AIDS RESEARCH AND HUMAN RETROVIRUSES
Volume 38, Number 6, 2022

DOI: 10.1089/aid.2021.0016

Predictors of Virological Failure Among People Living with HIV Switching from an Effective First-Line Antiretroviral Regimen

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Abstract

Aim of this study was to assess the predictors of virological failure (VF) among patients living with HIV (PLWHIV) switching from an effective first-line antiretroviral therapy (ART) regimen, and to evaluate the emergence of resistance-associated mutations. All adult patients enrolled in the Antiviral Response Cohort Analysis cohort who started ART after 2010, with at least 6 months of virological suppression (VS) before ART switch and with an available genotypic resistance test (GRT) at baseline were included. Thirty-two patients out of the 607 PLWHIV included (5.3%) experienced VF after a median of 11 months from ART switch. Younger age (adjusted Hazard Ratio [aHR] 0.96, 95% confidence interval [CI] 0.92–0.99, $p = .023$), being male who have sex with male (aHR 0.15, 95% CI 0.03–0.69, $p = .014$), and longer time from VS to ART switch (aHR 0.97, 95% CI 0.95–1.00, $p = .021$) resulted protective toward VF, while receiving a first-line regimen containing a backbone other than ABC/3TC or TXF/FTC (aHR 3.61, 95% CI 1.00–13.1, $p = .050$) and a boosted protease inhibitor as anchor drug (aHR 3.34, 95% CI 1.20–9.28, $p = .021$) were associated with higher risk of VF. GRT at the moment of VF was available only for 13 patients (40.6%). ART switch in patients with stable control of HIV infection is a safe practice, even if particular attention should be paid in certain cases of patients switching from regimens containing low-performance backbones or protease inhibitors.

Keywords: second-line antiretroviral therapy, resistance-associated mutations, optimization

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Introduction

Current antiretroviral therapy (ART) regimens allow stable control of HIV replication with achievement of stable virological suppression (VS) in >90% of treated patients.[1] However, given the lifelong nature of ART treatment, there is growing concern regarding long-term side effects and adherence issues.[2,3] Thus, individual optimization strategies to tailor the best ART regimen and prevent such complications have been widely implemented in everyday HIV clinical practice,[4–6] and simplification has been described as the main reason for first-line ART discontinuation in Italy in recent years.[7]

Genotypic resistance test (GRT) at baseline and upon virological failure (VF) has been recommended by most international guidelines.[8–10] Indeed, it can be a useful tool to guide optimization strategies, especially among heavily ART-experienced patients for whom the risk of mutations acquired from previous VF or planned treatment interruptions is consistent.[11,12]

Aim of our study was to assess the predictors of VF among patients living with HIV (PLWHIV) switching from an effective first-line ART regimen, and to evaluate the emergence of new resistance-associated mutations (RAMs).

Materials and Methods

Study design

We conducted a multicenter retrospective study among PLWHIV enrolled in the Antiviral Response Cohort Analysis (ARCA). Inclusion criteria for this study were (1) age ≥18 years, (2) start of ART in year 2010 or following years, (3) baseline GRT available upon ART initiation, and (4) stable VS for at least 6 months before switch to a second-line regimen. Moreover, all patients enrolled in the study had a follow-up period of at least 42 months to better allow the detection of late VF as well as emergence of new resistance to antivirals.

Definitions and methods

VS was defined as HIV-RNA values <50 copies/mL for ≥6 consecutive months, VF as either two consecutive HIV-RNA determinations ≥50 copies/mL or a single determination ≥1,000 copies/mL. ART switch was defined as (1) change in backbone or (2) change in the anchor drug or (3) reduction in the number of drugs contained in the regimen. The switch from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF) was not considered for the study, and both formulations are further addressed in the text with the acronym TXF.

All RAMs at baseline GRT were recorded, as well as emerging RAMs upon VF, whenever available. Clinical significance of RAMs was defined according to the IAS-USA Drug Resistance Mutations Group 2019 definitions.[13]

Study cohort and data collection

All PLWHIV enrolled in the ARCA cohort were screened for inclusion in the study. ARCA is a public database developed as a tool for investigating resistance to antiretroviral drugs that records all ART regimens administered to patients together with GRT results (dbarca.net). For each patient, demographic, virological and immunological data, risk factor for HIV infection, composition and duration of previous and current ART regimens, viral genotype, and baseline GRT mutations were collected. For patients meeting the criteria for VF, GRT results at VF were retrieved, whenever available.

Statistical analysis

Continuous variables were expressed as median and interquartile range (IQR), whereas categorical variables were indicated as absolute values and relative frequencies. The Mann–Whitney U test was used to compare continuous variables and the chi-square test to compare categorical ones. A Cox proportional-hazards model was used to identify independent factors of VF, including all variables with a p value <.1 at univariable analysis. Two-sided p value <.05 were deemed statistically significant. Statistical analyses were performed using the Statistical Package for Social Sciences statistical software (IBM® SPSS Statistics® for Windows, version 26.0; IBM Corporation, Armonk, NY).

Endpoints

The primary endpoint investigated was the development of VF. Moreover, we aimed at exploring predictors of VF and the emergence of new mutations to antiretrovirals upon VF, whenever a GRT was available. A further secondary endpoint investigated was the durability over time of different second-line regimens, stratified according to the anchor drug of the regimen itself.

Ethical considerations

The study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and later amendments. All patients signed an informed consent for the use of their clinical and laboratory data in an aggregated and anonymous form. Access to the ARCA database and data analyses were regulated by local institutional ethics committees and by Italian and European privacy legislation (Approval code ARCA/2014 of 21 July 2014).

Results

Virological failure

A total of 607 PLWHIV undergoing ART switch during the study period were enrolled in the study. Demographic, immunological, virological, and treatment data of the enrolled patients are outlined in Table 1.

Overall, 32 patients (5.3%) experienced VF, defined by two consecutive determinations of HIV-RNA ≥50 copies/mL in 8 patients (25%) and a single determination ≥1,000 copies/mL in 24 (75%). Median time from ART switch to VF was 11 months (IQR 4–33); the probability of VF at the end of the observation period was 6.9% for non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens, 2.8% for protease inhibitor (PI)-based, 8.3% for integrase inhibitor (INSTI)-based ART and 3.1% for regimens combining other drugs. Comparison of characteristics of patients experiencing VF or maintaining VS after ART switch is shown in Table 1.

Among all patients receiving a first-line regimen containing a boosted protease inhibitor (bPI), 35.4% ($n = 123/347$) maintained a bPI in the second-line regimen, 32.6% ($n = 113$)

Table 1. Baseline Demographic, Immunological, Virological, and Treatment Data of the Overall Population, and Comparison of Characteristics of Patients Experiencing VF versus Those Maintaining VS After ART Switch

Characteristics	*Overall population,* n = *607 (100%)*	*VF,* n = *32 (5.3%)*	*No VF,* n = *575 (94.7%)*	p
Male sex	467 (76.9)	22 (68.8)	445 (77.4)	.259
Median (IQR) age, years	41.0 (33.0–49.0)	37.0 (30.0–46.8)	41.0 (33.0–49.0)	.144
HIV-1 B viral subtype	432 (71.2)	22 (68.7)	410 (71.3)	.756
Risk factor for HIV infection				**.013**
IDU	38 (5.7)	5 (15.6)	33 (5.7)	
Heterosexual	339 (55.8)	22 (68.8)	317 (55.1)	
MSM	150 (24.7)	2 (6.3)	148 (25.7)	
Other	80 (13.2)	3 (9.4)	77 (13.4)	
Median (IQR) $\log_{10}$ of HIV-RNA value at baseline	4.72 (4.14–5.26)	4.85 (4.22–5.15)	4.71 (4.14–5.26)	.815
Median (IQR) value of CD4+ cells count at baseline	318 (205–416)	296 (100–408)	318 (209–419)	.371
$CD4^+$ cells count ≤200/mL	145 (24.5)	11 (35.5)	134 (23.8)	.334
$CD4^+$ cells count 201–500/mL	373 (62.9)	17 (54.8)	356 (63.3)	
$CD4^+$ cells count >500/mL	75 (12.6)	3 (9.7)	72 (12.8)	
Missing data	14 (2.3)	1 (3.1)	13 (2.3)	
Median (IQR) time from VS to ART switch, months	30.0 (15.0–47.0)	18.0 (10.0–36.8)	30.0 (16.0–47.0)	**.023**
Median (IQR) calendar year of ART start	2012 (2011–2013)	2011 (2010–2012)	2012 (2011–2013)	.073
First-line regimen composition				
Anchor drug				.165
NNRTI	216 (35.6)	6 (18.8)	210 (36.5)	
PI	347 (57.2)	24 (75.0)	323 (56.2)	
INSTI	12 (2.0)	1 (3.1)	11 (1.9)	
Other	32 (5.3)	1 (3.1)	31 (5.4)	
Backbone				**.050**
ABC/3TC	177 (29.2)	7 (21.9)	170 (29.6)	
TXF/FTC	394 (64.9)	20 (62.5)	374 (65.0)	
Other	36 (5.9)	5 (15.6)	31 (5.4)	
No. of drugs composing first-line regimen				.841
2	5 (0.8)	0 (0.0)	5 (0.9)	
3	578 (95.2)	31 (96.9)	547 (95.1)	
4	24 (4.0)	1 (4.2)	23 (4.0)	
Second-line regimen composition				
Anchor drug				.575
NNRTI	216 (35.6)	14 (43.8)	202 (35.1)	
PI	174 (28.7)	9 (28.1)	165 (28.7)	
INSTI	153 (25.2)	5 (15.6)	148 (25.7)	
Other	64 (10.5)	4 (12.5)	60 (10.4)	
Backbone				.376
ABC/3TC	149 (24.5)	9 (28.1)	140 (24.3)	
TXF/FTC	276 (45.5)	17 (53.1)	259 (45.0)	
Other	133 (21.9)	3 (9.4)	130 (22.6)	
No backbone	49 (8.1)	3 (9.4)	46 (8.0)	
No. of drugs composing second-line regimen				.601
2	172 (28.3)	7 (21.9)	165 28.7)	
3	418 (68.9)	25 (78.1)	393 (68.3)	
4	17 (2.8)	0 (0.0)	17 (3.0)	
RAMs at baseline GRT				.668
None	521 (85.8)	26 (81.3)	495 (86.1)	
1 class	77 (12.7)	6 (18.8)	71 (12.3)	
≥2 classes	9 (1.5)	0 (0.0)	9 (1.6)	

Bold values underlines the statistically significant values.

ABC/3TC, abacavir/lamivudine; ART, antiretroviral therapy; GRT, genotype resistance test; IDU, intravenous drug use; INSTI, integrase inhibitor; IQR, interquartile range; MSM, men who have sex with men; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RAMs, resistance-associated mutations; TXF/FTC, tenofovir/emtricitabine (both tenofovir alafenamide or tenofovir disoproxil fumarate); VF, virological failure; VS, virological suppression.

switched to an NNRTI, 21.9% ($n=76$) switched to an INSTI and 10.1% ($n=35$) to other nonconventional regimens. Intravenous drug users and heterosexuals were significantly more represented among patients who experienced VF, as well as patients receiving a first-line backbone different from abacavir/lamivudine (ABC/3TC) or tenofovir/emtricitabine (TXF/FTC), mainly 3TC or zidovudine (AZT), alone or in combination. Also, median time from VS to ART switch was significantly shorter among patients experiencing VF (18 vs. 30 months, respectively).

At multivariable analysis, younger age (adjusted Hazard Ratio [aHR] 0.96, 95% confidence interval [CI] 0.92–0.99, $p=.023$), being male who have sex with male (MSM; aHR 0.15, 95% CI 0.03–0.69, $p=.014$) and longer time from VS to ART switch (aHR 0.97, 95% CI 0.95–1.00, $p=.021$) resulted protective toward VF. On the contrary, VF was associated with first-line regimen composition, in particular receiving a backbone other than ABC/3TC or TXF/FTC (aHR 3.61, 95% CI 1.00–13.1, $p=.050$) and receiving a bPI as anchor drug (aHR 3.34, 95% CI 1.20–9.28, $p=.021$). No association was noted among second-line regimen composition and VF.

Table 2. Results of Multivariable Analysis Analyzing Predictors of Virological Failure

	aHR	*95% confidence interval*	p
Male sex	1.25	0.54–2.89	.60
Age	**0.96**	**0.92–0.99**	**.02**
Risk factor for HIV infection			
Heterosexual	Ref	Ref	
IDU	2.24	0.71–7.03	.17
MSM	**0.15**	**0.03–0.69**	**.01**
Other	0.42	0.12–1.47	.18
Log_{10} of HIV-RNA value at baseline	0.99	0.60–1.63	.96
$CD4^+$ cells count at baseline	1.00	1.00–1.00	.92
Time from VS to ART switch	**0.97**	**0.95–1.00**	**.02**
First-line regimen composition			
Backbone			
ABC/3TC	Ref	Ref	
TXF/FTC	1.93	0.74–5.02	.18
Other	**3.61**	**1.00–13.07**	**.05**
Anchor drug			
NNRTI	Ref	Ref	
bPI	**3.34**	**1.20–9.28**	**.02**
INSTI	1.28	0.14–11.81	.83
Other	0.79	0.08–7.77	.84
Second-line regimen composition			
Backbone			
ABC/3TC	Ref	Ref	
TXF/FTC	1.18	0.45–3.13	.74
Other	0.32	0.08–1.28	.11
No backbone	0.62	0.07–5.15	.66
Anchor drug			
NNRTI	Ref	Ref	
bPI	1.34	0.44–4.07	.61
INSTI	1.31	0.42–4.10	.64
Other	1.50	0.26–8.69	.65

Significant results are underlined in bold text. For continuous variables, the hazard ratio is intended per one-unit increase.

ART, antiretroviral therapy; bPI, boosted protease inhibitor.

Table 2 summarizes the results of multivariable analysis, whereas Figure 1 depicts the survival curve for patients receiving the different classes of anchor drugs.

We further investigated the durability of second-line regimens, and found that 259 patients out of 607 (42.7%) discontinued second-line ART. At multivariable analysis, the class of anchor drug in the second-line regimen was found to be associated with discontinuation ($p<.001$). Average durability observed stratified according to anchor drug is as follows: NNRTI ($n=75$) 25 months (95% CI 11.0–40.0); PI ($n=118$) 24.5 months (95% CI 11.8–37.3); INSTI ($n=35$) 9 months (95% CI 4.0–20.0); other drugs ($n=31$) 11.0 months (95% CI 5.0–24.0).

Resistance-associated mutations

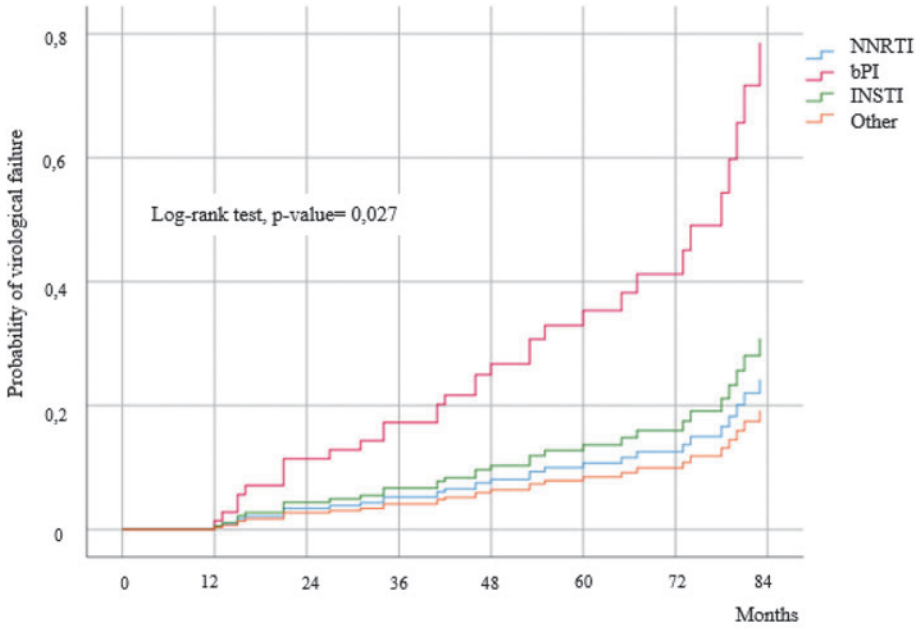
The overall rate of observed RAMs at baseline was not different among patients experiencing VF and those maintaining VS, with 85.8% of patients infected with a wild-type virus at baseline. Only 1 patient (1/21, 4.8%) with baseline RAMs to nucleoside reverse transcriptase inhibitors (NRTIs) experienced VF while receiving an NRTI as part of both first- and second-line regimens. Moreover, 13 and 5 patients showed baseline RAMs to NNRTIs and PIs, respectively, but reached VS despite being administered a first-line regimen containing these drugs. After ART switch, the regimen was adjusted according to baseline GRT in all of these patients and NNRTIs and bPIs were discontinued. The distribution of major RAMs detected at baseline is depicted in Figure 2.

GRT at the moment of VF was available for 13 (40.6%) of failing patients; characteristics of GRT at baseline and at VF for these patients, as well as the composition of their first- and second-line regimens, are outlined in Table 3. Emergence of new key mutations in reverse transcriptase and PI genes were noted in 4 (30.7%) and 3 patients (23.1%), respectively. Mutations to INSTI were detected in 3/6 patients with available GRT to INSTI, and in particular key mutations in one case and minor mutations in two of them.

Discussion

In our multicenter study, conducted in a cohort of selected PLWHIV with available data about baseline GRT, we reported a low rate of VF (5.3%) among patients switching to a second-line regimen after achieving stable VS. The observed rate of VF was much lower than that reported in a recent study conducted in another Italian cohort, despite the different primary endpoint and the absence of data about baseline GRT.[14]

ART switch in virologically suppressed patients is nowadays a common practice as its efficacy and safety have been confirmed by many studies,[15–25] with the issue being extensively investigated also in Italian cohorts.[5,19,26–33] However, to the best of our knowledge, no study has specifically assessed possible predictors of VF among virologically suppressed patients undergoing ART switch. Indeed, predictors of VF to second-line treatments have been investigated mainly in low-income countries where ART switch is usually performed in viremic patients[15,34–37] or at most in patients with persistent low-level viremia.[16] Such predictors included younger age, shorter time of first-line ART duration, lower $CD4^+$ cells count at the moment of switch to second-line ART, higher WHO score, and second-line ART composition.



NNRTI	216	216	214	213	201	161	118	67
bPI	347	346	340	337	302	230	160	80
INSTI	12	12	12	12	12	8	4	4
Other	32	32	31	31	23	16	8	3

FIG. 1. Increased risk of virological failure among patients receiving first-line treatment with a boosted protease inhibitor. In the table is shown the number of persons at risk over time. INSTI, integrase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor. Color images are available online.

In our cohort, only first-line regimen composition (in particular a backbone different from ABC/3TC or TXF/FTC and/or a bPI as anchor drug) predicted a threefold higher probability of experiencing VF. This might be explained by the fact that 3TC or AZT alone have a much lower efficacy and genetic barrier than other backbones, as well as by the fact that regimens containing bPIs are frequently reserved for patients with supposed difficult-to-treat infection, both because of poorer immunovirological status at baseline or because of adherence issues.

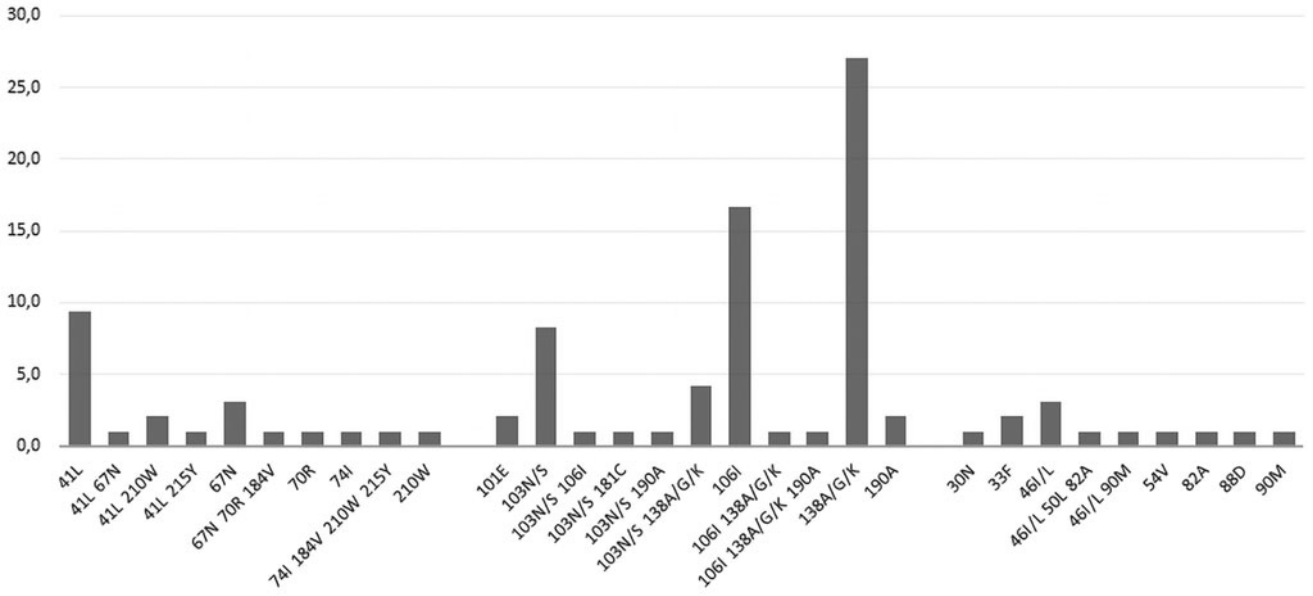


FIG. 2. Prevalence of major resistance-associated mutations detected at baseline genotypic resistance test in the study population. Results displayed refer (from *left* to *right*) to resistance to nucleos(t)ide analog reverse transcriptase inhibitors, non-nucleoside analog reverse transcriptase inhibitors and protease inhibitors, respectively.

Table 3. Characteristics of Baseline GRT and GRT at Virological Failure, Associated to Corresponding Composition of First- and Second-Line Regimens and Pre-ART Virological and Immunological Parameters

Patient ID	*Pre-ART viral load (log)*	*Pre-ART CD4+ cell count (cells/ml)*	*First-line regimen composition*	*RT mutations at baseline*	*PI mutations at baseline*	*Second-line regimen composition*	*RT mutations at VF*	*PI mutations at VF*	*INSTI mutations at VF*
1	4.8	236	DRV+TDF/FTC	No RAMs	62V 63P 77I 93L	EFV+TDF/FTC	NRTI: 65Rw 184Iw NNRTI: No RAMs	62V 71V 77I 93L	No RAMs
2	3.2	85	LPV +3TC+AZT	No RAMs	10V 16E 20I 36I 69K 89M	RPV+TDF/FTC	NRTI: 98Gw 184I NNRTI: 138K	10V 16E 20I 36I 69K 89M	N/A
3	5.0	396	EFV+TDF/FTC	No RAMs	36Iw	RPV+TDF/FTC	NRTI: 65R NNRTI: 101E 181C	No RAMs	N/A
4	5.2	156	EFV+TDF/FTC	No RAMs	64V 77I 93L	DRV+MVC	No RAMs	64V 77I 93L	No RAMs
5	4.6	N/A	LPV +3TC+AZT	No RAMs	63P 64Vw	DRV+RAL+MVC	No RAMs	63P	155H
6	3.8	417	RAL+TDF/FTC	No RAMs	16E 20I 36I 69K 89I	RPV+TAF/FTC	No RAMs	16E 20I 69K 89I	No RAMs
7	4.4	367	DRV+TDF/FTC	No RAMs	No RAMs	ATV+TDF/FTC	No RAMs	No RAMs	N/A
8	4.4	240	DRV+TDF/FTC	No RAMs	16E 36I 62V 93L	EVG+TDF/FTC	No RAMs	12P 16E 36I 93L	N/A
9	3.9	309	LPV+TDF/FTC	No RAMs	69K 89M 93L	EFV+ABC/3TC	No RAMs	69K 89M 93L	N/A
10	4.8	591	EFV+TDF/FTC	No RAMs	62Vw 63P 77I	EFV+TDF/FTC	No RAMs	63P 69N 77I	N/A
11	5.4	23	LPV+AZT +3TC	No RAMs	10I 16E 20R 36I 89M	RPV+TDF/FTC	NRTI: 184I NNRTI: 90I 138K	10I 16E 20R 36I 89M	N/A
12	5.1	357	EFV+TDF/FTC	No RAMs	60E 62V 63P 93L	EFV+ABC/3TC	No RAMs	60E 62V 63P 93L	No RAMs
13	5.2	168	LPV+TDF/FTC	No RAMs	63P	EVG+TAF/FTC	No RAMs	36Iw	No RAMs

Only major RAMs are displayed in the table.

3TC, lamivudine; ATV, atazanavir; AZT, zidovudine; DRV, darunavir; EFV, efavirenz; EVG, elvitegravir; LPV, lopinavir; MVC, maraviroc; N/A, not available; NRTI, nucleoside reverse transcriptase inhibitor; RAL, raltegravir; RPV, rilpivirine; TAF/FTC, tenofovir alafenamide/emtricitabine; TDF/FTC, tenofovir disoproxil/emtricitabine.

In contrast, younger age, being MSM, and a longer time from VS to ART switch proved to be protective with regard to VF. This latter observation has already been reported in a cohort addressing the durability of dual regimens in patients with a specific RAM,[38] and further supported by the description of an HIV-DNA decay proportional to the duration of effective therapy.[39]

In addition, the long follow-up period available for our study allowed a more accurate real-life picture of durability of second-line regimens than that provided by clinical trials, where follow-up is usually censored at 48 weeks. The transmitted RAMs observed in our cohort were consistent with the prevalence previously described in Italy.[40] The emergence of new RAMs upon VF was evaluated only for a small number of patients for whom a second GRT was available.

Moreover, we observed a high rate of discontinuation (>40%), possibly due to the constantly evolving availability of new antiviral drugs with improved tolerability profiles and new co-formulated drugs. However, precise reasons for such an observation will have to be extensively addressed in dedicated study.

Limitations of this study are its retrospective design and thus the impossibility to exclude the presence of unmeasured confounders, the small number of events observed, as well as the lack of reasons for ART switch. On the contrary, study strengths are the real-life nature of data presented, their national representativity and the long time span of observation for patients included.

Conclusions

Based on our observations, ART switch among patients under stable VS is a safe practice, allowing to maintain VS in ~95% of patients. However, particular attention should be paid in certain cases of patients switching from regimens containing low-performance backbones or bPIs.

Authors Contributions

Conceptualization and supervision by A.D.B., B.R., and V.B.; methodology by A.D.B. and V.B.; software by V.B. and A.B.; validation by A.D.B.; formal analysis by G.P. and V.B.; data curation by V.B., A.B., and F.I.; writing—original draft preparation by L.M. and R.P.; writing—review and editing by L.M., R.P., Y.B., F.S., D.F.B., A.D.V., R.L., R.C., M.Z., F.I., B.R., A.B., V.B., and A.D.B.; project administration by A.D.B. and M.Z. All authors have read and agreed to the published version of the article.

Acknowledgments

Members of the ARCA Study Group are as follows: Andrea Giacometti (ANCONA-Clinica di Malattie Infettive), Luca Butini (ANCONA-Immunologia Clinica), Romana del Gobbo (ANCONA-Malattie Infettive), Patrizia Bagnarelli (ANCONA-Virologia), Danilo Tacconi (AREZZO-Malattie Infettive), Giovanni Corbelli (ASCOLI PICENO-Malattie Infettive), Stefania Zanussi (AVIANO Centro di Riferimento Oncologico), Laura Monno (BARI Clinica Malattie Infettive Universita'), Grazia Punzi (BARI-Virologia), Franco Maggiolo (BERGAMO-Malattie Infettive), Leonardo Calza (BOLOGNA-Malattie Infettive S. Orsola), Maria Carla Re (BOLOGNA-UO Microbiologia, Lab. Retrovirus), Raffaele Pristera' (BOLZANO-Malattie Infettive), Paola Turconi (BRESCIA-Fleming Labs), Antonella Mandas (CAGLIARI Centro S.I.D.A., Policlinico Universitario), Sauro Tini (CITTA DI CASTELLO-Medicina Generale), Alessia Zoncada (CREMONA-Malattie Infettive), Elisabetta Paolini (CREMONA-Servizio Immunoematologia e Medicina Trasfusionale), Giorgio Amadio (FERMO-Malattie Infettive), Laura Sighinolfi (FERRARA-Malattie Infettive AOU S. Anna), Paola Corsi FIRENZE-Malattie Infettive CAREGGI), Luisa Galli (FIRENZE-Malattie Infettive Pediatria Meyer), Massimo Di Pietro (FIRENZE-Malattie Infettive SM Annunziata), Grazia Colao (FIRENZE-Virologia CAREGGI), Andrea Tosti (FOLIGNO-Malattie Infettive/SERT), Maurizio Setti (GENOVA Clinica Medica Immunologia), Bianca Bruzzone (GENOVA-Laboratorio diIgiene Ospedale S. Martino), Antonio Di Biagio e Chiara Dentone (GENOVA-Malattie Infettive Ospedale S. Martino), Giovanni Cenderello (SANREMO-Malattie Infettive), Michele Trezzi (GROSSETO-Malattie Infettive), Irene Arcidiacono (LODI-Malattie Infettive), Alberto Degiuli (LODI-Virologia Lodi), Michele De Gennaro (LUCCA Malattie Infettive), Alessandro Chiodera (MACERATA Malattie Infettive), Alfredo Scalzini (MANTOVA-Malattie Infettive Ospedale ''C. Poma''), Loredana Palvarini (MANTOVA-Virologia), Giovanni Todaro (MESSINA-Malattie Infettive), Stefano Rusconi (MILANO Dipart. Scienze Cliniche, Sez. Malattie Infettive-Universita' degli Studi), Maria Rita Gismondo (MILANO-Laboratorio Microbiologia Ospedale L. Sacco [Prima Divisione Malattie Infettive]), Valeria Micheli (MILANO-Laboratorio Microbiologia Ospedale L. Sacco [Seconda Divisione Malattie Infettive]), Maria Luisa Biondi (MILANO Laboratorio di diagnostica molecolare infettivologica AO S. Paolo), Amedeo Capetti (MILANO-Prima Divisione Malattie Infettive Ospedale L. Sacco), Paola Meraviglia (MILANO-Seconda Divisione Malattie Infettive Ospedale L. Sacco), Enzo Boeri (MILANO-Virologia HSR), Cristina Mussini (MODENA-Clinica Malattie Infettive), Monica Pecorari (MODENA-Virologia), Alessandro Soria (MONZA-Malattie Infettive), Laura Vecchi (MONZA-UO Microbiologia AO S. Gerardo), Maurizio Santirocchi (NARNI-SERT), Diego Brustia (NOVARA Malattie Infettive AO Maggiore), Paolo Ravanini (NOVARA-Virologia), Federico Dal Bello (PADOVA Virologia), Nino Romano PALERMO-Centro Riferimento AIDS Universita'), Salvatrice Mancuso (PALERMO Servizio Riferimento Regionale Diagnosi AIDS), Carlo Calzetti (PARMA-Divisione Malattie Infettive ed Epatologia Azienda Ospedaliera), Renato Maserati (PAVIA Ambulatorio Clinica Malattie Infettive S. Matteo), Gaetano Filice (PAVIA-Clinica Malattie Infettive e Tropicali), Fausto Baldanti (PAVIA-Virologia S. Matteo), Daniela Francisci (PERUGIA-Malattie Infettive), Giustino Parruti (PESCARA-Malattie Infettive), Ennio Polilli (PESCARA Virologia Pescara), Daria Sacchini (PIACENZA-Malattie Infettive), Chiara Martinelli (PISA-Malattie Infettive), Rita Consolini (PISA-Pediatria I Universita), Linda Vatteroni (PISA-Virologia), Angela Vivarelli (PISTOIA-Malattie Infettive), Alessandro Nerli (PRATO-Malattie Infettive), Lucia Lenzi (PRATO-Virologia), Giacomo Magnani (REGGIO EMILIA-Malattie Infettive), Patrizia Ortolani (RIMINI-Malattie Infettive RIMINI), Massimo Andreoni (ROMA-Cattedra

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Author Disclosure Statement

No competing financial interests exist.

Funding Information

This study was supported by an unconditional grant from Gilead Sciences.

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