





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 

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

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

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

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

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

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

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

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

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

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

¹¹InformaPRO S.r.l., Rome, Italy

¹²EuResist Network GEIE, Rome, Italy

Correspondence

Ilaria Rancan, Department of Experimental & Clinical Medicine, University of Florence, Florence, Italy.
Email: ranca.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/ μ L increase aOR = 0.95, $p = 0.013$). At

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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 Society-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 [<i>n</i> (%)]									
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 [<i>n</i> (%)]									
Caucasian		4063 (67.9%)		18 355 (64.4%)					
Route of transmission [<i>n</i> (%)]									
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 [<i>n</i> (%)]									
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 [<i>n</i> (%)]									
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 [<i>n</i> (%)]		781 (13.1%)		11 732 (41.2%)					
GSS or cGSS <1 for EFV [<i>n</i> (%)]		642 (10.7%)		11 221 (39.3%)					
GSS or cGSS <1 for ETR [<i>n</i> (%)]		853 (14.3%)		9865 (34.6%)					
GSS or cGSS <1 for RPV [<i>n</i> (%)]		855 (14.3%)		9893 (34.7%)					
GSS or cGSS <1 for DOR [<i>n</i> (%)]		480 (8.0%)		8913 (31.3%)					
Naïve PLWH predictors for TDR									
		Univariate			Multivariate				
		<i>p</i>	OR	95% CI	<i>p</i>	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				
		<i>p</i>	OR	95% CI	<i>p</i>	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				
	<i>p</i>	OR	95% CI	<i>p</i>	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.

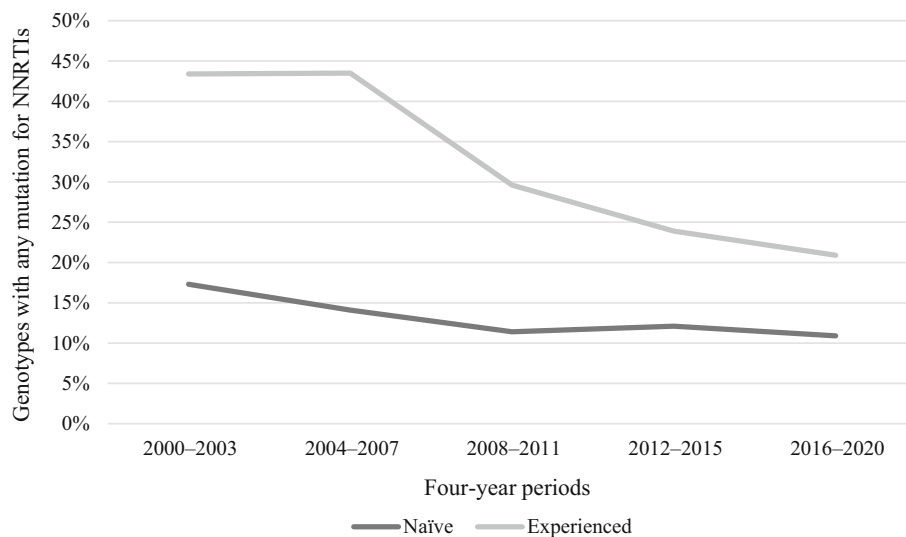


FIGURE 1 Prevalence of nonnucleoside reverse-transcriptase inhibitor (NNRTI) resistance over time.

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/ μ L (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/ μ L 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/ μ L (52–282), and CD4 count at genotype was 349.5 cells/ μ L (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/ μ L 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.

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CONFLICTS OF INTEREST

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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>

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