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Short communication

Is the rate of virological failure to cART continuing to decline in recent calendar years?☆

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ARTICLE INFO

This manuscript is dedicated to the memory of Professor Andrea De Luca: a great friend, physician, mentor, and scientist.

ABSTRACT

Background: Despite the high rate of virological success of combined antiretroviral therapy (cART), HIV infected individuals continue to fail. In this contest, it is unclear whether having previously experienced virological failure (VF) of cART remains an important predictor of future risk of VF in people receiving cART in modern times. We investigated the rate of VF and factors potentially associated with this event in 9220 HIV-1 infected patients enrolled in the Icona Cohort who showed a stable viral suppression on modern cART regimens after January 1, 2006.

Methods: We investigated two main exposure factors: current calendar period (2006–2009; 2010–2013; 2014–2017) and number of VFs (0; 1–3; > 3) prior to baseline. Relative rates of VF were estimated from fitting a Poisson regression model.

Results: Seven-hundred-seventy-nine patients experienced VF over follow-up for an overall rate of 2.08 per 100 person years of follow-up (PYFU, 95%CI: 1.93–2.22). The rate of VF increased with higher numbers of previous VFs: patients with > 3 previous VFs had a rate of 4.87 (4.10–5.78), 2.75-fold higher than that observed in patients without any previous VF ($p < 0.001$). The rate of VF was lower in recent years: 3.81 (3.36, 4.32) in 2006–2009; 1.36 (1.20–1.53) in 2014–2017 ($p < 0.001$). Other factors independently associated with lower risk of VF were Italian origin, longer history of virological suppression, and university education level.

Conclusions: In HIV-infected patients virologically suppressed after January 2006, the rate of VF continues to show a decline even in the most recent years. Previous VFs should be carefully considered.

1. Background

Despite huge advances in terms of the impact of combined antiretroviral therapy (cART) on HIV-related morbidity and mortality, patients continue to fail therapy [1–4]. A history of prior virological failure (VF) has been shown to be associated with the risk of subsequent VF, emergence of resistance, and death [5–7]. However, the dynamics of VF in HIV-infected population receiving modern cART and factors associated with a greater risk of VF in this population have been not thoroughly investigated [8,9]. Specifically, in people whose viral load is

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Table 1
Socio-demographic characteristics overall and according to calendar year and previous virological failures.

Variables	Overall population	Calendar period of baseline				No. of previous virological failures			
	Total N = 9220	2006-2009 N = 2,695	2010-2013 N = 2,898	2014-2017 N = 3,627	p-value*	None N = 7,981	1-3 N = 717	> 3 N = 522	p-value*
Gender, n (%)					< .001				< .001
Female	2,043 (22.2%)	799 (29.6%)	583 (20.1%)	661 (18.2%)		1664 (20.8%)	221 (30.8%)	158 (30.3%)	
Age, Median (IQR)					< .001				< .001
Years	41 (34, 48)	43 (38, 48)	40 (33, 48)	40 (32, 48)		40 (33, 48)	44 (39, 50)	44 (39, 49)	
Mode of HIV Transmission, n (%)					< .001				< .001
Injection drug user	1,119 (12.2%)	675 (25.1%)	247 (8.5%)	197 (5.5%)		743 (9.4%)	210 (29.3%)	166 (31.8%)	
Homosexual contacts	3,748 (40.8%)	702 (26.1%)	1261 (43.6%)	1785 (49.7%)		3459 (43.6%)	174 (24.3%)	115 (22.0%)	
Heterosexual contacts	3,698 (40.1%)	1156 (42.9%)	1200 (41.4%)	1342 (37.0%)		3193 (40.0%)	298 (41.6%)	207 (39.7%)	
Other/Unknown	615 (6.7%)	161 (6.0%)	183 (6.3%)	271 (7.5%)		546 (6.9%)	35 (4.9%)	34 (6.5%)	
Nationality, n (%)					< .001				< .001
Not Italian	1,519 (16.5%)	220 (8.2%)	512 (17.7%)	787 (21.7%)		1386 (17.4%)	71 (9.9%)	62 (11.9%)	
Education, n (%)					< .001				< .001
Primary school	581 (6.3%)	280 (10.4%)	159 (5.5%)	142 (3.9%)		443 (5.6%)	76 (10.6%)	62 (11.9%)	
Secondary school	2,112 (22.9%)	1011 (37.5%)	550 (19.0%)	551 (15.2%)		1649 (20.7%)	275 (38.4%)	188 (36.0%)	
College	2,868 (31.1%)	813 (30.2%)	885 (30.5%)	1170 (32.3%)		2512 (31.5%)	207 (28.9%)	149 (28.5%)	
University	1,012 (11.0%)	202 (7.5%)	313 (10.8%)	497 (13.7%)		937 (11.7%)	47 (6.6%)	28 (5.4%)	
Other/Unknown	2,647 (28.7%)	389 (14.4%)	991 (34.2%)	1267 (34.9%)		2440 (30.6%)	112 (15.6%)	95 (18.2%)	
Employment, n (%)					< .001				< .001
Unemployed	1,103 (12.0%)	381 (14.1%)	307 (10.6%)	415 (11.4%)		892 (11.2%)	121 (16.9%)	90 (17.2%)	
Employed	4,057 (44.0%)	1395 (51.8%)	1273 (43.9%)	1389 (38.3%)		3479 (43.6%)	332 (46.3%)	246 (47.1%)	
Self-employed	1,390 (15.1%)	469 (17.4%)	416 (14.4%)	505 (13.9%)		1153 (14.4%)	143 (19.9%)	94 (18.0%)	
Occasional	278 (3.0%)	113 (4.2%)	75 (2.6%)	90 (2.5%)		209 (2.6%)	37 (5.2%)	32 (6.1%)	
Student	267 (2.9%)	49 (1.8%)	90 (3.1%)	128 (3.5%)		253 (3.2%)	10 (1.4%)	4 (0.8%)	
Retired	243 (2.6%)	76 (2.8%)	90 (3.1%)	77 (2.1%)		219 (2.7%)	11 (1.5%)	13 (2.5%)	
Invalid	18 (0.2%)	4 (0.1%)	9 (0.3%)	5 (0.1%)		18 (0.2%)	0 (0.0%)	0 (0.0%)	
Housewife	297 (3.2%)	170 (6.3%)	71 (2.4%)	56 (1.5%)		225 (2.8%)	46 (6.4%)	26 (5.0%)	
Other/unknown	1,567 (17.0%)	38 (1.4%)	567 (19.6%)	962 (26.5%)		1533 (19.2%)	17 (2.4%)	17 (3.3%)	

* Chi-squared test (for categorical variables), and Kruskal-Wallis test (for quantitative variables) were used, as appropriate, to compare the characteristics of the different patients' groups stratified according to the two main exposure factors of interest: current calendar year periods of baseline (stratified as: 2006–2009, 2010–2013, 2014–2017) and number of virological failures experienced before baseline (stratified as: 0, 1–3, > 3).

currently suppressed, it is unclear whether having previously experienced VF of cART remains an important predictor of future risk of VF in people receiving cART in modern times. There are several factors that could lead to the development of VF, such as lack of adherence, which can impact on the efficacy of different drug regimens [10,11], high levels of pre-cART viremia, which are associated with a lower probability of achieving virological suppression, and drug resistance [12–18].

In the present work, we aimed at identifying the rate and the presence of independent predictors of VF in HIV-1 infected individuals with plasma viral load ≤50 copies/mL on modern cART regimens after January 1, 2006.

2. Study design

2.1. Study population

All patients analyzed were from the ICONA Foundation Study (ICONA), a multi-centre prospective observational study (http://www.fondazioneicona.org/). Each patient included in the present analysis had a record of two consecutive plasma HIV-RNA ≤50 copies/mL after January 1, 2006: baseline was defined at the date of the second of these values. A patient was classified as having experienced VF to a regimen before baseline if, after at least 4 months from starting the regimen and while he/she was receiving the same regimen, plasma HIV-RNA was still > 400 copies/mL. A counter for the number of regimens to which a participant had experienced VF prior to baseline was constructed. Plasma HIV-RNA cut-off was chosen by considering the different limits of quantification of assays used to quantify this parameter before 2006.

2.2. Estimation of rates of virological failure during prospective follow-up by Poisson regression model

VF over prospective follow-up was defined at the time of the first of two consecutive values of HIV-RNA > 50 copies/mL while the person was still receiving cART after baseline. Participants' follow-up accrued from baseline until the date of estimated VF or the date of their last available HIV-RNA value. Rates of current VF were calculated as number of VF divided by person years of follow-up (PYFU) and unadjusted and adjusted relative rates (RR) were estimated from fitting a Poisson regression model. Main exposure factors investigated were: i) current calendar year periods of baseline (stratified as: 2006–2009, 2010–2013, 2014–2017); ii) number of VFs experienced before baseline (stratified as: 0, 1–3, > 3). Whether the risk associated with previous number of VFs varied according to current calendar period of viral suppression was formally investigated by fitting an interaction term in the Poisson regression model. The association between other socio-demographic, viro-immunological and clinical factors measured at baseline and the risk of VF were also investigated. Analyses were repeated after using a plasma HIV-RNA value of 200 copies/mL as the threshold to define VF.

All the analyses were performed using SAS version 9.4 (SAS Institute Cary NC, U). In all the analyses a p-value < 0.05 was considered as statistically significant.

3. Results

3.1. Patients' characteristics

Nine-thousand and two-hundred-twenty HIV-infected patients, who

Table 2
Clinical characteristics overall and according to calendar year and previous virological failures.

Variables		Calendar period of baseline				No. of previous virological failures			
	Total N = 9220	2006-2009 N = 2,695	2010-2013 N = 2,898	2014-2017 N = 3627	p-value*	None N = 7,981	1-3 N = 717	> 3 N = 522	p-value*
Calendar year of baseline, Median (IQR)	2012 (2009, 2015)	2006 (2006, 2008)	2012 (2011, 2013)	2015 (2014, 2016)	< .001	2013 (2010, 2015)	2006 (2006, 2008)	2007 (2006, 2010)	< .001
AIDS diagnosis, n (%) Yes	1,287 (14.0%)	523 (19.4%)	370 (12.8%)	394 (10.9%)	< .001	1005 (12.6%)	155 (21.6%)	127 (24.3%)	< .001
CNS diagnosis, n (%) Yes	1,029 (11.2%)	413 (15.3%)	334 (11.5%)	282 (7.8%)	< .001	832 (10.4%)	109 (15.2%)	88 (16.9%)	< .001
HBsAg, n (%)					< .001				< .001
Negative	7,549 (81.9%)	2457 (91.2%)	2327(80.3%)	2765(76.2%)		6394 (80.1%)	666(92.9%)	489 (93.7%)	
Positive	127 (1.4%)	75 (2.8%)	30 (1.0%)	22 (0.6%)		85 (1.1%)	21 (2.9%)	21 (4.0%)	
Not tested	1,544 (16.7%)	163 (6.0%)	541 (18.7%)	840 (23.2%)		1502 (18.8%)	30 (4.2%)	12 (2.3%)	
HCVAb, n (%)					< .001				< .001
Negative	6,539 (70.9%)	1744(64.7%)	2150 (74.2%)	2645 (72.9%)		5766 (72.2%)	462 (64.4%)	311 (59.6%)	
Positive	1,296 (14.1%)	790 (29.3%)	288 (9.9%)	218 (6.0%)		871 (10.9%)	227 (31.7%)	198 (37.9%)	
Not tested	1,385 (15.0%)	161 (6.0%)	460 (15.9%)	764 (21.1%)		1344 (16.8%)	28 (3.9%)	13 (2.5%)	
Hepatitis co-infection, n (%)					< .001				< .001
No	6,172 (66.9%)	1673 (62.1%)	2015 (69.5%)	2484 (68.5%)		5433 (68.1%)	444 (61.9%)	295 (56.5%)	
Yes	1,391 (15.1%)	841 (31.2%)	312 (10.8%)	238 (6.6%)		939 (11.8%)	241 (33.6%)	211 (40.4%)	
Not tested	1,657 (18.0%)	181 (6.7%)	571 (19.7%)	905 (25.0%)		1609 (20.2%)	32 (4.5%)	16 (3.1%)	
CD4 count, cells/mm^3, Median (IQR)	498 (340, 675)	495 (351, 678)	457 (319, 600)	534 (351, 732)	< .001	495 (337, 666)	532 (373, 741)	482 (323,707)	< .001
CD4 count nadir, cells/mm^3, Median (IQR)	285 (156, 410)	225 (112, 310)	294 (177, 385)	358 (186, 500)	< .001	299 (172, 426)	226 (108, 322)	166 (57, 292)	< .001
CD8 count, cells/mm^3, Median (IQR)	893 (647, 1230)	873 (635, 1200)	886 (633, 1206)	917 (667, 1278)	< .001	886 (646, 1228)	906 (638, 219)	974 (692, 1326)	0.005
No. of previous viral failures**					0. 037				< .001
Median (IQR)	3 (3, 4)	3 (3, 4)	4 (3, 4)	4 (3, 4)		0 (0, 0)	3 (2, 3)	5 (4, 6)	
Time from HIV diagnosis to baseline, months, Median (IQR)	23 (7, 83)	100 (47, 151)	17 (8, 47)	10 (5, 30)	< 0.001	16 (7, 55)	116 (85, 178)	129 (99, 187)	< 0.001
Number of blips > 50 copies/mL***					< 0.001				0.016
Median (IQR)	1 (1, 5)	1 (1, 5)	1 (1, 4)	1 (1, 3)		1 (1, 5)	1 (1, 5)	1 (1, 4)	
Duration of viral suppression at baseline, months, Median (IQR)	20 (9, 36)	21 (10, 36)	5 (3, 15)	6 (3, 12)	< .001	21 (10, 39)	19 (9, 32)	16 (8, 26)	0.002
VL at starting cART, log_{10} copies/mL, Median (IQR)	4.64 (3.92, 5.16)	4.68 (3.95, 5.17)	4.67 (3.99, 5.19)	4.58 (3.83, 5.12)	0.003	4.62 (3.91, 5.15)	4.67 (3.94, 5.18)	4.78 (4.07, 5.34)	0.003
GSS of baseline treatment**** n (%)					< .001				< .001
≥ 1 active drug in regimen	2786 (30.2%)	519 (19.3%)	1253 (43.2%)	1014 (28.0%)		2617 (32.8%)	102 (14.2%)	67 (12.8%)	
No active drugs in regimen	759 (8.2%)	211 (7.8%)	315 (10.9%)	233 (6.4%)		634 (7.9%)	59 (8.2%)	66(12.6%)	
No GRT results available	5,675(61.6%)	1965(72.9%)	1330(45.9%)	2380(65.6%)		4730 (59.3%)	556 (77.5%)	389(74.5%)	

Acronyms: cART, combined antiretroviral therapy; CNS, central nervous system (indicates the psychological disorders diagnosis); GRT, genotypic resistance test; GSS, genotypic susceptibility score for treatment administered; IDU, injecting drug user; IQR, interquartile range; VL, viral load.

* Chi-squared test (for categorical variables), and Kruskal-Wallis test (for quantitative variables) were used, as appropriate, to compare the characteristics of the different patients' groups stratified according to the two main exposure factors of interest: current calendar year periods of baseline (stratified as: 2006–2009, 2010–2013, 2014–2017) and number of virological failures experienced before baseline (stratified as: 0, 1–3, > 3).

** Among patients with at least one virological failure prior baseline (N = 1239).

*** Over the first 4 years from baseline, ignoring therapy switches and among patients with at least one viral blip (N = 1831).

**** In patients with an available genotypic resistance test performed before the baseline, the GSS for treatment administered at baseline was determined by using the HIVDB WEB-SERVICE (Stanford HIV drug resistance database: https://hivdb.stanford.edu). The five HIVDB predicted sensitivity scores were re-classified in 3 groups (susceptible/intermediate/resistant), which were assigned the numerical values of 1.0/0.5/0.0, respectively. Each combination regimen was then given a GSS based on the sum of the scores coded for the individual drugs included in the regimen which indicates how many of these drugs are still fully active.

had been under viral suppression after January 1, 2006 were included. The median (interquartile range, IQR) calendar year of baseline was 2012 (2009, 2015). At baseline, patients have been virologically suppressed for a median (IQR) of 20 (9, 36) months and have been subsequently followed for a total of 37,499 PYFU. Baseline characteristics, stratified by calendar year periods at baseline, and previous history of VFs are shown in Tables 1 and 2 and Fig. 1.

3.2. Rates of virological failures during follow-up and independent predictors

Seven-hundred and seventy-nine patients showed a current VF (cut-off 50 copies/mL) with a rate of 2.08 per 100 PYFU (95%CI: 1.93–2.22). The median value of HIV-RNA (log_{10}) at VF did not differ among the 3 current time periods: 4.10 (2.99–4.88) in 2006–2009, 3.82 (2.95–4.72) in 2010–2013, 3.91 (2.91–4.22) in 2014–2017 (p = 0.320). In contrast, the risk of the current VF was higher with larger number of VFs

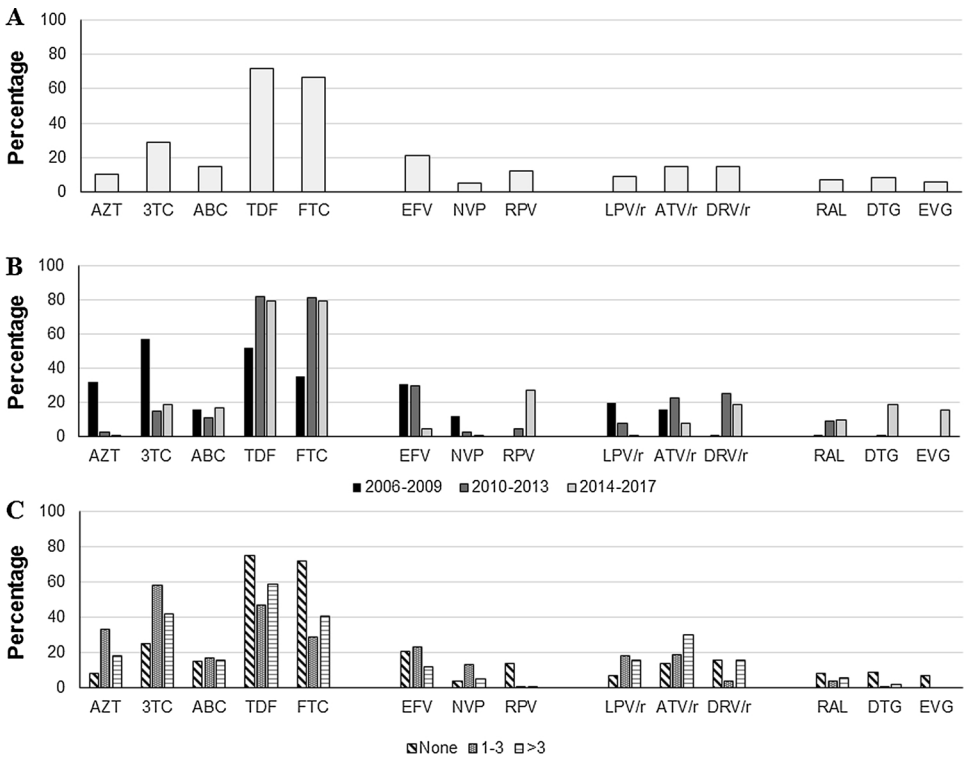

Fig. 1. Antivirals included in the suppressive regimen received at baseline among the overall patients analyzed in study (panel A), according to calendar year (panel B) and to previous virological failures (panel C). Among the antiretrovirals used at baseline, tenofovir was the nucleoside reverse transcriptase inhibitor (NRTI) mostly used (71.8%) together with emtricitabine (66.4%) or lamivudine (3.7%). As far as the third drug used in the current regimen, 3494 (37.9%) patients were receiving a non-NRTI (NNRTI), 3745 (40.6%) were treated with a ritonavir-boosted protease inhibitor, while 1941 (21.0%) were treated with an integrase inhibitor.

experienced before baseline. Specifically, patients with > 3 previous VFs had a rate (95%CI) of 4.87 (4.10–5.78) per 100 PYFU, 2.87-fold higher than that observed in patients without any previous VF (Table 3). This result was confirmed after controlling for potential confounding factors (adjusted RR = 2.75; 95% CI: 2.13–3.56, $p < 0.001$).

In addition, the rate of VF was lower with more recent calendar years, ranging from 3.81 (3.36, 4.32) in 2006–2009 to 1.36 (1.20–1.53) in 2014–2017. This association remained significant after adjustment for a number of potential confounding factors: adjusted RR = 0.36 (95%CI: 0.29-0.44, $p < 0.001$: comparison 2014–2017 *vs.* 2006–2009). The association between number of previous failures and the risk of subsequent VF was also confirmed in different multivariable models after controlling for several socio-demographic, viro-immunological and clinical variables (Supplementary Table 1), and did not vary by current calendar period. This was documented by the lack of evidence for an interaction between previous VFs and calendar years ($p = 0.18$, Supplementary Fig. 1).

Other independent predictors negatively associated with the risk of VF were Italian origins, a longer duration of time with virological suppression, declaring University as the highest level of education achieved, and use of efavirenz. The GSS at baseline showed no association with the risk of VF.

We obtained similar results after repeating the analyses with a plasma HIV-RNA value of 200 copies/mL as the threshold to define VF (Supplementary Table 2).

4. Discussion

In our large cohort of virologically suppressed HIV-1 infected patients, we found that, after controlling for a number of demographic, health-related, viro-immunologic and therapeutic factors, the rate of VF continues to show a decline even in the most recent study period, *i.e.* 2014–2017. Although the association between history of previous VFs on cART and subsequent risk of VF has been previously documented [5–7], our data extend this finding to more recent years for people exposed to modern cART. In addition, our data show that, despite the introduction of new drugs/drug classes with reduced cross-resistance and the increased tolerability of modern compounds, the impact of having virologically failed in the past remains unchanged on the current risk of VF.

Other factors were identified as independent predictors of higher risk of VF over prospective follow-up and should be considered to identify people at greater risk of treatment failure: foreign nationality, shorter duration of viral suppression, and having the highest level of education lower than University. We understand that our large cohort study is observational, so that issues such a confounding and collision are less likely to be adequately controlled as it is in randomized trial. On the other hand, not many trials have sample sizes or duration of follow-up similar to that of our study, which extends over several decades and has allowed the time-periods comparison.

In conclusion, our data supports the concept that people with a current suppressed plasma viral load but a history of extensive VF (> 3 regimens) are still a fragile population for whom careful monitoring of viral load should be maintained. Similarly, even in our ART modern era, a history of virological failure should be carefully examined and accounted for when a treatment switch is needed.

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Conflict of interest

The authors declare no conflict of interest.

Contributors

SR and MMS conceived the study and coordinated the manuscript. AA, SB, AC, NG, FCS collected patients' data and gave their input on data analysis. AT managed all data from the ICONA cohort. AdAM coordinated all clinical activities. AC-L performed all statistical evaluations. SR, MMS and AC-L wrote and circulated the final version of

the manuscript.

Ethical approval

This study was conducted on data collected for clinical purposes. All data used in the study were previously anonymized, according to the requirements set by Italian Data Protection Code (leg. decree 196/2003) and by the General authorizations issued by the Data Protection Authority. The ICONA Foundation study has been separately approved by IRB of all the participating centers; sensitive data from patients are seen only in aggregate form. Written informed consent for medical procedures/interventions performed for routine treatment purposes was collected for each patient included in the Icona Foundation Study or from other clinical centers involved in the study, in accordance with the ethics standards of the committee on human experimentation and the Helsinki Declaration (1983 revision).

Acknowledgements

This manuscript is dedicated to the memory of Professor Andrea De Luca: a great friend, physician, mentor, and scientist.

The authors wish to thanks Miss A. Rodano' for excellent technical assistance and data management.

Appendix A

Icona Foundation Study Group

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Appendix B. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jcv.2019.04.009.

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