Received: 28 February 2023 | Accepted: 19 June 2023

DOI: 10.1111/hiv.13525

SHORT COMMUNICATION

Trend over time of HIV-1 drug resistance to nonnucleoside reverse transcriptase inhibitors (NNRTIs) and their drivers: A cohort study from Antiviral Response Cohort Analysis (ARCA)

Ilaria Rancan[1,2] | **Chiara Cassol**[3] | **Lucia Graziani**[1] | **Marta Tilli**[1] | **Costanza Malcontenti**[4] | **Chiara Russo**[5,6] | **Martina Bottanelli**[7,8] | **Fiorenza Bracchitta**[9] | **Rebecka Papaioannu**[7,8] | **Laura Labate**[5,6] | **Sara Mora**[10] | **Antonia Bezenchek**[11,12] | **Adrian Shallvari**[11,12] | **Antonio Di Biagio**[5,6] | **Barbara Rossetti**[3]

[1]Department of Experimental & Clinical Medicine, University of Florence, Florence, Italy

[2]Infectious and Tropical Diseases Unit, Department of Medical Sciences, University Hospital of Siena, Siena, Italy

[3]Infectious Disease Department, USL SUDEST, Toscana, Misericordia Hospital, Grosseto, Italy

[4]SOD Malattie Infettive e Tropicali AOU Careggi, Florence, Italy

[5]Infectious Diseases Unit, San Martino Policlinico Hospital-IRCCS for Oncology and Neuroscience, Genoa, Italy

[6]Department of Health Sciences (DISSAL), University of Genoa, Genoa, Italy

[7]School of Medicine, Vita-Salute San Raffaele University, Milan, Italy

[8]Infectious Diseases Unit, San Raffaele Scientific Institute, Milan, Italy

[9]Laboratory of Clinical Microbiology, Virology and Bioemergencies, ASST Fatebenefratelli Sacco, L. Sacco University Hospital, Milan, Italy

[10]Department of Informatics, Bioengineering, Robotics and System Engineering, University of Genoa, Genoa, Italy

[11]InformaPRO S.r.l., Rome, Italy

[12]EuResist Network GEIE, Rome, Italy

Correspondence
Ilaria Rancan, Department of Experimental & Clinical Medicine, University of Florence, Florence, Italy.
Email: rancan.ilaria@gmail.com

Abstract

The rise of HIV-1 drug resistance to nonnucleoside reverse transcriptase inhibitors (NNRTIs) threatens the long-term success of NNRTI-based therapies. Our study aims to describe the circulation of major resistance-associated mutations (RAMs) for NNRTIs in people living with HIV (PLWH) in Italy from 2000 to 2020. We included 5982 naïves and 28 505 genotypes from 9387 treatment-experienced PLWH from the Antiviral Response Cohort Analysis (ARCA) cohort. Transmitted drug resistance (TDR) was found in 12.5% and declined from 17.3% in 2000–2003 to 10.9% in 2016–2020 ($p = 0.003$). Predictors of TDR were viral subtype B [vs. non-B, adjusted odds ratio (aOR) = 1.94, $p < 0.001$], zenith viral load (VL) (per 1 $\log_{10}$ higher, aOR = 0.86, $p = 0.013$), nadir CD4 cell count (per 100 cells/μL increase aOR = 0.95, $p = 0.013$). At

least one RAM for NNRTIs among treatment experienced PLWH was detected in 33.2% and pre-treatment drug resistance (PDR) declined from 43.4% in 2000–2003 to 20.9% in 2016–2020 ($p < 0.001$). Predictors of PDR were sexual transmission route (vs. others, aOR = 0.78, $p < 0.001$), time since HIV diagnosis (per 1 month longer, aOR = 1.002, $p < 0.001$), viral subtype B (vs. non B, aOR = 1.37, $p < 0.001$), VL (per 1 $\log_{10}$ higher, aOR = 1.12, $p < 0.001$), nadir CD4 count (per 100 cells/μL increase, aOR = 0.91, $p < 0.001$), previous exposure to any NNRTI (aOR = 2.31, $p < 0.001$) and a more recent calendar year sequence (any time span > 2008 vs. 2000–2003, any aOR <1, $p < 0.001$). Circulation of RAMs to NNRTIs declined during the last 20 years in Italy. NNRTIs remain pivotal drugs for the management of HIV-1 due to safety concerns and long-acting options.

KEYWORDS

antiretroviral therapy, HIV-1, HAART, NNRTIs, resistance, RAMs

INTRODUCTION

Nonnucleoside reverse-transcriptase inhibitor (NNRTI)-based regimens have been one of the pivotal options for both naïve and treatment-experienced people living with HIV (PLWH) worldwide [1]. Currently rilpivirine (RPV), already widely employed in three-drug and two-drug antiretroviral regimens, is acquiring a central role due to its combination with the new integrase inhibitor cabotegravir in a long-acting two-drug regimen administered every 8 weeks [1, 2]. Likewise, doravirine (DOR) has shown high efficacy, good safety, and tolerability profiles, in particular in PLWH affected with cardiovascular and metabolic disorders and carrying a resistance mutation pattern fairly different from same-class compounds [3].

According to the World Health Organization (WHO), pretreatment drug resistance (PDR) to nevirapine (NVP) or efavirenz (EFV) in naïve patients reached levels above 10% in several countries of Africa and South America, while resistance to second-generation NNRTIs ranged from 0.5% to 13.2% for DOR, from 1.0% to 10.3% for etravirine (ETR), and from 2.4% to 18.7% for RPV. High levels of NNRTI drug resistance were also reported by WHO in experienced patients taking NNRTI-based regimens unable to reach viral suppression, underlining the importance of genotype testing and of adherence to antiretroviral therapy (ART) [4].

The present study aims to describe the circulation of major resistance-associated mutations (RAMs) for NNRTIs in both naïve and treatment-experienced PLWH in an Italian real-life cohort from 2000 to 2020 and to investigate their predictors.

MATERIALS AND METHODS

We retrieved HIV-1 RNA protease/reverse transcriptase sequences, demographic and clinical data of adult PLWH from the Antiviral Response Cohort Analysis (ARCA) database, a public observational database containing data from more than 100 Italian centres for the study of resistance mutations to antiviral drugs for HIV, hepatitis B and hepatitis C virus infections [5]. Transmitted drug resistance (TDR) was defined as the presence of RAMs transmitted at the moment of the infection, considering genotypes of naïve PLWH [6], while pre-treatment drug resistance (PDR) identifies the sum of drug resistance mutations detected in all genotypes of experienced PLWH with previous ARV drug exposure initiating or reinitiating ART, including both transmitted and acquired RAMs, at the moment of the analysis [6]. TDR and PDR were defined as the presence of at least one mutation listed in the updated International Antiviral Sociey-USA and Stanford lists [7, 8]. The HIV-1 genotype was considered based on all the tests available (cumulative genotype).

The genotypic susceptibility score (GSS) for a single compound was obtained using the Stanford HIVdb genotypic resistance interpretation system: a GSS value of 0 corresponds to high-level resistance, 0.25 to intermediate resistance, 0.50 to low-level resistance, 0.75 to potential low-level resistance, and 1 to full susceptibility.

The cumulative GSS (cGSS) of the single compound was calculated for the cumulative genotype using the Stanford algorithm interpretation as the minimum value [9].

TABLE 1 Characteristics of the study population; univariate and multivariate analysis for naïve and experienced people living with HIV (PLWH). Only factors significantly associated with nonnucleoside reverse-transcriptase inhibitor (NNRTI) resistance in the univariate analysis are reported in the table.

Characteristics of PLWH		
	Naïve ($N = 5982$)	**Experienced ($N = 28\,505$)**
Gender [*n* (%)]		
Male	4422 (73.9%)	19 261 (67.6%)
Age (years) [median (IQR)]	39.00 (32.00–47.00)	43.00 (37.00–49.00)
Ethnicity [*n* (%)]		
Caucasian	4063 (67.9%)	18 355 (64.4%)
Route of transmission [*n* (%)]		
Sexual	3266 (54.6%)	11 362 (39.9%)
Zenith HIV-RNA ($\log_{10}$ copies/mL)	4.83 (4.26–5.37)	5.13 (4.50–5.62)
Viral load at sequencing ($\log_{10}$ copies/mL) [median (IQR)]	4.74 (4.16–5.30)	3.61 (2.47–4.54)
Nadir CD4 count (cells/μL)	326 (159–495)	154 (52–282)
CD4 at sequencing (cells/μL) [median (IQR)]	354 (179–528)	349.5 (192–543)
Viral subtype [*n* (%)]		
B	4324 (72.3%)	23 046 (80.8%)
Non-B	1658 (27.7%)	5459 (19.2%)
Time of HIV seropositivity (weeks) [median (IQR)]	3.14 (0.86–41.93)	136.73 (65.07–213.10)
Time periods [*n* (%)]		
2000–2003	421 (7.0%)	4457 (15.6%)
2004–2007	1394 (23.3%)	8120 (28.5%)
2008–2011	2214 (37.0%)	6027 (21.1%)
2012–2015	1347 (22.5%)	4579 (16.1%)
2015–2020	606 (10.1%)	5322 (18.7%)
GSS or cGSS <1 for NVP [*n* (%)]	781 (13.1%)	11 732 (41.2%)
GSS or cGSS <1 for EFV [*n* (%)]	642 (10.7%)	11 221 (39.3%)
GSS or cGSS <1 for ETR [*n* (%)]	853 (14.3%)	9865 (34.6%)
GSS or cGSS <1 for RPV [*n* (%)]	855 (14.3%)	9893 (34.7%)
GSS or cGSS <1 for DOR [*n* (%)]	480 (8.0%)	8913 (31.3%)

Naïve PLWH predictors for TDR

	Univariate				**Multivariate**			
	p	**OR**	**95% CI**		***p***	**aOR**	**95% CI**	
Virus subtype B	<0.001	1.965	1.618	2.388	<0.001	1.936	1.534	2.445
Zenith HIV-RNA ($\log_{10}$ copies/mL)	0.007	0.876	0.795	0.965	0.013	0.856	0.757	0.968
Nadir CD4 per 100 cells/μL	0.004	0.959	0.932	0.987	0.013	0.953	0.917	0.990

Experienced PLWH predictors for PDR

	Univariate				**Multivariate**			
	p	**OR**	**95% CI**		***p***	**aOR**	**95% CI**	
Ethnicity								
Caucasian	1				1			
Others	<0.001	0.714	0.650	0.784	0.014	1.211	1.040	1.409
Unknown	<0.001	0.660	0.622	0.699	0.629	1.039	0.891	1.211

TABLE 1 (Continued)

	Univariate				Multivariate			
	p	**OR**	**95% CI**		***p***	**aOR**	**95% CI**	
Modality of transmission of HIV infection (sexual vs. others)	<0.001	0.753	0.716	0.792	<0.001	0.779	0.716	0.847
Time since HIV diagnosis	<0.001	1.002	1.001	1.002	<0.001	1.002	1.001	1.002
Time periods								
2000–2003	1				1			
2004–2007	0.888	1.005	0.934	1.082	0.093	0.913	0.821	1.015
2008–2011	<0.001	0.548	0.505	0.594	<0.001	0.580	0.513	0.656
2012–2015	<0.001	0.410	0.374	0.448	<0.001	0.513	0.444	0.592
2016–2020	<0.001	0.345	0.315	0.378	<0.001	0.514	0.437	0.606
Virus subtype (B vs. non-B)	<0.001	1.897	1.770	2.032	<0.001	1.368	1.187	1.576
Viral load at sequencing log	<0.001	1.215	1.186	1.243	<0.001	1.120	1.081	1.160
Nadir CD4	<0.001	0.870	0.855	0.885	<0.001	0.910	0.881	0.939
Exposure to NNRTIs	<0.001	2.870	2.728	3.020	<0.001	2.308	2.136	2.494

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; DOR, doravirine; EFV, efavirenz; ETR, etravirine; NVP, nevirapine; RPV, rilpivirine; TDR, transmitted drug resistance.

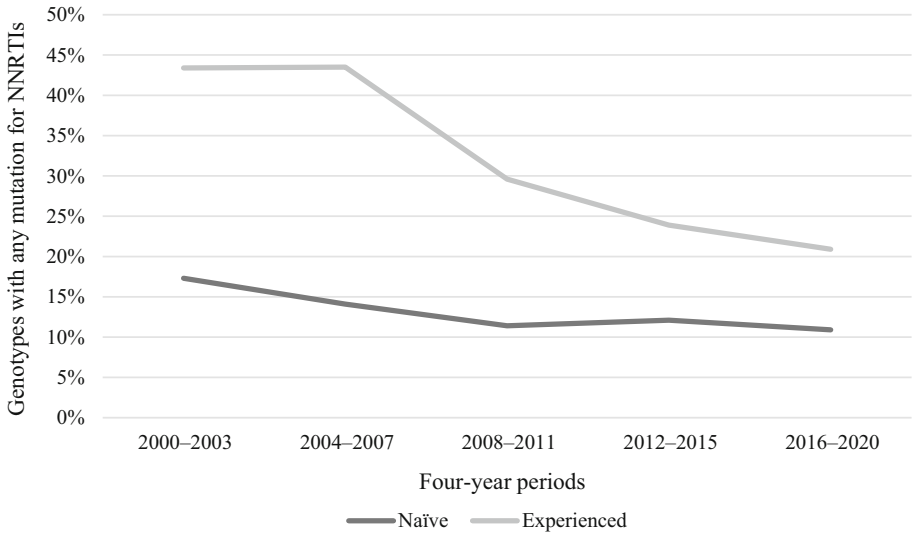

FIGURE 1 Prevalence of nonnucleoside reverse-transcriptase inhibitor (NNRTI) resistance over time.

Univariate and multivariate logistic regression analyses were performed to evaluate the association between NNRTI drug resistance and its predictors. Factors significantly associated with NNRTI resistance were included in the multivariate analysis. A $p < 0.05$ value was considered significant. The changes in the prevalence of RAMs over time were evaluated using the χ^2-test for trend. All analyses were performed using the SPSS software package (v. 25).

RESULTS

We included 5982 naïves: 73.9% were males, median age was 39 years [interquartile range (IQR): 32–47] and 67.9% were Caucasian. The main route of transmission was sexual intercourse (54.6%). The median time since HIV diagnosis was 3.14 weeks (0.86–41.93), nadir CD4 count was 326 cells/μL (159–495) and zenith HIV-1 RNA (viral load, VL) was 4.8 $\log_{10}$

copies/mL (4.3–5.4); 72.3% carried viral subtype B (Table 1).

Transmitted drug resistance was found in 12.5% of the enrolled subjects and declined from 17.3% in 2000–2003 to 10.9% in 2016–2020 ($p = 0.003$) (Figure 1). All NNRTIs were fully active in more than 85%, according to GSS: full susceptibility was present in 85.7% for RPV and ETR, 86.9% for NVP, 89.3% for EFV and 92% for DOR.

Predictors of TDR were viral subtype B [vs. non-B, adjusted odds ratio (aOR) = 1.94, 95% confidence interval (CI): 1.53–2.45, $p < 0.001$], zenith VL (per 1 $\log_{10}$ higher, aOR = 0.86, 95% CI: 0.76–0.97, $p = 0.013$), nadir CD4 count (per 100 cells/μL increase aOR = 0.95, 95% CI: 0.92–0.99, $p = 0.013$) (Table 1).

We retrieved 28 505 genotypes from 9387 treatment-experienced PLWH (67.6% from males and 64.4% from Caucasians) and the median age was 43 years (IQR: 37–49). Sexual route accounted for 39.9% of the modalities of transmission. Median time since HIV diagnosis was 136.7 months (65.1–213.1), nadir CD4 count was 154 cells/μL (52–282), and CD4 count at genotype was 349.5 cells/μL (192–543). Median zenith VL was 5.13 $\log_{10}$ copies/mL (4.50–5.62) and VL at genotype was 3.6 $\log_{10}$ copies/mL (4.5–5.6); 80.8% carried viral subtype B (Table 1).

At least one RAM for NNRTIs was detected in 33.2% and any PDR declined from 43.4% in 2000–2003 to 20.9% in 2016–2020 ($p < 0.001$) (Figure 1). Cumulative GSS < 1 was found in 41.2% for NVP, in 39.3% for EFV, in 34.7% for RPV, in 34.6% for ETR and in 31.3% for DOR.

Predictors of PDR were sexual transmission route (vs. others, aOR = 0.779, 95% CI: 0.72–0.85, $p < 0.001$), time since HIV diagnosis (per 1 month longer, aOR = 1.002, 95% CI: 1.001–1.002, $p < 0.001$), viral subtype B (vs. non-B, aOR = 1.37, 95% CI: 1.19–1.58, $p < 0.001$), VL (per 1 $\log_{10}$ higher, aOR = 1.12, 95% CI: 1.08–1.16, $p < 0.001$), nadir CD4 count (per 100 cells/μL increase, aOR = 0.91, 95% CI: 0.88–0.94, $p < 0.001$), previous exposure to any NNRTIs (aOR = 2.31, 95% CI: 2.14–2.49, $p < 0.001$) and a more recent calendar year sequence (any span time >2008 vs. 2000–2003, any aOR <1, $p < 0.001$) (Table 1).

Among PLWH with viral subtype non-B HIV-1 infection, resistance was found in 7.8% of naïves and 33.2% of the treatment-experienced individuals. Among non-B ones, the most representative subtypes were CRF_02AG (22% of non-B subtype HIV-1 infected naïve subjects, 31% of non-B subtype HIV-1 infected experienced PLWH genotypes), F (19% for naïves and 15% for experienced), CRF01_AE (9% for naïves and 7% for experienced), and C (8% for naïves and 6% for experienced). Each was significantly associated with a minor rate of mutations among treatment-experienced individuals, while for naïve individuals, only CRF01_AE and F were associated with fewer RAMs.

Those PLWH born in Italy were the most represented group among subtypes B, F and CRF01_AE, while PLWH from sub-Saharan Africa were prevalent among CRF02_AG and C subtypes. NNRTI resistance was higher among Italians.

Considering both naïve and experienced patients, the most represented RAMs were E138A, K103N, G190A, V108I, K101E, and Y181C. All these mutations were more frequent among individuals carrying viral subtype B HIV-1.

DISCUSSION

The rise of HIV-1 drug resistance to NNRTIs threatens the long-term success of antiretroviral therapies [4]. Susceptibility to NNRTIs in our population was in agreement with data reported by WHO [4]. At least one RAM for NNRTI was detected in 33.2% of the cumulative genotypes from treatment-experienced PLWH and in 12.5% from naïve individuals, highlighting the role of previous exposure to an NNRTI-based regimen as a predictor for resistance to the class, which can compromise future therapy strategies because of the long-term persistence of NNRTI mutations [10]. However, both PDR and TDR prevalence is declining, as already reported in a European cohort by Miranda et al. [11], probably because of the introduction of other classes as anchor drugs, in particular, integrase strand transfer inhibitors (INSTIs) and thanks to the higher efficacy and tolerability of later NNRTIs. Only DOR is currently included in recommended initial regimens by the European AIDS Clinical Society (EACS) Guidelines, while EFV and RPV are listed among the alternative regimens [1]. In fact, it has been shown that generally several concomitant mutations are required to reduce susceptibility to DOR, while for ETR, RPV, EFV, and NVP, only two or three NNRTI PDRs/TDRs are enough to reduce the efficacy of the compounds. The maintenance of the activity of Doravirine despite the presence of NNRTI mutations such as K103N, V106I and Y181C contributes to the success of DOR-containing regimens [12, 13].

Rilpivirine has recently acquired new relevance thanks to its use as a long-acting (LA) agent together with cabotegravir. Data from a 7-year observational cohort has shown the long-term durability of RPV because of its effectiveness and good tolerability, encouraging its use in this innovative regimen [14]. The LA formulation has also shown excellent results in terms of virological and patient-reported outcomes, even if some

cases with virological failure and newly emerged resistance mutations to NNRTIs have been reported [15].

In our cohort, a lower nadir CD4 count was a predictor for both TDR and PDR. Regarding VL, a lower zenith of HIV-1-RNA was a predictor of TDR, probably due to the lower replication capacity of resistant variants over wild-type HIV [16]. Instead, as regards experienced patients, a higher viral load at sequencing was a predictor of PDR. This could be explained by the fact that genotyping on RNA was performed exclusively in cases of virological failure with detectable viraemia. Subtype B was also a predictor for resistance to NNRTIs and it was the most represented subtype in our cohort, as expected. Prevalent NNRTI mutations were E138A, K103N, G190A, V108I, K101E and Y181C. All these were more represented among viral subtype B HIV-1-infected individuals. As regards non-B subtypes, CRF_02AG, F, CRF01_AE and C were the most frequent. Considering naïve PLWH, only CRF01_AE and F were predictors of fewer RAMs. Previous studies in the literature confirm a higher prevalence of resistance among subtype B HIV-1-infected patients [17–19]. By contrast, in a Spanish cohort of treatment-naïve patients NNRTI resistance was two-fold higher in non-B subtypes, in contrast to our study, in particular in CRF02_AG individuals, perhaps explained by the use of an NNRTI-based regimen in the countries of origin of most foreign non-B-infected patients in Spain [20].

The strengths of the study are the large sample size and the wide representation of PLWH in care across Italy, the national representativeness of the real-life setting, the enrolment of individuals typically not included in randomized trials due to the presence of baseline resistance, and the wide calendar time span analysed.

Limitations include the lack of information on the reasons for NNRTI discontinuation and the lack of last genotype and adherence data at virological failure.

In conclusion, in Italy, RAMs to NNRTI circulation declined during the last 20 years. NNRTIs remain pivotal drugs for the management of HIV-1 due to safety concerns and long-acting options.

AUTHOR CONTRIBUTIONS

BR and ADB conceptualized the study. IR, CC, y, MT, CM, CR, MB, FB, RP, LL, SM, AB, AS, ADB and BR prepared the methodology. BR, IR and CC carried out the formal analysis. IR, CC, LG, MT, CM, CR, MB, FB, RP, LL, SM, AB, AS, ADB and BR carried out the investigation and performed the data curation. IR prepared the original draft. BR, ADB and CC reviewed and edited the manuscript. All authors have read and approved the final version of the manuscript.

ACKNOWLEDGEMENTS

We thank the patients who shared their data, the ARCA clinical and laboratory units and the ARCA Scientific Board. The following centres currently contribute clinical and laboratory data to the ARCA database initiative: Luca Butini (ANCONA-Immunologia Clinica); Romana del Gobbo (ANCONA-Malattie Infettive); Andrea Giacometti (ANCONA-Clinica di Malattie Infettive); Patrizia Bagnarelli (ANCONA-Virologia); Danilo Tacconi (AREZZO-Malattie Infettive); Laura Monno (BARI-Clinica Malattie Infettive Università); Paola LAghetti (BARI-Virologia); Annapaola Callegaro (BERGAMO-Microbiologia e Virologia); Franco Maggiolo (BERGAMO-Malattie Infettive); Alessia Zoncada (CREMONA-Malattie Infettive); Massimo Crotti (CREMONA-Immunoematologia e Medicina Trasfusionale); Vincenzo Mellace (CATANZARO-SERT Soverato); Surace/Latella (CATANZARO-Centro Mallattie Epatiche e Trapianti); Lucio Cosco (CATANZARO-U.O. Malattie Infettive Ospedale Pugliese Ciaccio); Alfredo Focà (CATANZARO-U.O. di Microbiologia Clinica); Laura Sighinolfi (FERRARA-Malattie Infettive AOU S. Anna); Sergio Ferrara (FOGGIA-SC Malattie Infettive Universitarie AOU Ospedali Riuniti di Foggia); Maria Rosaria Lipsi (FOGGIA-SSD Microbiologia e Virologia AOU Ospedali Riuniti di Foggia); Paola Corsi (FIRENZE-Malattie Infettive CAREGGI); Francesca Vichi (FIRENZE-Malattie Infettive SM Annunziata); Luisa Galli (FIRENZE-Malattie Infettive Pediatria Meyer); Grazia Colao (FIRENZE-Virologia CAREGGI); Andrea Tosti (FOLIGNO-Malattie Infettive/SERT); Maurizio Setti (GENOVA-Clinica Medica Immunologia); Emanuele Pontali (GENOVA-Malattie Infettive Ospedali Galliera); Antonio Di Biagio (GENOVA-Malattie Infettive Ospedale S. Martino); Bianca Bruzzone (GENOVA-Laboratorio di Igiene Ospedale S. Martino); Cesira Nencioni (GROSSETO-Malattie Infettive); Barbara Rossetti (GROSSETO-Malattie Infettive); Stefano Rusconi (LEGNANO-Malattie Infettive); Riccardo Pardelli (LIVORNO-Malattie Infettive); Irene Arcidiacono (LODI-Malattie Infettive); Alberto Degiuli (LODI-Virologia Lodi); Michele De Gennaro (LUCCA-Malattie Infettive); Alessandro Soria (MONZA-Malattie Infettive); Sergio Malandrin (MONZA-UO Microbiologia AO S. Gerardo); Eleonora Gabrielli (MACERATA-Malattie Infettive); Giovanni Pellicano (MESSINA-Malattie Infettive A.O.U. Policlinico G. Martino); Paola Cicconi (MILANO-Clinica di Malattie Infettive Ospedale S. Paolo); Andrea Gori (MILANO-Fondazione IRCCS Ca′ Granda Ospedale Maggiore Policlinico, UOC Malattie Infettive); Valeria Micheli (MILANO-Laboratorio Microbiologia Ospedale L. Sacco [Seconda Divisione Malattie Infettive]); Paola Meraviglia (MILANO-Seconda Divisione Malattie Infettive Ospedale L. Sacco); Amedeo Capetti (MILANO-Prima Divisione Malattie Infettive Ospedale L. Sacco); Maria Luisa Biondi (MILANO-Laboratorio di diagnostica molecolare

infettivologica AO S. Paolo); Cristina Mussini (MODENA-Clinica Malattie Infettive); Monica Pecorari (MODENA-Virologia); Nicola Gianotti (HSR-Studio MUSA); Antonio Cascio (PALERMO-Malattie Infettive Policlinico "P. Giaccone"); Daria Sacchini (PIACENZA-Malattie Infettive); Giustino Parruti (PESCARA-Malattie Infettive); Ennio Polilli (PESCARA-Virologia Pescara); Daniela Francisci (PERUGIA-Malattie Infettive); Stefania Zanussi (AVIANO-Centro di Riferimento Oncologico); Alessandro Nerli (PRATO-Malattie Infettive); Lucia Lenzi (PRATO-Virologia); Carlo Calzetti (PARMA-Divisione Malattie Infettive ed Epatologia Azienda Ospedaliera); Angela Vivarelli (PISTOIA-Malattie Infettive); Renato Maserati (PAVIA-Ambulatorio Clinica Malattie Infettive S. Matteo); Gaetano Filice (PAVIA-Clinica Malattie Infettive e Tropicali); Fausto Baldanti (PAVIA-Virologia S. Matteo); Claudia Lazzaretti (REGGIO EMILIA-Malattie Infettive); Alessandro Zerbini (REGGIO EMILIA-S.S Autoimmunità, Allergologia e Biotecnologie Innovative); Francesca Lombardi (ROMA-Laboratorio virologia Cattolica); Simona Di Giambenedetto (ROMA-Università Cattolica del Sacro Cuore, Roma Italia, Istituto di Clinica Malattie Infettive); Massimo Andreoni (ROMA-Cattedra Malattie Infettive Tor Vergata); Marco Montano (ROMA-Virologia per Malattie Infettive Tor Vergata); Vincenzo Vullo (ROMA-Malattie Infettive e Tropicali La Sapienza-Umberto I); Ombretta Turriziani (ROMA-Medicina Sperimentale e Patologia-Sezione Virologia-La Sapienza); Andrea Antinori (ROMA-Malattie Infettive INMI Spallanzani); Maurizio Zazzi (SIENA-Virologia); Enzo Boeri (MILANO-Virologia HSR); Stefano Bonora (TORINO-Malattie Infettive Amedeo di Savoia); Valeria Ghisetti (TORINO-Laboratorio di Virologia, Ospedale Amedeo di Savoia); Paolo Grossi (VARESE-Clinica Malattie Infettive e Tropicali); Federica Poletti (VERBANIA-Malattie Infettive VERBANIA); Vincenzo Mondino (VERBANIA-Virologia); Marina Malena (VERONA-Centro di Medicina Preventiva-ULSS 20).

FUNDING INFORMATION

No funding was received to perform this study.

CONFLICT OF INTEREST STATEMENT

IR received support for travel to meetings from Gilead Sciences, ViiV Healthcare and Merck Sharp & Dohme (MSD). CC received support for travel to meetings from ViiV Healthcare. CM received speakers' honoraria and support for travel to meetings from Gilead Sciences and ViiV Healthcare. ADB served as a consultant or attended advisory boards for Janssen, Gilead Sciences, ViiV Healthcare, MSD and received research grant by Gilead Sciences and ViiV Healthcare. BR received speakers' honoraria and support for travel to meetings from Bristol-Myers Squibb (BMS), Gilead Sciences, Janssen-Cilag, Merck Sharp & Dohme (MSD) and ViiV Healthcare, and fees for attending advisory boards from Gilead Sciences, Janssen-Cilag and ViiV Healthcare.

CONFLICTS OF INTEREST

Antiviral Response Cohort Analysis (ARCA) was supported by unconditional educational grants from ViiV Healthcare, GILEAD Sciences, MSD, Janssen and Thera technologies.

ORCID

Ilaria Rancan https://orcid.org/0000-0001-6393-4212
Chiara Cassol https://orcid.org/0000-0001-8976-1671
Antonia Bezenchek https://orcid.org/0000-0002-9921-3684
Barbara Rossetti https://orcid.org/0000-0003-1659-9241

REFERENCES

1. European AIDS Clinical Society (EACS) Guidelines. Version 11.1, October 2022. Available at: https://www.eacsociety.org/guidelines/eacs-guidelines/
2. Overton ET, Richmond G, Rizzardini G, et al. Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 48-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study. *Lancet*. 2021;396(10267):1994-2005. doi:10.1016/s0140-6736(20)32666-0
3. Iannone V, Farinacci D, D'Angelillo A, et al. Cardiovascular disease risk in a cohort of Virologically suppressed people living with HIV switching to Doravirine: preliminary data from the real life. *AIDS Res Hum Retroviruses*. 2022;38(11):878-880. doi:10.1089/AID.2022.0050
4. World Health Organisation (WHO). HIV Drug Resistance Report 2021. Avalilable at: https://www.aidsdatahub.org/sites/default/files/resource/who-hiv-drug-resistance-report-2021.pdf.
5. Antiviral Response Cohort Analysys. ARCA database. Available at https://www.dbarca.net/
6. HIV Drug Resistance. *HIV drug resistance report 2021*. World Health Organization; 2021 Available at: https://apps.who.int/iris/rest/bitstreams/1394483/retrieve
7. Wensing AM, Calvez V, Ceccherini-Silberstein F, et al. Update of the Drug Resistance Mutations in HIV. International Antiviral Sociey-USA (IAS-USA) 2022. 2022 https://www.iasusa.org/resources/hiv-drug-resistance-mutations/
8. HIV Drug Resistance Mutations Database, Stanford University. Version 8.9–1, November 2019. Available at: https://cms.hivdb.org/prod/downloads/asi/HIVDB_8.9-1.xml
9. HIValg Program: Sequence analysis, Stanford University. Version 8.9.1, November 2019. Available at: https://hivdb.stanford.edu/hivalg/by-sequences
10. Jain V, Sucupira MC, Bacchetti P, et al. Differential persistence of transmitted HIV-1 drug resistance mutation classes. *J Infect Dis*. 2011;203(8):1174-1181. doi:10.1093/infdis/jiq167
11. Miranda MNS, Pingarilho M, Pimentel V, et al. Trends of transmitted and acquired drug resistance in Europe from 1981 to 2019: a comparison between the populations of late presenters and non-late presenters. *Front Microbiol*. 2022;13(13):846943. doi:10.3389/fmicb.2022.846943

12. Pham HT, Xiao MA, Principe MA, Wong A, Mesplède T. Pharmaceutical, clinical, and resistance information on doravirine, a novel non-nucleoside reverse transcriptase inhibitor for the treatment of HIV-1 infection. *Drugs Context*. 2020;9:2019-11-4. doi:10.7573/dic.2019-11-4
13. Asante-Appiah E, Lai J, Wan H, et al. Impact of HIV-1 resistance-associated mutations on susceptibility to Doravirine: analysis of real-world clinical isolates. *Antimicrob Agents Chemother*. 2021;65(12):e0121621. doi:10.1128/AAC.01216-21
14. Taramasso L, Lo Caputo S, Magnasco L, et al. Long-term effectiveness of Rilpivirine-based single-tablet regimens in a seven-year, two-center observational cohort of people living with HIV. *AIDS Res Hum Retroviruses*. 2022 Jun;38(6):472-479. doi:10.1089/AID.2021.0161
15. Rizzardini G, Overton ET, Orkin C, et al. Long-acting injectable cabotegravir + Rilpivirine for HIV maintenance therapy: week 48 pooled analysis of phase 3 ATLAS and FLAIR trials. *J Acquir Immune Defic Syndr*. 2020;85(4):498-506. doi:10.1097/QAI.0000000000002466
16. Nijhuis M, Deeks S, Boucher C. Implications of antiretroviral resistance on viral fitness. *Curr Opin Infect Dis*. 2001;14(1):23-28. doi:10.1097/00001432-200102000-00005
17. Rossetti B, di Giambenedetto S, Torti C, et al. Antiviral response cohort analysis (ARCA) collaborative group. Evolution of transmitted HIV-1 drug resistance and viral subtypes circulation in Italy from 2006 to 2016. *HIV Med*. 2018;19(9):619-628. doi:10.1111/hiv.12640
18. Bracciale L, Colafigli M, Zazzi M, et al. Prevalence of transmitted HIV-1 drug resistance in HIV-1-infected patients in Italy: evolution over 12 years and predictors. *J Antimicrob Chemother*. 2009;64(3):607-615. doi:10.1093/jac/dkp246
19. Bavaro DF, Di Carlo D, Rossetti B, et al. Pretreatment HIV drug resistance and treatment failure in non-Italian HIV-1-infected patients enrolled in ARCA. *Antivir Ther*. 2020;25(2):61-71. doi:10.3851/IMP3349
20. Yebra G, de Mulder M, del Romero J, Rodríguez C, Holguín A. HIV-1 non-B subtypes: high transmitted NNRTI-resistance in Spain and impaired genotypic resistance interpretation due to variability. *Antiviral Res*. 2010;85(2):409-417. doi:10.1016/j.antiviral.2009.11.01

How to cite this article: Rancan I, Cassol C, Graziani L, et al. Trend over time of HIV-1 drug resistance to nonnucleoside reverse transcriptase inhibitors (NNRTIs) and their drivers: A cohort study from Antiviral Response Cohort Analysis (ARCA). *HIV Med*. 2023;24(11):1150-1157. doi:10.1111/hiv.13525