4-CLASS RESISTANCE IS RARE IN TREATMENT EXPERIENCED PATIENTS ACROSS EUROPE

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Maurizio Zazzi[1], Anne-Mieke Vandamme[2], Barbara Rossetti[3], Massimiliano Fabbiani[3], Francesca Incardona[4,10], Kristof Theys[2], Ana Abecasis[5], Carole Devaux[6], Rolf Kaiser[7], Anders Sönnerborg[8], Giuseppe Pasculli[9], Jurgen Vercauteren[2], for the EuResist Network study group.

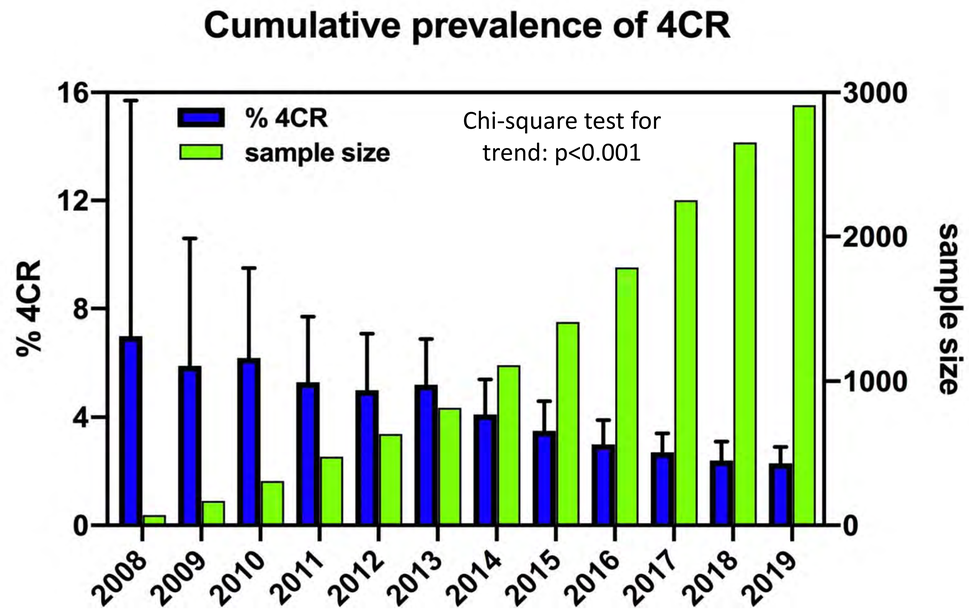
[1]University of Siena, Siena, Italy, [2]Katholieke University Leuven, Leuven, Belgium, [3]Siena University Hospital, Siena, Italy, [4]I-PRO, Roma, Italy, [5]Instituto de Higiene e Medicina Tropical Universidade NOVA de Lisboa, Lisboa, Portugal, [6]Centre Hospitalier de Luxembourg, Luxembourg, Luxembourg, [7]University of Cologne, Cologne, Germany, [8]Karolinska Institute, Stockholm, Sweden, [9]La Sapienza University, Rome, Italy, [10]EuResist Network, Rome, Italy

BACKGROUND

While most HIV-1 patients starting antiretroviral therapy (ART) in recent years achieve and maintain undetectable viral load, patients with a long ART history and failure of multiple therapy lines may have accumulated substantial drug resistance, challenging the possibility for virus control both at individual and population level. However, the prevalence of patients harboring virus with resistance to the four main drug classes (4CR) is largely unknown.

METHODS

From the EuResist database, we selected treated patients with protease, reverse transcriptase and integrase genotype information available at one or more time points in 2008-2019. HIV-1 sequences were interpreted by the Stanford HIVdb 8.8 algorithm. Cumulative resistance scores were generated at each sequencing time point and 4CR was defined as high-level resistance to at least one drug in each of the four classes, considering 3TC, FTC, ABC, TDF and AZT as NRTIs; NVP, EFV, ETR, RPV and DOR as NNRTIs; ATV, DRV, LPV and SQV as boosted PIs; RAL, EVG, DTG and BIC as INSTIs. The frequency of 4CR at each calendar year was estimated as the number of unique patients with 4CR divided by the number of unique patients with at least one sample, up to that year. The factors associated with the development of 4CR were statistically determined by Chi-square tests, Wilcoxon rank sum tests and univariate and multivariate logistic regression in RStudio©.



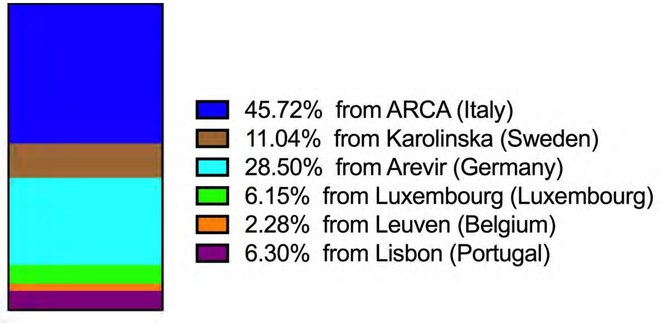
RESULTS

3414 distinct patients matched the inclusion criteria contributing 4594 genotype data from the EuResist database (January 2020 update), with 78.5%, 14.8% and 6.7% of patients contributing genotypic data at one, two and more than two time points. Over time, the 4CR status was reached by 85 (2.5%) patients only. The distribution of data with respect to database source, region of origin of participants and HIV-1 subtype is shown in the graphs below. The cumulative prevalence of 4CR over the last 12 years (2008-2019) indicated a significant decrease over time (p <0.001; see main graph above). The table on the right shows factors univariately or multivariately associated with 4CR.

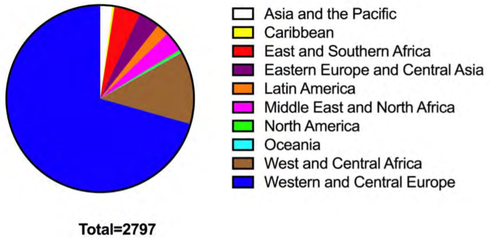
	4CR	Non-4CR	OR (Univariable)	OR (Multivariate)
Age, median (IQR)	49.2 (43.7 to 53.4)	48.0 (40.1 to 54.5)	1.01 (0.99-1.03, p=0.435)	ns
Gender, % male	71.8	66.2	1.30 (0.82-2.13, p=0.284)	ns
Subtype B, %	79.7	65	2.12 (1.25-3.82, p=0.008)	ns
Region of origin, % Europe	87.5	70.2	2.98 (1.55-6.45, p=0.002)	ns
Log zenith VL, mean±SD	12.6 (1.7)	11.4 (2.7)	1.26 (1.13-1.42, p<0.001)	ns
Nadir CD4 cells/mm3, median (IQR)	49 (102)	150 (233)	0.99 (0.99-1.00, p<0.001)	0.99 (0.99-1.00, p=0.005)
Nr of years since HIV diagnosis, mean±SD	27.2 (5.5)	17.6 (9.7)	1.12 (1.09-1.16, p<0.001)	ns
Previous exposure to mono/dual therapy, % yes	69.4	32.1	4.80 (3.05-7.78, p<0.001)	2.23 (0.94-5.58, p=0.075)
Nr of previous therapies, mean±SD	14.9 (9.7)	6.2 (5.4)	1.15 (1.12-1.18, p<0.001)	ns
Number of previous virologic failures (VL>50), mean±SD	4.1 (3.3)	1.3 (1.7)	1.54 (1.43-1.67, p<0.001)	1.29 (1.13-1.47, p<0.001)
Months spent with VL >50 copies/ml, mean±SD	157.3 (79.1)	105.8 (81.2)	1.01 (1.00-1.01, p<0.001)	ns
Calendar year of first treatment, mean±SD	1997.7 (6.6)	2005.8 (7.8)	0.86 (0.83-0.89, p<0.001)	ns

ns = not significant (not retained in final model)

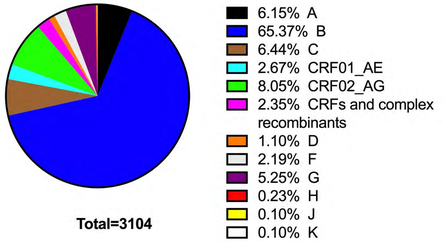
Source of the data: % of total nr of sequences (n=4594)



Region of origin of participants



HIV-1 subtype distribution



CONCLUSION

In a large population of patients across Europe with complete HIV-1 genotype information, the prevalence of 4CR appears to be relatively low and possibly declining over recent years. Significant predictors of 4CR at multivariable analysis included lower nadir CD4 cell counts, a higher number of treatment failures and previous exposure to mono/dual terapy (borderline significance). Continuous surveillance of this challenging population is warranted to provide effective treatment at the individual level and define factors predicting accumulation of resistance over time.

Funding for this study was provided by ViiV Healthcare. The authors are solely responsible for final content and interpretation.