen, ViiV, MSD.

Patrizia Lorenzini, Alessandro Cozzi-Lepri, Laura Sighinolfi, Carmela Pinnetti, Carmen Santoro, Paola Meraviglia: no potential conflict of interest to declare.

Authors' contribution

Nicola Gianotti, Study conceptualization, study design, patients follow-up, writing of the first draft and following versions of the manuscript.

Patrizia Lorenzini, Study design, statistical analysis, writing of the first draft e following versions of the manuscript.

Alessandro Cozzi-Lepri, Study design, statistical analysis, manuscript revision.

Andrea De Luca, Patients follow-up, manuscript revision.

Giordano Madeddu, Patients follow-up, manuscript writing and revision.

Laura Sighinolfi, Patients follow-up, manuscript revision.

Carmela Pinnetti, Patients follow-up, manuscript revision.

Carmen Santoro, Patients follow-up, manuscript revision.

Paola Meraviglia, Patients follow-up, manuscript revision.

Cristina Mussini, Patients follow-up, manuscript revision.

Andrea Antinori, Study conceptualization, study design, patients follow-up, manuscript revision.

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Table 1. Baseline characteristics.

	Overall	**NNRTI**	**bPI**	**InSTI**	**p-value**
	1195	**184**	**696**	**315**	
Male gender, n(%)	920 (77.0%)	142 (77.2%)	533 (76.6%)	245 (77.8%)	0.914
Age, median (IQR)	42 (35-51)	42 (34-50)	42 (35-50)	44 (36-54)	0.022
Mode of HIV transmission, n(%)					*0.001*
Heterosexual	646 (54.1%)	107 (58.2%)	387 (55.6%)	152 (48.3%)	
IVDU	78 (6.5%)	15 (8.2%)	53 (7.6%)	10 (3.2%)	
MSM	358 (30.0%)	46 (25.0%)	202 (29.0%)	110 (34.9%)	
Other/unknown	113 (9.5%)	16 (8.7%)	54 (7.8%)	43 (13.7%)	
CDC stage C, n(%)	417 (34.9%)	68 (37.0%)	240 (34.5%)	109 (34.6%)	0.815
Antibodies against HCV, n(%)					*0.021*
negative	907 (75.9%)	139 (75.5%)	528 (75.9%)	240 (76.2%)	
positive	92 (7.7%)	23 (12.5%)	53 (7.6%)	16 (5.1%)	
not known	196 (16.4%)	22 (12.0%)	115 (16.5%)	59 (18.7%)	
HBsAg, n(%)					0.106
negative	939 (78.6%)	148 (80.4%)	552 (79.3%)	239 (75.9%)	
positive	66 (5.5%)	15 (8.2%)	31 (4.5%)	20 (6.3%)	
not known	190 (15.9%)	21 (11.4%)	113 (16.2%)	56 (17.8%)	
CD4+ cells/mm^3, median (IQR)	68 (29-129)	99 (34-150)	63 (24-125)	67 (32-120)	<0.001
CD4+ cells/mm^3, n(%)					*<0.001*
0-100	765 (64.0%)	93 (50.5%)	563 (66.5%)	209 (66.4%)	

101-200	430 (36.0%)	91 (49.5%)	233 (33.5%)	106 (33.6%)	
CD4+/CD8+ ratio, n(%)					*0.125*
<0.30	729 (61.0%)	102 (55.4%)	435 (62.5%)	192 (61.0%)	
0.30-0.45	54 (4.5%)	12 (6.5%)	30 (4.3%)	12 (3.8%)	
>0.45	35 (2.9%)	8 (4.4%)	13 (1.9%)	14 (4.4%)	
missing	377 (31.6%)	62 (33.7%)	218 (31.3%)	97 (30.8%)	
CD4+/CD8+ ratio, median (IQR)	0.12 (0.06-0.20)	0.15 (0.08-0.24)	0.11 (0.05-0.19)	0.11 (0.06-0.19)	0.002
HIV RNA copies/mL, n (%)					*0.069*
100,000-500,0000	771 (64.5%)	131 (71.2%)	448 (64.4%)	192 (61.0%)	
>500,000	424 (35.5%)	53 (28.8%)	284 (35.6%)	123 (39.0%)	
HIV-RNA (log_{10} copies/mL), median (IQR)	5.6 (5.3-5.9)	5.5 (5.2-5.7)	5.6 (5.3-5.9)	5.5 (5.3-5.9)	0.129
FIB-4 score, n(%)					*0.352*
<1.45	623 (52.1%)	103 (56.0%)	369 (53.0%)	151 (47.9%)	
1.45-3.25	340 (28.4%)	46 (25.0%)	193 (27.7%)	101 (32.1%)	
>3.25	104 (8.7%)	20 (10.9%)	58 (8.3%)	26 (8.2%)	
missing	128 (10.7%)	15 (8.2%)	76 (10.9%)	37 (11.8%)	
eGFR (CKD-EPI), min/ml/1.73m^2, n(%)					*0.737*
≤60	30 (2.5%)	170 (92.4%)	627 (90.1%)	285 (90.5%)	
>60	1082 (90.5%)	5 (2.7%)	16 (2.3%)	9 (2.9%)	
missing	83 (7.0%)	9 (4.9%)	53 (7.6%)	21 (6.7%)	
Ongoing opportunistic disease, n(%)	393 (32.9%)	63 (34.2%)	228 (32.8%)	102 (32.4%)	0.907
Haemoglobin , n(%)					*0.139*

<12 (F) OR <14 (M) g/dL	277 (23.2%)	53 (28.8%)	157 (22.6%)	67 (21.3%)	
≥12 (F) OR ≥14 (M) g/dL	867 (72.6%)	127 (69.0%)	510 (73.3%)	230 (73.0%)	
missing	51 (4.3%)	4 (2.2%)	29 (4.2%)	18 (5.7%)	
Haemoglobin g/dL, median (IQR)	12.2 (10.7-13.5)	12.4 (10.8-13.6)	12.3 (10.9-13.4)	11.9 (10.6-13.4)	0.278
Platelets, n(%)					*0.547*
normal (150,000-450,000)	722 (60.4%)	115 (62.5%)	414 (59.5%)	193 (61.3%)	
<150,000 or >450,000	418 (35.0%)	64 (34.8%)	250 (35.9%)	104 (33.0%)	
missing	55 (4.6%)	5 (2.7%)	32 (4.6%)	18 (5.7%)	
Platelets, x10^3, median (IQR)	177 (134-233)	185 (136-227)	176 (133-234)	178 (133-231)	0.807
Neutrophils, n(%)					<0.001
normal (2.000-7.000)	547 (45.8%)	99 (53.8%)	314 (45.1%)	134 (42.5%)	
<2.000 or >7.000	512 (42.9%)	77 (41.9%)	307 (44.1%)	128 (40.6%)	
missing	136 (11.4%)	8 (4.3%)	75 (10.8%)	53 (16.8%)	
Neutrophils, median (IQR)	2100 (1490-3000)	2130 (1479-2800)	2096 (1434-3060)	2115 (1600-3170)	0.306
Year of ART start, n(%)					*<0.001*
2004-2006	24 (2.0%)	6 (3.3%)	18 (2.6%)	0 (0%)	
2007-2009	146 (12.2%)	33 (17.9%)	112 (16.1%)	1 (0.3%)	
2010-2012	382 (32.0%)	96 (52.2%)	275 (39.5%)	11 (3.5%)	
2013-2015	403 (33.7%)	44 (23.9%)	245 (35.2%)	114 (36.2%)	
2016-2017	240 (20.1%)	5 (2.7%)	46 (6.6%)	189 (60.0%)	
NRTI combination, n(%)					*<0.001*
Tenofovir plus emtricitabine	1063 (89.0%)	180 (97.8%)	639 (91.8%)	244 (77.5%)	

Abacavir plus lamivudine	132 (11.0%)	4 (2.2%)	57 (8.2%)	71 (22.5%)

bPI: Ritonavir or cobicistat-boosted protease inhibitor; InSTI: integrase strand transfer inhibitor; IVDU: intravenous drug user; MSM: man who have sex with men; eGFR: estimated glomerular filtration rate; F: females; M: males; NRTI: nucleoside reverse transcriptase inhibitor.

Table 2. Univariable and multivariable analysis of factors associated with treatment failure. Multivariable models included variables retained from univariable because their p-value was <0.1.

	Unadjusted IRR (95% CI)	p-value	Adjusted IRR (95% CI)	p-value
Female versus male gender	0.98 (0.82-1.17)	0.798	-	
Age (10 yrs older)	1.06 (0.98-1.13)	0.124	-	
Age >45 yrs	1.25 (1.07-1.46)	0.006	*	
Mode of HIV transmission				
heterosexual	1.00		-	
IVDU	0.87 (0.63-1.21)	0.414	-	
MSM	1.15 (0.96-1.378)	0.128	-	
Other/unknown	1.20 (0.91-1.57)	0.191	-	
CDC stage C	1.05 (0.89-1.23)	0.583	-	
Antibodies against HCV				
negative	1.00		1.00	
positive	0.76 (0.56-1.03)	0.072	0.79 (0.58-1.08)	0.137
not known	0.90 (0.73-1.11)	0.337	0.93 (0.75-1.15)	0.491
HBsAg				
negative	1.00		-	
positive	0.92 (0.65-1.31)	0.635	-	
not known	0.95 (0.76-1.17)	0.617	-	
CD4+ cells/mm^3				
0-100	1.00		1.00	
101-200	0.82 (0.69-0.96)	0.015	0.89 (0.75-1.06)	0.182
CD4+/CD8+ ratio				

<0.3	1.00		-	
0.3-0.45	0.90 (0.61-1.32)	0.579	-	
>0.45	1.08 (0.67-1.73)	0.762	-	
missing	0.94 (0.79-1.11)	0.444	-	
HIV-RNA copies/mL				
100,000-500,000	1.00		1.00	
>500,000	1.32 (1.12-1.55)	0.001	1.26 (1.07-1.48)	0.006
FIB-4 score				
<1.45	1.00		1.00	
1.45-3.25	1.07 (0.90-1.28)	0.441	1.05 (0.88-1.26)	0.593
>3.25	1.06 (0.80-1.40)	0.678	1.10 (0.83-1.47)	0.493
missing	0.80 (0.60-1.06)	0.115	0.83 (0.56-1.22)	0.344
eGFR (CKD-EPI), mL/min/1.73m^2				
>60	1.00		1.00	
≤60	0.96 (0.59-1.58)	0.882	1.04 (0.62-1.73)	0.884
missing	0.74 (0.54-1.02)	0.063	0.78 (0.51-1.19)	0.252
Opportunistic disease at baseline	1.04 (0.88-1.22)	0.647	-	
Haemoglobin				
≥12(F) OR ≥14 (M) g/dL	1.00		1.00	
<12(F)OR <14 (M) g/dL	1.18 (0.98-1.43)	0.07	1.08 (0.89-1.31)	0.450
missing	0.86 (0.55-1.33)	0.493	1.18 (0.66-2.11)	0.566
Platelets				
normal (150,000-450,000)	1.00		-	
<150,000 or >450,000	1.04 (0.88-1.22)	0.656	-	
missing	0.78 (0.52-1.16)	0.215	-	
Neutrophils				

normal (2,000-7,000)	1.00		-	
<2,000 or >7,000	1.00 (0.85-1.17)	0.967	-	
missing	0.94 (0.72-1.23)	0.676	-	
Year of cART start (1 yr more)	1.00 (0.98-1.03)	0.728		
NRTI combination				
FTC+TDF	1.00		1.00	
ABC+3TC	1.03 (0.78-1.35)	0.838	1.05 (0.79-1.39)	0.731
Anchor drug class (alternative 1)				
NNRTI	1.00		1.00	
bPI	1.72 (1.38-2.14)	<0.001	1.62 (1.29-2.03)	<0.001
InSTI	0.89 (0.66-1.21)	0.469	0.68 (0.48-0.96)	0.030
Anchor drug class (alternative 2)				
NNRTI	0.58 (0.47-0.72)	<0.001	0.62 (0.50-0.78)	<0.001
bPI	1.00		1.00	
InSTI	0.52 (0.41-0.66)	<0.001	0.42 (0.32-0.56)	<0.001

* not included in the model because the variable “age” is already considered in the calculation of both the eGFR and the FIB4 score.

IVDU: intravenous drug user; MSM: man who have sex with men; eGFR: estimated glomerular filtration rate; F: females; M: males; bPI: Ritonavir or cobicistat-boosted protease inhibitor; InSTI: integrase strand transfer inhibitor.

Figure legends

Figure 1. Cumulative probability of treatment failure (TF) according to the anchor drug class of the initial ART regimen. bPI: Ritonavir or cobicistat-boosted protease inhibitor; InSTI: integrase strand transfer inhibitor.

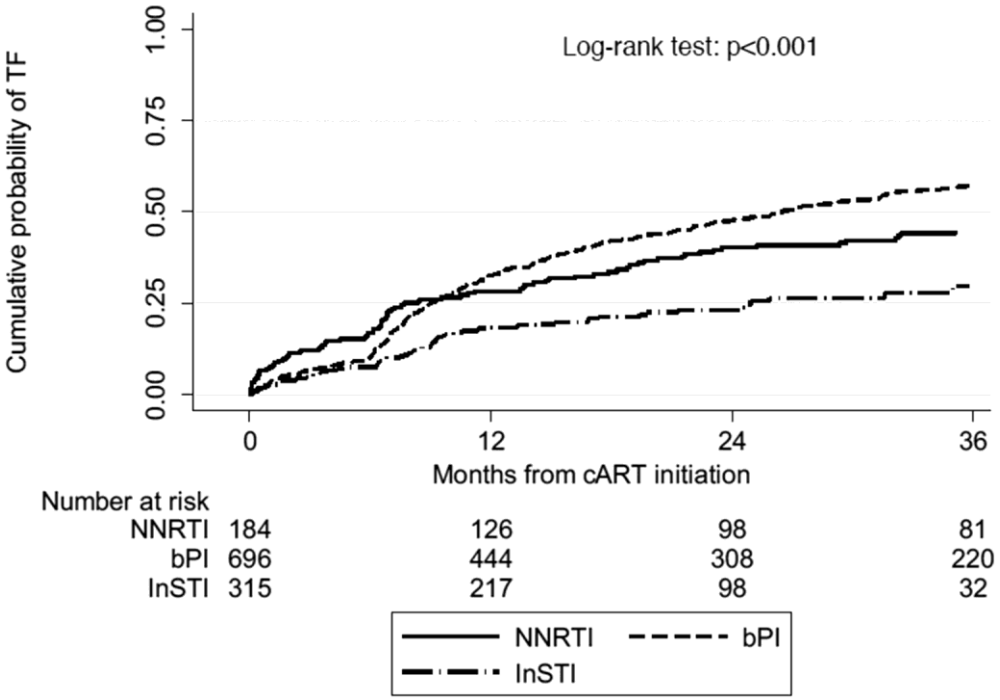

Figure 2. Cumulative probability of virological failure (VF) according to the anchor drug class of the initial ART regimen. bPI: Ritonavir or cobicistat-boosted protease inhibitor; InSTI: integrase strand transfer inhibitor.

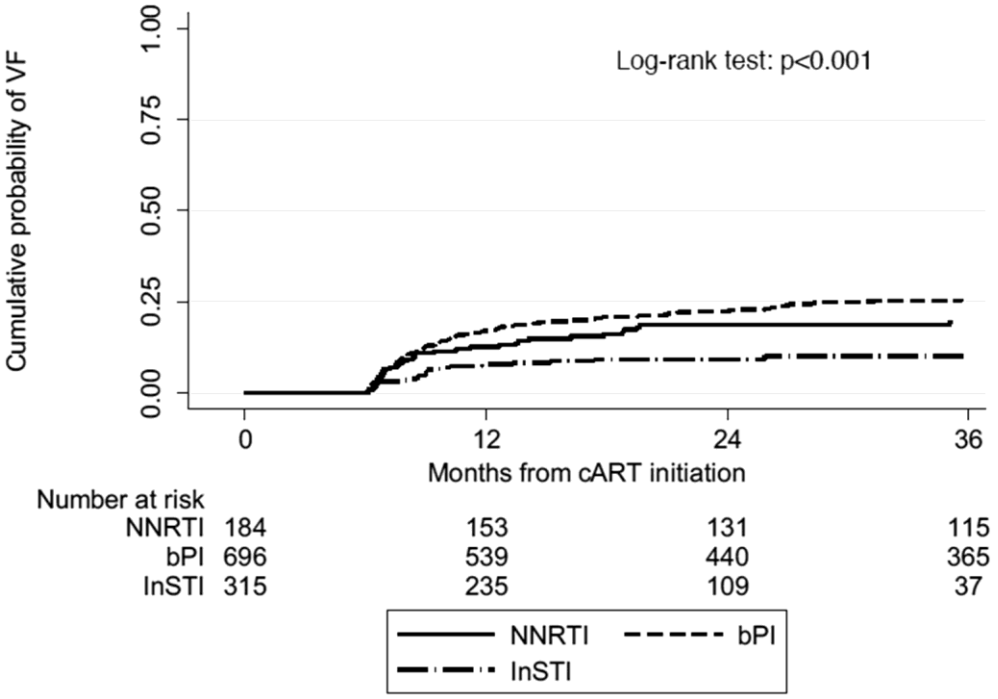

Figure 3. Cumulative probability of discontinuation for toxicity/intolerance according to the anchor drug class of the initial ART regimen. bPI: Ritonavir or cobicistat-boosted protease inhibitor; InSTI: integrase strand transfer inhibitor.

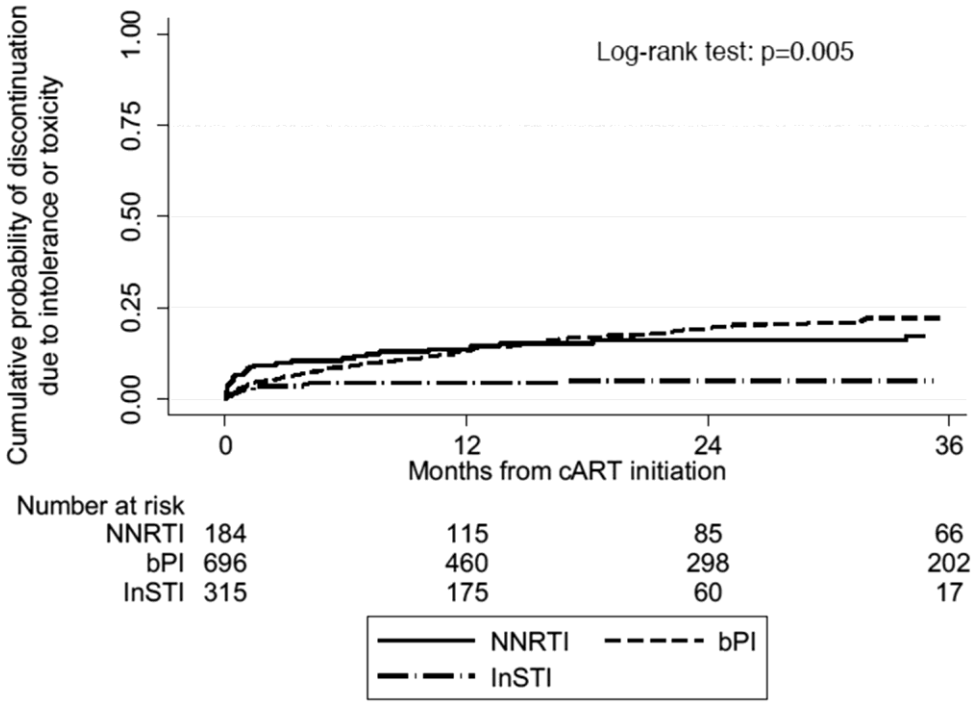

Figure 4. Median CD4+ cell counts at selected time-points during follow-up, according to the initial ART regimen. PI/r: ritonavir-boosted protease inhibitor; PI/c: cobicistat-boosted protease inhibitor; InSTI: integrase strand transfer inhibitor.