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Evaluation of virological response and resistance profile in HIV-1 infected patients starting a first-line integrase inhibitor-based regimen in clinical settings☆

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[1] *For further details, see the Appendix section*

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Abstract

Background: Virological response and resistance profile were evaluated in drug-naïve patients starting their first-line integrase inhibitors (INIs)-based regimen in a clinical setting.

Study design: Virological success (VS) and virological rebound (VR) after therapy start were assessed by survival analyses. Drug-resistance was evaluated at baseline and at virological failure.

Results: Among 798 patients analysed, 38.6%, 27.1% and 34.3% received raltegravir, elvitegravir and dolutegravir, respectively. Baseline resistance to NRTIs, NNRTIs, PIs and INIs was: 3.9%, 13.9%, 1.6% and 0.5%, respectively. Overall, by 12 months of treatment the probability of VS was 95%, while the probability of VR by 36 months after VS was 13.1%. No significant differences in the virological response were found according to the INI used. The higher pre-therapy viremia strata was (<100,000 vs. 100,000-500,000 vs. >500,000 copies/mL), lower was the probability of VS (96.0% vs. 95.2% vs. 91.1%, respectively, P<0.001), and higher the probability of VR (10.2% vs. 15.8% vs. 16.6%, respectively, P=0.010). CD4 cell count <200 cell/mm^3 was associated with the lowest probability of VS (91.5%, P<0.001) and the highest probability of VR (20.7%, P=0.008) compared to higher CD4 levels. Multivariable Cox-regression confirmed the negative role of high pre-therapy viremia and low CD4 cell count on VS, but not on VR. Forty-three (5.3%) patients experienced VF (raltegravir: 30; elvitegravir: 9; dolutegravir:4). Patients failing dolutegravir did not harbor any resistance mutation in integrase and reverse transcriptase.

Conclusions: Our findings confirm that patients receiving an INI-based first-line regimen achieve and maintain very high rates of VS in clinical practice.

Keywords: HIV-1; integrase inhibitors; antiretroviral therapy; drug resistance; virological response

1. Introduction

The introduction of integrase inhibitors (INIs) to the armamentarium of antiviral agents was a landmark event in the history of HIV treatment,[1] and has strengthened combined antiretroviral therapy (cART) due to their remarkable efficacy, excellent safety and tolerability profiles observed in both clinical trials and clinical practice.[2–4] Guidelines for the management of HIV infection generally recommend the use of INI-based regimens for the initial regimens of most people with HIV/AIDS.[5,6]

Although the first-waves of INIs showed high potency and good tolerability both in treatment-naïve and treatment-experienced HIV-infected patients [2], dolutegravir (DTG), the first member of second generation INIs [7] has advantages over prior INIs. In particular, this drug showed a high genetic barrier to the emergence of resistance mutations [7,8] and so far, in clinical trial studies no patients failing a first-line regimen based on DTG harboured resistance either in integrase (IN) or reverse-transcriptase (RT) [9,10].

Despite these excellent results, patients with high-viremia levels >500,000 copies/mL and or with low CD4 cell count at diagnosis are more prone to have delayed virological suppression or experience virological rebound, and often they are under-represented in clinical trials.[11–13] Thus, even though several biases might be introduced in observational cohorts, only studies from clinical practice can provide data for these patients. So far, only few data on INI-virological response in these difficult to treat patients are available.

Another important point to consider is the INI-resistance. In this regard, despite the current common usage of INIs in clinical practice, mutations associated with resistance to INIs were at the moment rarely detected in INI–naïve patients (both for patients starting INI as drug-naïve or drug–experienced); and so far, the prevalence of INI transmitted resistance is still not a concern in cART naïve patients.[14,15] However, natural polymorphisms with varying effect on INI susceptibility in the absence of specific primary mutations were already described in some studies.[16–18] In this

regard, potential subtype-specific differences may influence the effect of individual treatment regimens. Thus, the monitoring of integrase genetic variability in patients never exposed to INIs still deserves attention.

Therefore, mindful of the recent introduction of INIs in first-line regimen, we do not yet fully know the predictive factors to virological response of their long-term use in clinical settings. Thus, in this study, we evaluated the virological response and the resistance profile (before cART and at failure) in patients starting a first-line cART containing INIs in real-world clinical settings in Italy.

2. Study design

2.1. Study population

Data were collected from patients starting their first-line regimen containing an integrase inhibitor based on the following inclusion criteria: i) available pre-cART HIV-RNA and CD4 cell count; ii) at least 1 plasma HIV-RNA measurement after therapy start; iii) available genotypic resistance test (GRT) for protease/reverse transcriptase before therapy start.

2.2. Genotyping, subtyping and resistance evaluation

Sequences of protease, reverse transcriptase and integrase (when available) collected for the study were obtained from genotyping performed on plasma samples for clinical routine purposes. Genotyping and subtyping were carried out as previously described [19,20]. The presence of major resistance mutations (MRMs) to PIs, NRTIs, NNRTIs and INIs, and accessory RMs (ARMs) to INIs was evaluated at baseline and at virological failure through HIVdb version 8.9-1 (Stanford resistance list 2019). Virological failure was defined as viremia >50 copies/mL under INI-treatment, if virological success was never achieved, or after virological rebound (see statistical analysis for the definition). PI/NRTI/NNRTI and INI baseline resistance were evaluated taking into account whether mutations affected or not the first-line regimen received; thus, patients were grouped as follows: i) without any MRM; ii) with at least one MRM affecting regimen; iii) with only MRMs not affecting regimen.

2.3. Statistical analysis

All the analyses were performed using the software package SPSS *version 20.0* for Windows (SPSS Inc., Chicago, Illinois). Kaplan-Meier curves were used to evaluate the probability of virological success (VS: the achievement of viremia <50 copies/mL after cART INI-containing regimen start) and the probability of virological rebound (VR: the first of two consecutive viremia values >50 copies/mL or one >1000 copies/mL after the achievement of VS) according to pre-cART viremia and CD4 levels, and type of INI-drug used at first-line treatment. Cox regression analysis was performed to investigate factors associated to virological response by considering demographic, viro-immunological and treatment parameters (a list of variables included is reported in Table 2). Only variables significantly associated to virological response at univariable analyses (P<0.05) were retained in multivariable models. Analyses were performed on patients that did not discontinue their first-line treatment (on treatment approach). Patients' follow-up was censored before first-line INI-based cART discontinuation or at full treatment stop.

3. Results

3.1. Baseline patients' characteristics and resistance profiles

Overall, 798 cART naïve patients receiving a first-line INI-based therapy were included. Table 1 summarises the baseline demographic and viro-immunological characteristics, stratified per INI received. The majority of patients were male (85.2%) and infected with HIV-1 B subtype (63.9%). About half of the patients started therapy with a viremia <100,000 copies/mL (45.6%), and 40.1% had a CD4 cell count >500 cells/mm^3. Patients who received raltegravir (RAL) started treatment in a less recent calendar year, were older, showed the highest proportion of pre-cART viremia >500,000 copies/mL, and were more likely to be treated with a four-drug boosted-PI-based regimen, compared to those treated with elvitegravir (EVG) or DTG (P<0.05, Table 1).

Before cART start, 17.4% of patients showed at least one MRM to any-ARV class. In particular, 13.9%, 3.9%, 1.6% and 0.5% of them showed MRMs to NNRTIs, NRTIs, PIs and INIs, respectively. Despite this, the majority of patients (96.2%) were treated with a fully effective regimen, showing no resistance or only MRMs not affecting the regimen received. Among 598 patients with an available IN-GRT, three of them (0.5%) harbored INI-MRMs; in particular, R263K (N=2, 0.3%) and E92E/Q (N=1, 0.2%) were detected. INI-ARMs were found in around 5% of patients, including: E157Q (N= 13, 2.2%), T97A (N=9, 1.5%), G163K/R (N=5, 0.8%), D232N (N=2, 0.3%) and Q95K (N=1, 0.2%). Other substitutions at integrase amino acid positions associated with INI resistance and highly conserved in cART naïve patients were also found: E92D (N=1, 0.2%), E92K (N=1, 0.2%), G140W (N=1, 0.2%) and N155NK (N=1, 0.2%).

Patients receiving EVG based regimen showed the lowest proportion of resistance affecting companion drugs (0.9%) compared to patients receiving a RAL- (5.2%) or DTG-containing cART (4.4%, P=0.033, Table 1).

3.2. Virological success to first-line INI-based cART

By 12 months from INI start, the overall probability of achieving VS was about 95%, reached in a median (95% C.I.) time of 2.8 (2.6-3.0) months. Patients with pre-cART viremia >500, 000 copies/mL showed the lowest probability and the longest median time of achieving VS compared to other viremia strata (P<0.001, Fig. 1 A). An opposite trend was observed with increasing pre-CD4 cell count levels, where patients with CD4 cell count <200 cell/mm^3 showed the lowest probability and the longest median time of achieving VS compared to higher CD4 count levels (P<0.001; Fig. 1 B). Patients treated with RAL showed a slightly lower probability of VS (91.5%) compared to those receiving EVG (96.2%) and DTG (96.6%), with a trend toward significance (P=0.056, Fig. 1 C).

By Cox regression, at both uni - and multivariable analysis, a more recent calendar year of starting treatment and CD4 cell count levels >350 cells/mm^3 (compared to <200 cells/mm^3) were

independent factors positively associated with VS. Whereas, pre-cART viremia levels >100,000 copies/mL were negatively associated with VS (compared to <100,000 copies/mL) (Table 2). Pre-cART resistance was not associated with VS. Noteworthy, despite the presence of INI-MRMs or other substitutions at integrase amino acid positions associated with INI resistance before cART start, was that all patients harboring these substitutions achieved and maintained VS under INI-based first-line therapy, with the exception of one that was lost to follow-up (data not shown).

3.3. Virological rebound to first-line INI-based cART

The probability of VR after the achievement of VS was assessed in 581 patients with an available virological follow-up. In this subgroup, 50 VR events were observed with a median (IQR) viremia of 132 (74-4,682) copies/mL. The overall probability of VR at 36 months after VS under first line-cART was 13.1%. After stratification by viremia levels, high pre-cART viremia was found to be significantly associated with a higher probability of experiencing VR (P=0.010), with patients having >500,000 copies/mL showing a higher probability (16.6%) of experiencing VR compared to those with <100,000 copies/mL (10.2%, Fig. 2A). According to pre-cART CD4 cell count, patients with a pre-cART CD4 count <200 cells/mm^3 showed the highest probability of VR (20.7%) compared to patients with higher CD4 levels (P=0.008, Fig. 2B). By considering INI received, the probabilities of VR were about 7%, 16% and 18% for EVG, RAL and DTG respectively (Fig. 2C), but no statistically significant difference was found (P= 0.390).

By Cox regression, being a drug abuser (compared to being homosexual) was the only independent factor positively associated with VR in both uni - and multivariable analysis (Table 2). Of note, patients infected with HIV-1 F subtype showed a higher adjusted hazard ratio of VR compared to those infected with HIV-1 B subtype, with a trend toward significance (Table 2). No factor was negatively associated with VR.

3.4. Evaluation of emergent resistance mutations at failure to first-line INI-based regimen

Overall, 43 patients (5.3%) had an available GRT at virological failure. An overview of patients who harbored resistance at virological failure is reported in Table 3. Genotyping was performed in a median (IQR) time of 10 (6-18) months after therapy start. At GRT, contextual median (IQR) viremia was 2.6 (2.1-4.5) log_{10} copies/mL. Concerning the treatment, 30 (69.8%), 9 (20.9%), and 4 (9.3%) patients received RAL, EVG and DTG, respectively. Virological failure with INI-resistance associated mutations was observed only in patients failing first generation INI-based treatment. The 4 patients failing DTG-treatment did not harbor any resistance either in IN or RT. INI-MRMs were detected in 7 (23.3%) and 3 (33.3%) patients receiving RAL and EVG, respectively. The proportion of patients harboring resistance to both INI and NRTI was significantly higher in those who received EVG compared to those who received RAL (4 [44.4%] vs. 3 [10%], P=0.037). All 4 patients harboring INI resistance at EVG failure harbored the lamivudine/emtricitabine associated mutation M184V [4/4; 100%]; one of them also harbored the tenofovir-related mutation K65R [1/4; 25%] NRTI MRMs. No PI resistance was observed.

4. Discussion

In the present manuscript we evaluated the virological response and resistance profile according to the usage of INIs as part of first-line treatment in an Italian real-life setting. As previously demonstrated in clinical trials and clinical practice,[21,22] we reconfirmed that INIs have an excellent response at first-line therapy. Patients included in the present study had a very high probability of achieving VS at 12 months (about 95%) and a low probability of VR at 36 months after VS (about 13%), regardless of the INI-drug used.

Among the few treatment failures recorded, INI- and/or NRTI-resistance (especially with M184V mutation) was selected only in patients treated with first-generation INIs, reconfirming the high genetic barrier to develop resistance associated to DTG.[23–26]

We found that patients with very high pre-cART viremia levels (>500,000 copies/mL) and/or low pre-cART CD4 showed a slightly lower or only delayed chance to achieve VS compared to others (Fig. 1A). No significant associations of pre-cART viremia and CD4 cell count with VR were found at multivariable analyses. Thus, we can assert that the response in patients difficult to treat, who start an INI-based first-line treatment, is still not equal to other patients, though it is surely better than those observed in our previous studies evaluating boosted-PI or NNRTI based first-line treatments. [11,13,27].

Beyond treatment efficacy, even though integrase GRT is still not strongly recommended in cART-naïve patients,[5] it should be considered that in the present study, integrase baseline GRT was performed in >70% of the cART-naïve patients included. Based on the information retrieved from IN genotyping, we confirmed that INI resistance in cART-naïve patients is still not a concern in Italian clinical practice due to the low prevalence of both INI-MRMs (<1%) and INI ARMs (5%), as observed in several studies[14,15,28]. Moreover, by evaluating virological response in the few patients harbouring baseline ARMs, we found that these mutations had no effect in achieving and/or maintaining VS in our population. Probably, this is due to the fact that our patients with pre cART INI ARMs were more likely to be treated with DTG. Even though anecdotal, we found that 9 out of 11 (81%) of our patients with baseline E157Q mutation were treated with DTG and all 9 of them achieved and maintained VS. Whereas, the only patient with E157Q receiving EVG-based treatment failed, developing high-level resistance to EVG, emtricitabine and tenofovir (see table 4, ID 17840). These results agree with a recent study demonstrating that E157Q mutation might have a role in INI susceptibility, suggesting that antiretroviral-naïve patients harbouring this mutation should start a DTG-based treatment. [29] Thus, this observation underlines the importance of IN GRTs on tailoring INI usage (especially of first-generation) in cART-naïve patients.

In addition, integrase genotyping remains a crucial tool to evaluate the role of integrase genetic variability in response to second generation INIs for whom poor long-term data are available.

Concerning this point, we found that patients infected with HIV-1 F subtype showed an increased risk of experiencing VR compared to those infected with B, with a trend toward significance at multivariable analysis (Table 2). In this regard, recent data about a potential negative role on INI response of HIV-1 subtype F are available.[30] Thus, evaluating the impact of natural HIV-1 subtype-associated IN-polymorphisms deserves attention with *ad hoc* studies.

Beyond baseline INI-resistance, recent findings showed that NRTI transmitted drug resistance might play a role on first-line INI-based cART efficacy.[28] Probably due to the low prevalence of NRTI-resistance found (3.9%) and by the fact that the majority of resistant patients in our population received high genetic barrier regimens (based on DTG plus 2 NRTIs or RAL plus a PI and 2 NRTIs), this observation here was not confirmed.

This study has some limitations. Firstly, data such as adherence are absent, and information about seroconversion is incomplete, as it often happens in population retrieved from a real setting. In this context of observational study, clinicians' decisions (driven by socio-demographic and viro-immunological patients' characteristics) might also include selection-biases on the INI choice. Moreover, due to the recent considerable usage of DTG in Italian clinical practice, long-term data on this second-generation drug is lacking. Further studies should be warranted to overcome these shortcomings.

In conclusion, this study confirms that patients receiving an INI-based first-line cART for whom PR/RT and IN baseline genotyping is available achieve and maintain very high rates of virological suppression, with no negative impact of baseline resistance. The usage of DTG in patients harbouring baseline resistance might be preferred. Even though INI usage improved the management of patients with compromised viro-immunological status at HIV diagnosis, parameters such as high pre-cART viremia, low CD4 count and HIV-1 subtype remain factors individuating patients difficult to treat.

Figure legend

Figure 1. Kaplan-Meir estimates of the probability of achieving virological success by 12 months in patients starting an INI-based first-line therapy stratified according to pre-cART viremia, pre-cART CD4 cell count and INI received. A) Virological success stratified according to pre-cART viremia (copies/mL). B) Virological success stratified according to pre-cART CD4 cell count (cells/mm^3). Panel C) Virological success stratified per INI included in first-line. P values were calculated by using the Peto and Peto modification of the Gehan–Wilcoxon test. A p-value <0.05 was considered statistically significant.

Figure 2. **Kaplan-Meir estimates of the probability of achieving virological rebound at 36 months of cART in patients starting an INI-based first-line therapy stratified for pre-cART viremia, pre-cART CD4 cell count and INI received.** A) Virological rebound stratified according to pre-cART viremia (copies/mL). B) Virological rebound stratified according to pre-cART CD4 cell count (cells/mm^3). C) Virological rebound stratified according to INI included in first-line. P values were calculated by using the Peto and Peto modification of the Gehan–Wilcoxon test. A P-value <0.05 was considered statistically significant. VS: virological success; VR: virological rebound.

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Conflict of interest

The authors declare no conflict of interest.

Contributors

DA, MMS, FCS and CFP carried out study conception and design; DA and MMS carried out analysis and interpretation of data and drafting of manuscript; YB participated in the study conception and design and carried out drafting manuscript; CG, AB, WG, VM, APC and BB carried out the sequencing; RG, VB, LG, AG, VM, AV, IM, MC, ML, ADB, FM and GR carried out acquisition of data; ADM, MA, CM and AA participated in study conception and design revision; FCS, CFP and MMS carried out critical revision of the manuscript.

Ethical approval

This study was approved by the ethics committee of Tor Vergata Hospital (Ethics Approval No. 119/16, 12 July 2016). The research was conducted on anonymous samples in accordance with the principles of the Declaration of Helsinki and the Italian Ministry of Health. All information, including virological and clinical data, was recorded in an anonymized database.

Appendix

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Figure 1

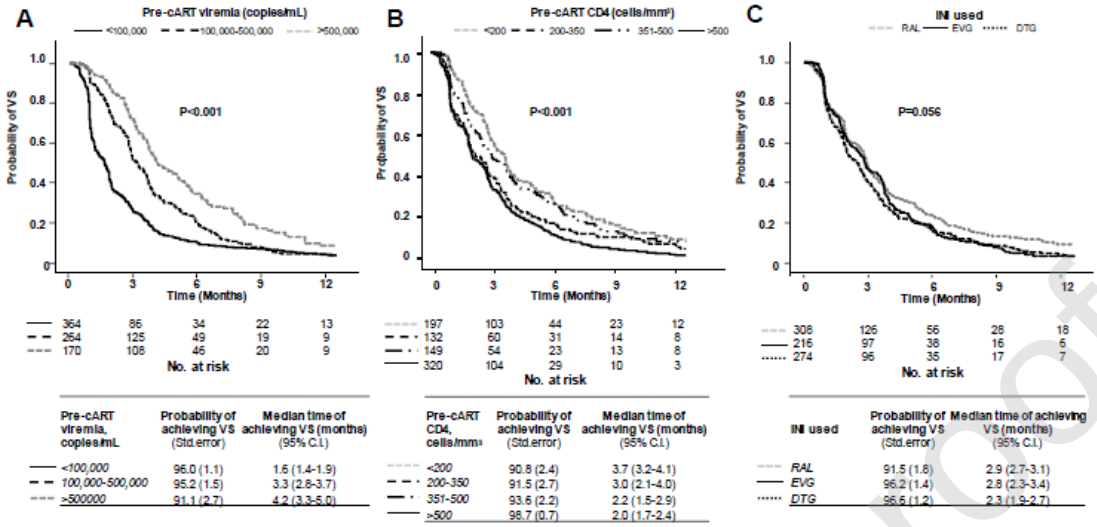

Figure 2

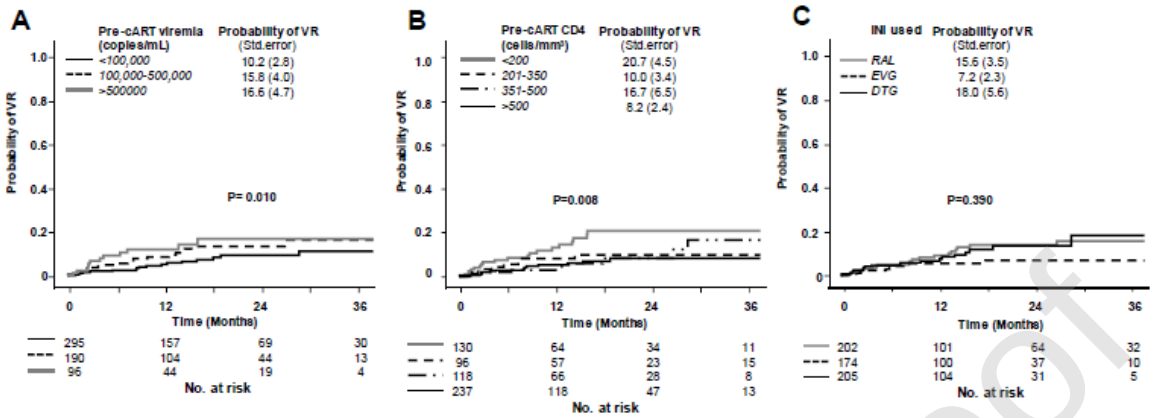

Table 1. Baseline characteristics of 798 drug naive HIV-1 infected patients starting an INI-based first-line therapy stratified by INI received.

Characteristics	Overall (N=798)	INI used			P-value
		Raltegravir (N=308)	Elvitegravir (N=216)	Dolutegravir (N=274)	
Calendar year start of cART, median (IQR)	2016 (2014-2017)	**2014 (2012-2015)**	**2016 (2015-2017)**	**2017 (2016-2017)**	**<0.001**
Male, n (%)	680 (85.2)	269 (87.3)	183 (84.7)	228 (83.2)	0.365
Age, years, median (IQR)	38 (30-47)	**40 (31-49)**	**37 (29-46)**	**38 (29-47)**	**0.022**
Risk factor, n (%)					
Homosexual	418 (52.4)	162 (52.6)	118 (54.6)	138 (50.4)	0.607
Heterosexual	227 (28.5)	**78 (25.3)**	**52 (24.1)**	**97 (35.4)**	**0.007**
Drug abuser	40 (5.0)	20 (6.5)	9 (4.2)	11 (4.0)	0.314
Bisexual	33 (4.1)	**18 (5.9)**	**11 (5.1)**	**4 (1.5)**	**0.011**
Other/Unknown	80 (10.0)	30 (9.7)	26 (12.0)	24 (8.8)	0.476
Subtype, n (%)					
B	510 (63.9)	206 (66.9)	142 (65.7)	162 (59.1)	0.122
CRF02_AG	53 (6.6)	21 (6.8)	16 (7.4)	16 (5.8)	0.777
F	50 (6.3)	24 (7.8)	9 (4.2)	17 (6.2)	0.241
C	46 (5.8)	**13 (4.2)**	**9 (4.2)**	**24 (8.8)**	**0.032**
Other	139 (17.4)	44 (14.3)	40 (18.5)	55 (20.1)	0.163
Nationality					
Italian	469 (58.8)	**227 (73.7)**	**123 (56.9)**	**119 (43.4)**	**<0.001**
Foreigner	144 (18.0)	59 (19.2)	36 (16.7)	49 (17.9)	0.764
Unknown	185 (23.2)	**22 (7.1)**	**57 (26.4)**	**106 (38.7)**	**<0.001**
Type of infection at therapy start, n (%)					
Acute	64 (8.0)	**44 (14.3)**	**7 (3.2)**	**13 (4.7)**	**<0.001**
Chronic	116 (14.6)	**65 (21.1)**	**34 (15.8)**	**17 (6.2)**	**<0.001**
Unknown	618 (77.4)	**199 (64.6)**	**175 (81.0)**	**244 (89.1)**	**<0.001**
Pre-cART viremia, copies/mL, n (%)					
<100,000	364 (45.6)	**124 (40.3)**	**111 (51.4)**	**129 (47.1)**	**0.035**
100,000-500,000	264 (33.1)	**91 (29.5)**	**86 (39.8)**	**87 (31.7)**	**0.041**
>500,000	170 (21.3)	**93 (30.2)**	**19 (8.8)**	**58 (21.2)**	**<0.001**
Pre-cART CD4 cell count (cells/mm^3), n (%)					
<200	197 (24.7)	**87 (28.2)**	**37 (17.1)**	**73 (26.7)**	**0.010**
200-350	132 (16.5)	43 (14.0)	44 (20.4)	45 (16.4)	0.151
351-500	149 (18.7)	53 (17.2)	50 (23.1)	46 (16.8)	0.141
>500	320 (40.1)	125 (40.6)	85 (39.4)	110 (40.1)	0.960
Type of INI-based first-line regimen, n (%)					
INI + 2 NRTIs	553 (69.3)	**97 (31.5)**	**194 (89.8)**	**262 (95.7)**	**<0.001**
INI + 2 NRTIs+ 1 PIb	168 (21.1)	**142 (46.1)**	**21 (9.7)**	**5 (1.8)**	**<0.001**
Dual	53 (6.6)	**48 (15.6)**	**0 (0.0)**	**5 (1.8)**	**<0.001**
Other	24 (3.0)	**21 (6.8)**	**1 (0.5)**	**2 (0.7)**	**<0.001**
Single tablet regimen (%)	322 (40.4)	**0 (0.0)**	**194 (89.8)**	**128 (46.7)**	**<0.001**
NRTI combinations used, n (%)					
FTC + TDF/TAF	593 (74.3)	**237 (76.9)**	**215 (99.5)**	**141 (51.5)**	**<0.001**
3TC + ABC	138 (17.3)	**10 (3.3)**	**0 (0.0)**	**128 (46.7)**	**<0.001**
Other or NRTI-sparing	67 (8.4)	**61 (19.8)**	**1 (0.5)**	**5 (1.8)**	**<0.001**
Pre-cART MRMs, n (%)[a]					
None	659 (82.6)	255 (82.8)	182 (84.3)	222 (81.0)	0.639
At least one MRM affecting regimen	30 (3.8)	**16 (5.2)**	**2 (0.9)**	**12 (4.4)**	**0.033**
Only MRMs not affecting regimen	109 (13.6)	37 (12.0)	32 (14.8)	40 (14.6)	0.561
Pre-cART INI resistance mutations, n (%)[b]					
At least one major	3 (0.5)	0 (0.0)	2 (1.1)	1 (0.4)	0.535
At least one accessory	31 (5.2)	4 (2.5)	9 (4.8)	18 (7.2)	0.109

[a]According to Stanford resistance list 2019 (HIVdb version 8.9-1). [b]Available for 598 patients with pre-cART integrase genotypic resistance test. 3TC: lamivudine; ABC: abacavir; c-ART: combined antiretroviral therapy; DTG: dolutegravir; EVG: elvitegravir; FTC: emtricitabine; INI: integrase inhibitor; IQR: interquartile range; MRM: Major resistance mutation; NRTI: nucleos(t)ide reverse transcriptase inhibitor; PIb: cobicistat/ritornavir boosted protease inhibitor; RAL: raltegravir; TD(A)F: tenofovir disoproxil fumarate or alafenamide.

Table 2. Factors associated with virological response in HIV-1 infected patients starting an INI-based first-line therapy.

Variables	Hazard ratio of achieving virological success				Hazard ratio of achieving virological rebound[b]			
	Crude		Adjusted[a]		Crude		Adjusted[a]	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Calendar year start of cART	**1.09 (1.05-1.13)**	**<0.001**	**1.08 (1.03-1.13)**	**0.001**	1.04 (0.90-1.19)	0.618		
Male	0.95 (0.77-1.16)	0.604			0.59 (0.31-1.12)	0.108		
Age, years	0.99 (0.95-1.02)	0.381			1.07 (0.95-1.20)	0.279		
Risk factor								
Homosexual[b]	1				1		1	
Heterosexual	0.97 (0.82-1.15)	0.73			**2.06 (1.08-3.92)**	**0.029**	1.99 (0.99-4.02)	0.055
Drug abuser	0.91 (0.64-1.28)	0.578			**3.34 (1.13-9.87)**	**0.03**	**3.31 (1.04-10.50)**	**0.042**
Bisexual	0.82 (0.54-1.24)	0.343			1.85 (0.43-8.01)	0.409	1.62 (0.36-7.26)	0.53
Other/Unknown	0.96 (0.74-1.25)	0.762			2.05 (0.86-4.91)	0.108	1.80 (0.69-4.75)	0.232
Subtype								
B[b]	1				1		1	
CRF02_AG	1.10 (0.81-1.49)	0.536			1.02 (0.31-3.37)	0.968	0.95 (0.28-3.20)	0.929
F	0.83 (0.6-1.14)	0.25			**3.44 (1.41-8.36)**	**0.006**	2.48 (0.97-6.31)	0.057
C	1.35 (0.98-1.87)	0.07			1.68 (0.59-4.80)	0.336	1.53 (0.52-4.50)	0.443
Other	1.02 (0.84-1.24)	0.841			1.40 (0.66-2.98)	0.376	1.48 (0.68-3.21)	0.327
Nationality								
Italian[b]	1				1			
Foreigner	0.84 (0.69-1.03)	0.089			1.74 (0.91-3.33)	0.096		
Unknown	0.92 (0.77-1.10)	0.376			1.20 (0.57-2.49)	0.633		
Type of infection at cART start								
Chronic[b]	1		1		1			
Acute	**1.53 (1.11-2.12)**	**0.01**	1.33 (0.95-1.86)	0.097	0.55 (0.12-2.58)	0.448		
Unknown	**1.32 (1.07-1.64)**	**0.01**	1.13 (0.88-1.43)	0.337	1.37 (0.63-2.96)	0.428		

Pre-cART viremia, copies/mL,								
<100,000[b]	1		1		1		1	
100,000-500,000	**0.60 (0.50-0.71)**	**<0.001**	**0.57 (0.49-0.68)**	**<0.001**	1.77 (0.94-3.36)	0.078	1.65 (0.84-3.27)	0.149
>500,000	**0.43 (0.35-0.52)**	**<0.001**	**0.44 (0.36-0.54)**	**<0.001**	**2.29 (1.10-4.76)**	**0.026**	1.79 (0.80-4.00)	0.155
Pre-cART CD4 cell count (cells/mm^3)								
<200[b]	1		1		1		1	
200-350	1.11 (0.87-1.41)	0.397	1.06 (0.84-1.35)	0.576	0.61 (0.29-1.32)	0.214	0.80 (0.35-1.85)	0.602
351-500	**1.43 (1.14-1.79)**	**0.002**	**1.28 (1.01-1.61)**	**0.038**	0.44 (0.19-1.01)	0.052	0.68 (0.28-1.65)	0.396
>500	**1.73 (1.43-2.10)**	**<0.001**	**1.55 (1.27-1.89)**	**<0.001**	**0.39 (0.19-0.79)**	**0.009**	0.49 (0.22-1.08)	0.078
Dolutegravir included in first-line regimen	**1.21 (1.03-1.41)**	**0.017**	1.05 (0.89-1.23)	0.585	1.18 (0.66-2.13)	0.573		
Type of INI-based first-line regimen								
1 INI + 2 NRTI[b]	1				1			
1 INI + 2 NRTI+ 1 Pib	0.87 (0.72-1.05)	0.146			0.75 (0.29-1.91)	0.544		
Dual	0.73 (0.46-1.15)	0.176			1.37 (0.33-5.72)	0.663		
Other	0.92 (0.68-1.25)	0.606			1.25 (0.55-2.83)	0.591		
Single tablet regimen	1.13 (0.97-1.31)	0.107			0.81 (0.45-1.44)	0.467		
NRTI combinations used								
FTC + TDF/TAF[b]	1				1			
3TC+ ABC	1.18 (0.97-1.43)	0.091			1.25 (0.61-2.55)	0.546		
Other or Nuc-sparing	0.87 (0.66-1.15)	0.324			1.71 (0.81-3.62)	0.157		
Pre c-ART MRMs[c]								
None[b]	1				1			
At least one MRM affecting regimen	0.74 (0.51-1.09)	0.126			0.97 (0.24-4.02)	0.971		
Only MRMs not affecting regimen	0.89 (0.72-1.11)	0.309			0.85 (0.34-2.16)	0.739		
Pre c-ART INI ARMs, n (%)								
None[b]	1				1			
At least one ARM	1.34 (0.92-1.94)	0.134			1.50 (0.46-4.893)	0.497		
Unknown	0.84 (0.70-1.01)	0.06			0.88 (0.44-1.77)	0.715		

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[a]Adjusted for variables significantly associated with virological response at univariable analyses. [b]Reference group (dummy). [c]According to Stanford HIV_DB algorithm (ver8.9.1). ARM: Accessory resistance mutation; sCI: confidence interval. cART: combined antiretroviral therapy. 3TC: lamivudine. ABC: abacavir. FTC: emtricitabine. HR: hazard ratio. INI: integrase inhibitor. MRM: Major resistance mutation; NRTIs: nucleos(t)ide reverse transcriptase inhibitors. PIb: ritonavir-cobicistat boosted protease inhibitor. TD(A)F: tenofovir disoproxil fumarate or alafenamide.. Boldface indicates factors that were significantly associated ($p<0.05$) with virological success

Table 3. Overview of patients harbouring resistance associated mutations at virological failure under INI-based first-line cART.

ID	Pre-cART CD4 count (cells/mm^3)	Pre-cART viremia (copies/mL)	HIV-1 Subtype	cART received	Time to GRT [a] (months)	Viremia at GRT (copies/mL)	Resistance mutations detected at failure [b]				
							INI MRM	INI ARM	PI MRM	NRTI MRM	NNRTI MRM
18216	407	2,950,259	B	EVG/COBI/FTC/TDF	3.8	235,745	**Q148R, G140A**	None	None	**M184V**	None
SA22	48	1,265,000	B	EVG/COBI/FTC/TDF	2.4	12,970	**T66I**	None	None	**M184V**	None
17840	833	234,095	B	EVG/COBI/FTC/TDF	9.8	10,888	**T66I**	E157Q **L74M/I**	None	**K65R, M184V**	K101E, E138A
18592	309	3,910,490	B	EVG/COBI/FTC/TAF	12.3	98	None	**Q146L, D232D/N**	None	**M184V**	None
17640	313	36,318	B	RAL+ FTC/TDF	12.6	92	**G140G/R/S**	None	None	None	None
SP57	101	640,297	B	RAL+ FTC/TDF	6.5	4,160	**G140S, Q148H**	None	None	None	None
SA32	131	875,200	B	RAL+ FTC/TDF	15.2	31,120	**E92E/Q, G140G/S, Q148Q/R, N155N/H**	None	None	**M184V**	None
8635	549	297,262	B	RAL+ FTC/TDF	4.0	54,987	**Y143C/H/R/Y, N155H**	**G163K**	None	**M184V**	None
18528	49	3,640,906	B	RAL+ FTC/TDF	5.2	102,085	**Y143R**	**L74M/I**	None	**K70K/E, M184V**	None
15850	453	13,937	B	RAL+ DRVb	4.9	2,270	None	**T97A/T**	None	M41L	None
11894	727	634,929	CRF01_AE	RAL+ DRVb	9.0	340	None	**T97A**	None	M41M/L, K219K/R	None
16380	420	129,529	F	RAL+ DRVb	33.3	408	**N155H**	None	None	None	E138A
15464	311	1,421,036	B	RAL+ DRVb	6.5	7,802	**N155H**	None	None	None	None

In bold are indicated the mutations that emerged at virological failure, mutations not in bold-face were already present at baseline GRT.

[a] Months from starting INI-based first-line regimen to GRT date. [b] *According to Stanford resistance list 2019 (HIVdb version 8.9-1).*

ARM: accessory resistance mutations; c-ART: combined antiretroviral therapy; FTC: emtricitabine; TDF: tenofovir disoproxil fumarate; EVG: elvitegravir; RAL: raltegravir; DRVb: ritonavir/cobicistat boosted darunavir; INI: integrase inhibitor; NRTI: non nucleos(t)ide reverse transcriptase inhibitor; PI: protease inhibitor; GRT: genotypic resistance test; MRM: major resistance mutations.