


RESEARCH ARTICLE

Early versus delayed antiretroviral therapy based on genotypic resistance test: Results from a large retrospective cohort study

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Abstract

Rapid start of antiretroviral therapy (ART) pending genotypic resistance test (GRT) has been recently proposed, but the effectiveness of this strategy is still debated. The rate of virological success (VS), defined as HIV-RNA < 50 copies/ml, with and without GRT was compared in drug-naïve individuals enrolled in the Italian ARCA cohort who started ART between 2015 and 2018. 521 individuals started ART: 397 without GRT (pre-GRT group) and 124 following GRT (post-GRT group). Overall, 398 (76%) were males and 30 (6%) were diagnosed with AIDS. In the pre-GRT group, baseline CD4+ cell counts were lower ($p < 0.001$), and viral load was higher ($p < 0.001$) than in the post-GRT group. The estimated probability of VS in pre-GRT versus post-GRT group was 72.54% (CI₉₅: 67.78–76.60) versus 66.94% (CI₉₅: 57.53–74.26) at Week 24 and 92.40% (CI₉₅: 89.26–94.62) versus 92.92% (CI₉₅: 86.35–96.33) at Week 48, respectively ($p = 0.434$).

Davide F. Bavaro, Andrea De Vito, and Giuseppe Pasculli equally contributed to this study.

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At Week 48, VS was less frequent among individuals with baseline CD4+ cell counts <200 versus >500 (90.33% vs. 97.33%), log viral load <5.00 versus >5.70 log₁₀ cps/ml (97.17% vs 78.16%; $p < 0.001$), and those treated with protease inhibitors or non-nucleoside reverse transcriptase inhibitors versus those treated with integrase strand transfer inhibitors ($p < 0.001$). The rate of VS does not seem to be affected by an early ART initiation pending GRT results, but it could be influenced by the composition of the ART regimen, as well as immuno-virological parameters.

KEYWORDS

early start, first-line antiretroviral treatment, genotypic-resistance test, HIV, rapid ART

1 | INTRODUCTION

Along with the introduction of more potent and better tolerated antiretroviral therapy (ART), the correct timing of treatment initiation in individuals with a new diagnosis of HIV infection has been anticipated. Until November 2011, European guidelines¹ recommended deferring the treatment in people living with HIV (PLWH) until CD4+ cells count fell below 350 cells/mm³ or in case of symptomatic infection. However, in the following years, many studies proved that early ART initiation, even among PLWH with good immunological status, reduced the risk of mortality,²⁻⁵ HIV transmission⁶ and occurrence of AIDS-defining events,⁷ protecting from the risk of virologic failure⁸ and the selection of HIV drug-resistant strains.⁹ Consequently, current international guidelines recommend starting ART as soon as possible, regardless of the CD4+ cell count. Moreover, in the last few years, a new strategy for ART initiation called “same-day”¹⁰ or “rapid”¹¹ ART has been proposed, pushing forward the concept of “early initiation.” According to this strategy, ART should be provided during the first visit or within a short period thereafter. However, the disadvantages or the potential risks of this strategy are still debated.¹² Indeed, this approach might not be the safest in patients with mental health disorders, who are at risk for low compliance to ART, or whenever an underlying mycobacterial or cryptococcal opportunistic infection is suspected. Moreover, this strategy could be burdened by an increased risk of virologic failure due to undiagnosed transmitted drug resistance mutations.^{13,14} Nevertheless, the advent of the newest ART regimens with a higher genetic barrier, like those containing the second-generation integrase strand inhibitors (INSTIs), has significantly reduced the risk of transmitted or acquired resistance-associated failure.¹⁵ This stimulated the debate whether the availability of a genotypic resistance test (GRT) before treatment initiation is still needed. Recent studies concluded that baseline GRT offers minimal clinical benefits and is not cost-effective,¹⁵ whereas current European guidelines¹⁶ still suggest to keep performing the GRT before starting the treatment in the absence of conclusive studies on this topic, and the World Health Organization neither formally recommends nor discourages pretreatment GRT.¹⁷

Our study aimed at investigating the rate of virological success (VS) among PLWH who started first-line ART pending GRT or with available GRT results, and clarifying predictors of VS.

2 | PATIENTS AND METHODS

2.1 | Patients

ARCA (Antiviral Response Cohort Analysis) is an Italian observational database (dbarca.net) created for the surveillance of HIV-1 drug resistance and the implementation of models to predict virological response to ART. To date, ARCA contains demographic, clinical, treatment and virological data of more than 40,000 HIV-1 infected patients followed at >50 clinical centers in Italy. Of note, Italy has around 120 Infectious Diseases clinical centers that represent the point of care of PLWH in our Country. Importantly, all major Italian academic centers are included in ARCA cohort, as well as most of the principal nonacademic hospitals. Thus, this database can be considered highly representative of the Italian cohort of PLWH currently on ART.

For the present study, demographic, clinical, and treatment data, HIV-1 RNA load, CD4+ cell count, and drug resistance information were retrieved from ART-naïve PLWH who started treatment between 2015 and 2018 with at least 1 year of follow-up available.

Data of patients were retrieved from ART initiation since discontinuation, intended both as switch to other regimens or treatment interruption, for any cause.

VS was defined as the achievement of an HIV-1 RNA plasma value <50 copies/ml after the treatment initiation. Accordingly, the primary outcome was the probability of obtaining the VS at 24 and 48 weeks after ART initiation; on the contrary virological failure (VF) was defined as the first of two consecutive HIV-1 RNA plasma value >50 copies/ml or the at least one >200 copies/ml, after achievement of the VS.

2.2 | Pre- and post-GRT group categorization

The GRT was performed at diagnosis, or, when not feasible, within the next 72 h; in fact, the availability of a baseline GRT before the

ART initiation is the “entry criteria” of ARCA cohort. In all cases, GRT testing was performed on plasma deriving from blood samples.

Accordingly, the date of diagnosis matches the date of GRT. However, the actual date of GRT results availability is not recorded in the ARCA database. Therefore, a survey of the minimum time to acquire GRT after the blood sample collections was performed among centers included in the present study. In no case, the GRT was obtained in less than 14 days, except in selected and anecdotal cases with motivated request by clinicians; consequently, to divide individuals according to GRT availability, PLWH were categorized into (i) pre-GRT group, if ART was started within 14 days of GRT collection, assuming pending GRT; and (ii) post-GRT group, if ART was started more than 14 days after the date of GRT collection, assuming available GRT.

2.3 | HIV-1 genotyping and drug resistance evaluation

HIV-1 GRT was performed at each participating center based on local procedures (Sanger sequencing) and checked for consistency upon sequence uploading into the ARCA database. The database automatically extracts the mutations based on HIV-1 consensus B sequence using a built-in local alignment script based on ClustalW and returns a 5-level susceptibility score based on the built-in AntiRetroScan algorithm.¹⁸ Pretreatment drug resistance-associated mutations (PDRAMs) were defined as the detection of at least one mutation included in the World Health Organization (WHO)-recommended surveillance drug resistance mutation (SDRM) list¹⁹ and/or in the International Antiviral Society-USA (IAS-USA)²⁰ drug resistance mutations list.

2.4 | Statistical analysis

The marginal and stratified survival distributions were estimated through the Kaplan–Meier product-limit estimator. The association between viral suppression and its predictors was evaluated by means of Cox proportional hazard regression at both univariable and multivariable levels. A significance level of $\alpha = 5\%$ was specified before data analysis. At multivariable analysis, for assessment of the independent prognostic performance of VS, we first performed variable selection through univariable analysis of all variables correcting the p value for false discovery rate (FDR) for multiple testing (q value < 0.01), and then including all the significantly associated confounders in the multivariable model. The differences of numerical covariate between the two groups were evaluated with unpaired t -test or Wilcoxon rank-sum test depending on the distributions of the residuals in a linear regression model. For categorical variables, the differences in terms of proportions between the two groups were evaluated with Pearson's χ^2 or Fisher's exact tests for count data depending on their expected values. All analyses were conducted in R version 4.0.2 (2020-06-22) running under Windows 10 $\times 64$ (build 18362).

3 | RESULTS

3.1 | General demographic and immuno-virologic features of patients

Of 521 ART-naïve individuals included in the study, 397 and 124 started ART pending GRT results and with available GRT results, respectively. Patients were followed up for a median (Q1–Q3) time of 90 (54–131) weeks. Overall, 76.4% ($n = 398$) were males, the median (Q1–Q3) age was 40 (31–49) years, and 30 (5.8%) were diagnosed with an AIDS-defining event. The overall median (Q1–Q3) CD4+ cell count and mean (Q1–Q3) HIV-RNA load were 284 (110–481) cells/mm³ and 4.86 (4.28–5.51) log₁₀ cp/ml, respectively. Detailed baseline characteristics of the population included are outlined in Table 1.

3.2 | Analysis of pretreatment drug resistance-associated mutations

Overall, 92 (17.7%) individuals showed at least one PDRAM to any class (Figure 1), without significant difference between pre- and post-GRT groups. In particular, individuals who showed at least one PDRAMs to non-nucleos(t)ide reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), nucleos(t)ide reverse transcriptase inhibitors (NRTIs), and INSTIs were 64 (12.3%), 22 (4.2%), 11 (2.1%), and 1 (0.2%), respectively. PDRAMs associated with reduced susceptibility to NNRTIs were the most frequently identified; in particular, E138A/G/K was detected in 7.2%, followed by V106I in 3.2%, and K103N in 1.1%. For NRTIs, the more frequent PDRAM observed was M41L (1.1%), followed by D67N (0.9%) and L210W (0.6%) For PIs, L33F was detected in 2.8% and M46I/L in 1.7%. For INSTIs, only one case with T66I was found. Concomitant resistance to two and three drug classes was detected in 4 (0.8%) and 1 (0.2%) cases, respectively, all in the post-GRT group.

3.3 | First-line ART regimens

A three-drug ART regimen was administered in 97.3% of patients, while the remaining 2.7% started a four-drug ART regimen. In particular, an INSTI-based regimen was the most frequent ART prescribed in both groups (59.4% in the pre-GRT group and 59.7% in the post-GRT group), with dolutegravir prescribed in 187 (60%) cases, followed by elvitegravir/cobicistat in 81 (26%) and raltegravir in 42 (14%) subjects. An NNRTI-based regimen was more frequently prescribed in the post-GRT group (27.4% vs. 13.6% in the pre-GRT group, $p < 0.001$) while a PI-based regimen was preferred in the pre-GRT group (23.7% vs. 12.1% in the post-GRT group, $p = 0.003$). Interestingly, a significant increase of INSTI-based regimens was noticed in 2016 (62%), 2017 (71%), and 2018 (68%) if compared with 2015 (41%; $p < 0.001$). As a consequence, the prescription of PI-based regimens and NNRTI-based regimens has reduced over the years (see Table S1, panel A). Similar results were found by replicating the analysis in the pre- and post-GRT groups (Table S1, panels B and C).

TABLE 1 General features of patients stratified by GRT groups.

	Post (N = 124)	Pre (N = 397)	Total (N = 521)	p
Weeks of follow-up				0.144 ^a
Count	124	397	521	
Median	95.35	87.28	90.14	
Q1, Q3	64.14, 140.74	53.00, 125.85	54.00, 130.85	
Gender				0.428 ^b
Female	26 (20.97%)	97 (24.43%)	123 (23.61%)	
Male	98 (79.03%)	300 (75.57%)	398 (76.39%)	
Age (years)				0.566 ^a
Count	115	386	501	
Median	39.00	40.00	40.00	
Q1, Q3	30.50, 48.50	31.00, 49.00	31.00, 49.00	
Baseline CD4+ cells count (cells/μl)				<0.001 ^a
Count	124	396	520	
Median	383.50	257.00	284.00	
Q1, Q3	253.00, 564.25	93.50, 448.75	110.00, 480.25	
Baseline HIV-1 viral load (log₁₀ copies/ml)				<0.001 ^c
Count	124	397	521	
Mean	4.54	4.95	4.86	
SD	0.84	0.88	0.88	
AIDS stage				0.166 ^b
No	120 (96.77%)	371 (93.45%)	491 (94.24%)	
Yes	4 (3.23%)	26 (6.55%)	30 (5.76%)	
Calendar year of starting ART				0.984 ^b
2015	35 (28.23%)	108 (27.20%)	143 (27.45%)	
2016	37 (29.84%)	119 (29.97%)	156 (29.94%)	
2017	38 (30.65%)	128 (32.24%)	166 (31.86%)	
2018	14 (11.29%)	42 (10.58%)	56 (10.75%)	
Anchor drug class				<0.001 ^d
INSTIs	74 (59.68%)	236 (59.45%)	310 (59.50%)	
PIs	15 (12.10%)	94 (23.68%)	109 (20.92%)	
NNRTIs	34 (27.42%)	54 (13.60%)	88 (16.89%)	
Other	1 (0.81%)	13 (3.27%)	14 (2.69%)	
ART backbone				0.23 ^d
3TC/ABC	22 (17.74%)	63 (15.87%)	85 (16.31%)	
FTC/TXF	102 (82.26%)	331 (83.38%)	433 (83.11%)	
Other	0 (0.00%)	3 (0.76%)	3 (0.58%)	
ART drugs number				0.205 ^d
3	123 (99.19%)	384 (96.73%)	507 (97.31%)	
4	1 (0.81%)	13 (3.27%)	14 (2.69%)	

(Continues)

TABLE 1 (Continued)

	Post (N = 124)	Pre (N = 397)	Total (N = 521)	p
HIV-1 viral subtype				0.627 ^b
Unknown	2	1	3	
NON-B	52 (42.62%)	159 (40.15%)	211 (40.73%)	
B	70 (57.38%)	237 (59.85%)	307 (59.27%)	
Baseline number of mutations				0.018 ^a
Count	124	397	521	
Median	4.00	4.00	4.00	
Q1, Q3	2.75, 5.00	3.00, 6.00	3.00, 6.00	
Number of drug classes resistance				0.435 ^b
No resistances	105 (84.68%)	324 (81.61%)	429 (82.34%)	
Resistance to at least 1 Class	19 (15.32%)	73 (18.39%)	92 (17.66%)	
Resistance to INSTIs				1.000 ^d
	0 (0.00%)	1 (0.25%)	1 (0.19%)	
Resistance to PIs				0.253 ^b
	3 (2.42%)	19 (4.79%)	22 (4.22%)	
Resistance to NNRTIs				0.484 ^b
	13 (10.48%)	51 (12.85%)	64 (12.28%)	
Resistance to NRTIs				0.785 ^b
	3 (2.42%)	8 (2.02%)	11 (2.11%)	

Note: Q1, Q3 = first-third quartile.

Abbreviations: GRT, genotypic resistance test; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleos(t)ide reverse transcriptase inhibitor; NRTI, nucleos(t)ide reverse transcriptase inhibitor; PI, protease inhibitor.

^aWilcoxon rank-sum test.

^bPearson's Chi-squared test.

^cUnpaired t-test.

^dFisher's exact test for count data.

3.4 | Rate and predictors of virologic suppression

The median time to virologic suppression was 14.43 (CI₉₅: 13.10–15.90) weeks, with an overall probability of reaching virologic suppression of 71.21% (CI₉₅: 67.05–74.85) at Week 24 and 92.51% (CI₉₅: 89.83–94.48) at Week 48. This probability did not differ comparing the pre- and post-GRT groups (Figure 2A). However, there was a significant difference in the rate of VS at Week 48 according to baseline CD4+ cell counts: 90.33 (CI₉₅: 84.96–93.79) among individuals with <200 cells/μl, 91.60% (CI₉₅: 84.79–95.36) with 200–350 cells/μl, 91.70% (CI₉₅: 83.43–95.84) with 350–500 cells/μl, and 97.33% (CI₉₅: 91.91–99.12) with >500 cells/μl (Figure 2B).

Baseline viral load also influenced the probability of achieving VS at 48 weeks (Figure 2C): 97.17% (CI₉₅: 94.40–98.57) among individuals with HIV-RNA load <5.00 log₁₀ cp/ml, 92.04% (CI₉₅: 85.99–95.48) with 5.00–5.70 log₁₀ cp/ml, and 78.16% (CI₉₅: 67.60–78.16) with >5.70 log₁₀ cp/ml.

Finally, VS rates differed with different anchor drugs: 96.07% (CI₉₅: 93.39–97.88) for INSTIs, 83.80% (CI₉₅: 76.26–90.03) for PIs, 93.18% (CI₉₅: 86.66–97.21) for NNRTIs and 78.57% (CI₉₅: 55.21–94.79) for other drugs (Figure 2D).

After performing a univariable Cox regression (Table S2) to select variables associated with VS, a multivariable Cox regression model identified higher viral load at baseline and a PI or NNRTI versus INSTI anchor drug as significant negative predictors of VS. By contrast, a baseline CD4+ cells count >500 cells/μl was an independent predictor of VS when compared with the <200 cells/μl reference group (Table 2).

4 | DISCUSSION

To the best of our knowledge, this study is one of the largest, which aimed to compare virologic outcomes of PLWH who started ART pending GRT versus those who started a GRT-based ART in a real-life setting. We did not detect any difference in the rate of virologic

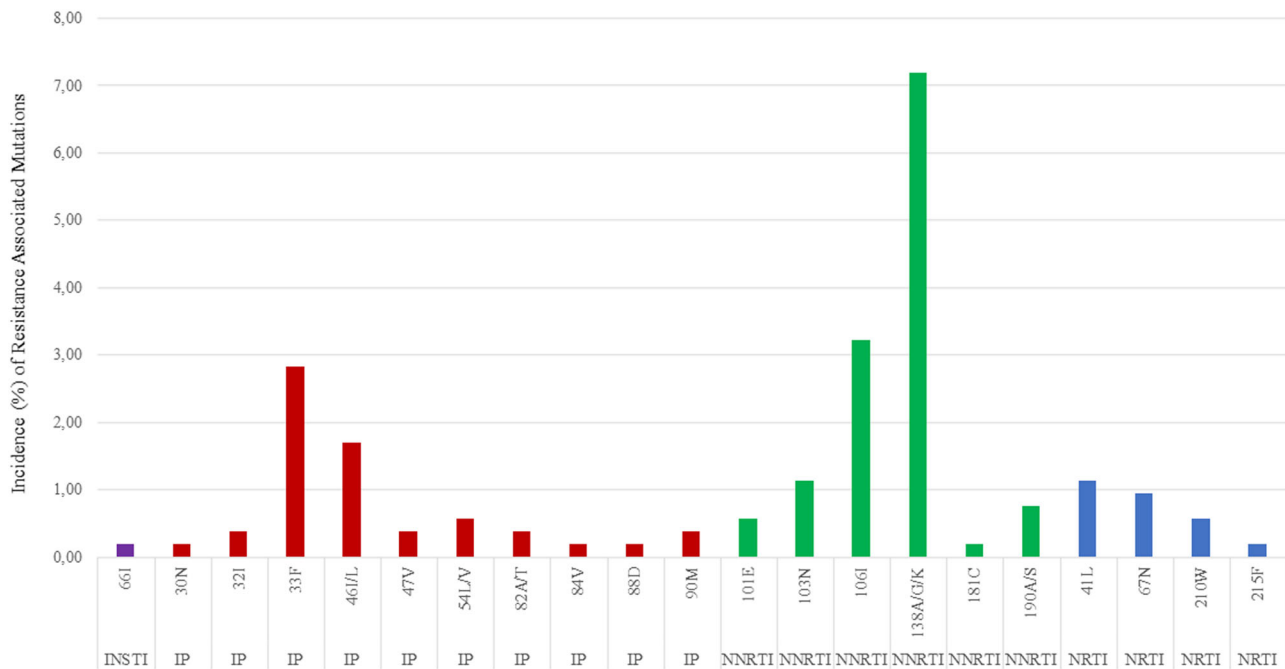


FIGURE 1 Resistance associated mutations detected at baseline GRT, expressed in absolute numbers. GRT, genotypic resistance test; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleos(t)ide reverse transcriptase inhibitor; NRTI, nucleos(t)ide reverse transcriptase inhibitor; PI, protease inhibitor.

suppression between ART initiation with or without baseline GRT results. Rather, significant predictors of virologic failure included baseline CD4+ cell counts, HIV-RNA load, and type of anchor drug.

However, it should be noticed that PLWH in the pre-GRT group had a lower median CD4+ cell count and a higher median HIV-RNA load, if compared with those in the post-GRT group. It is assumable that the more compromised immune-virological status of these patients forced clinicians to earlier ART initiation, while on the other side, a GRT-based treatment choice was preferred. This is a possible explanation of the baseline difference between the two groups.

In line with previous studies conducted in Italy,²¹ VS was largely achieved in both groups, highlighting the potency and tolerability of current antiretroviral treatments. On the other hand, the limited number of VFs observed (2.9%) may have limited the analysis of the impact of GRT results. While the role of baseline CD4+ cell counts and viral load is expected, the higher probability of failure with NNRTI- and PI-based regimens, compared with INSTIs, corroborates the efficacy of this class, especially second-generation INSTIs that demonstrated their potency also in late or AIDS-presenters and/or with baseline RAMs.^{21–26}

In our cohort, NNRTIs were less frequently used in the pre-GRT group, probably because of the lower genetic barrier with respect to the other anchor drug classes. In the post-GRT group, NNRTIs were instead used more frequently than PIs (27% vs. 12%), probably due to the lower rate of drug–drug interactions and adverse effects and comparable level of effectiveness in absence of RAMs.²³ Still, it should be noted that the rate of PDRAMs at the first GRT in our study was lower if compared with other studies. For instance, Fogel et al.²⁷ observed a relatively high prevalence of PDRAMs; in particular, 12% of

subjects had a multiclass resistance, and 8% had a resistance to INSTIs. Rich et al.²⁸ found a lower prevalence of transmitted drug resistance. Mbisa et al.²⁹ evaluated the presence of pre-ART resistance through the use of next-generation sequencing in 655 naive PLWH in the United Kingdom. They detected 3.9% of major INSTI RAMs and 4.4% for PIs at the low-frequency variants (2%–20%), while at the high variant frequency ($\geq 20\%$) no resistance at INSTI were found and 2.4% of individuals had a PIs resistance. On the contrary, the prevalence of PDRAMs in our cohort was dissimilar: resistance to at least one class and multiclass resistance were detected in 17.7% and 0.8% of cases, respectively; only one subject (0.2%) showed resistance to INSTI; this was also different from other recent Italian surveillance studies that recorded a resistance rate around 8%–10%.^{14,30,31} Probably, these differences among studies may be explained by multiple reasons, including: (i) the different mutations lists used for the analysis; (ii) the dissimilar management of patients in different geographic areas; (iii) the different epidemiology of circulating pretreatment drug resistance mutations in different regions.

In any case, this feature should be considered since the low prevalence of RAMs could have influenced the probability of virologic suppression in individuals starting ART pending GRT, particularly when a low/intermediate genetic barrier anchor drug was chosen to build the first-line regimen. In fact, by performing a post hoc analysis of pretreatment drug resistance mutations detected at baseline GRT (in both pre- and post-GRT groups), stratified according to anchor drug class prescribed (see Table S3), we found a very low incidence of RAMs; accordingly, different results may occur in case of a higher incidence of baseline PDRM, that could increase, in

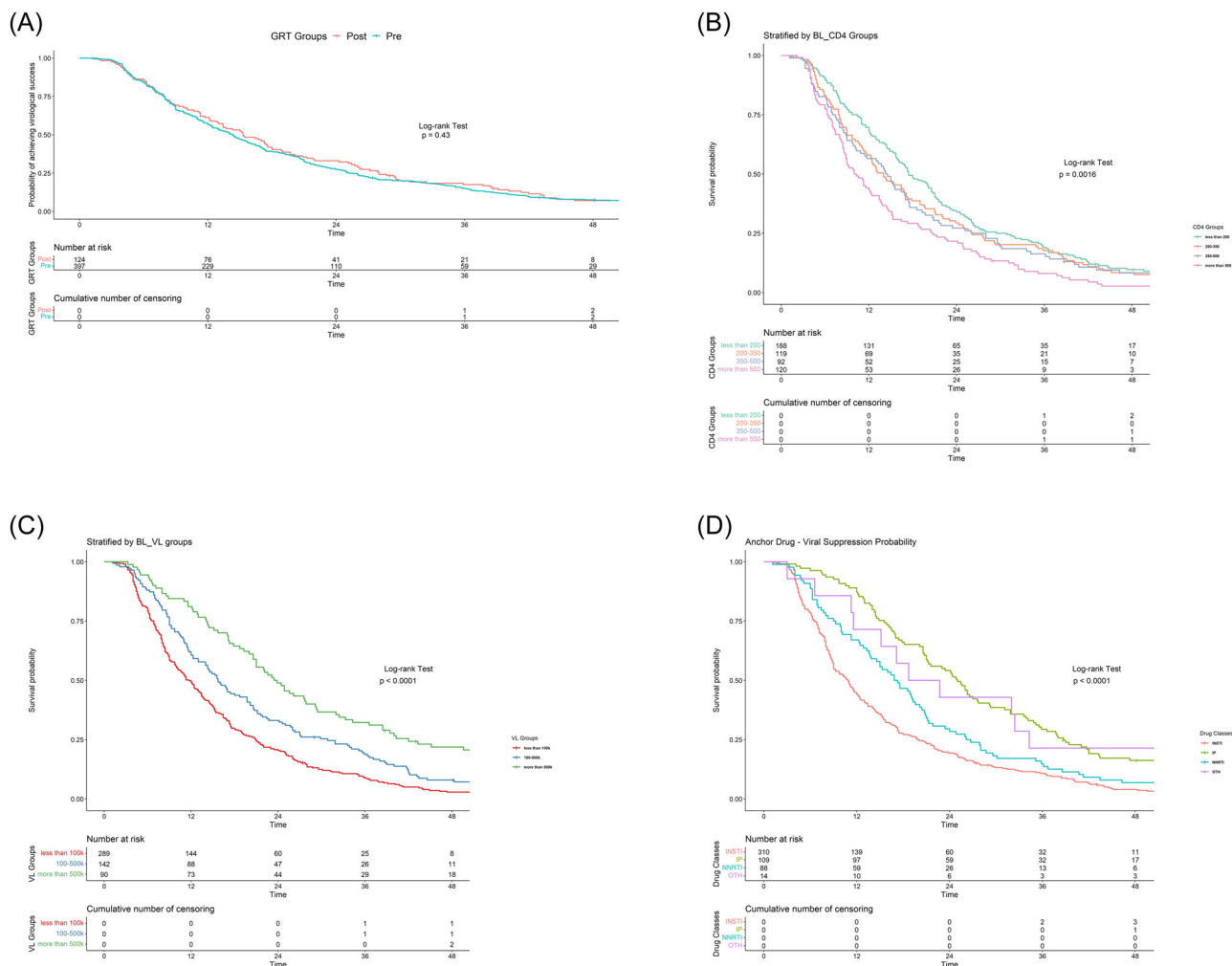


FIGURE 2 Rate of virologic suppression according to GRT group (A), baseline CD4+ cells count (B), baseline HIV viral load (C), and anchor drug class (D). GRT, genotypic resistance test; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleos(t)ide reverse transcriptase inhibitor; NRTI, nucleos(t)ide reverse transcriptase inhibitor; PI, protease inhibitor; VL, viral load.

turn, the risk of prescribing a suboptimal first-line regimen pending the GRT results.

The knowledge of baseline RAMs remains pivotal even in patients who achieved virologic suppression to sequentially use antiretroviral drugs, particularly for simplification strategy to a dual-treatment regimen.^{32,33} Hence, although “rapid-ART” strategies could probably be implemented without a significant risk of virologic failure, baseline GRT should still be performed, particularly in high-income settings in any ART-naïve PLWH to ensure optimal subsequent ART strategies. In fact, tailoring and optimizing the first-line and the subsequent ART regimens is pivotal to obtain virologic suppression by limiting the risks of long-term toxicity, drug–drug interaction, emergence of resistance, and improve the overall quality of life of PLWH by selecting the most practical regimen for each patient. Accordingly, the knowledge of baseline GRT is necessary to address all these needs without increasing the risk of virologic failure and selecting resistance mutations.

Of note, in this study, PLWH were censored when ART discontinuation occurred; consequently, further therapeutic changes

were not recorded and analyzed; however, possible implication of GRT acquisition in subjects who started ART pending GRT are still discussed. Consequently, further studies exploring this particular setting are needed.

The strengths of this study are the real-life setting, the large sample size, the inclusion of regimens approved by current guidelines, the recent span of time included and the national representativeness. The main limitations are the retrospective nature of the cohort and the low rate of VF in both groups which could underestimate the impact of potential predictors. Second, it should be noticed that the early or delayed ART initiation was totally based on provider evaluation and multiple clinical or socioeconomic factors, including other unknown variables, could have influenced the final clinical decision and, in turn, our results. Finally, it should be considered that ART compliance was unavailable among variables analyzed as a predictor of virologic failure. However, the limited virologic failure rates in this cohort stand for a good adherence overall.

In conclusion, an early ART strategy with the current recommended first-line antiretroviral drugs starting pending GRT did not

TABLE 2 Multivariable Cox PH regression results (from FDR univariable correction). aHR as exponential coefficient.

Term	Estimate	Std. error	p	Conf. low	Conf. high
Type of anchor drug					
INSTIs	1				
PIs	0.472	0.118	0.000	0.374	0.595
NNRTIs	0.509	0.135	0.000	0.391	0.664
Others	0.809	0.288	0.463	0.460	1.423
CD4+ cells count (cell/μl)					
<200	1				
\geq 200 and <350	1.094	0.123	0.464	0.860	1.393
\geq 350 and <500	1.015	0.137	0.911	0.777	1.327
\geq 500	1.351	0.124	0.015	1.060	1.723
Basal HIV-1 VL (log₁₀ cp/ml)					
<5	1				
\geq 5 and <5.7	0.671	0.114	0.000	0.536	0.838
\geq 5.7	0.441	0.141	0.000	0.335	0.581

Note: Sign = p value ranges 0–0.001 “****”; 0.001–0.01 “***”; 0.01–0.05 “**.” Abbreviations: FDR, false discovery rate; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleos(t)ide reverse transcriptase inhibitor; PH, proportional hazard; PI, protease inhibitor; VL, viral load.

seem to influence the achievement of a high rate of VS when compared with those starting a GRT-informed ART, in particular INSTIs-based. Notably, despite the efficacy of the newest ART regimens, a high baseline HIV-RNA load and low CD4+ cell counts remain independent risk factors of virologic failure in naïve PLWH. Further studies are needed to define the ideal profile of patients for whom rapid ART could not be a safe practice.

AUTHOR CONTRIBUTIONS

Conceptualization and Supervision: Maurizio Zazzi, Francesca Incardona, Barbara Rossetti, Borghi Vanni, and Antonio Di Biagio. *Data analysis:* Giuseppe Pasculli, Serena Arima, Yagai Bouba, and Davide F. Bavaro. *First draft production:* Davide F. Bavaro, Andrea De Vito, and Giuseppe Pasculli. *Draft revision:* Laura Magnasco, Rachele Pincino, Francesco Saladini, Rossana Lattanzio, and Romina Corsini. *Final approval:* All authors.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Dataset used for analysis is available from corresponding author on reasonable request.

ETHICS STATEMENT

The database used was approved by the Ethics Committees at each clinical center and written informed consent was obtained from all patients before participation. The study was performed in accordance with the ethical guidelines of the Declaration of Helsinki (7th revision) and with the International Conference on Harmonization Good Clinical Practice guidelines.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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