Two-fold increased risk of cardiovascular events in people with multidrug-resistant HIV: data from the PRESTIGIO Registry

T. Clemente[1,2], S. Diotallevi[2], D. Minisci[3], A. Di Biagio[4], R. Lolatto[2], L. Attala[5], G. Cenderello[6], A. Siribelli[1,2], C. Muccini[1,2], S. Lo Caputo[7], M. Tavio[8], R. Papaioannu Borjesson[1,2], A. Giacomelli[9], A. Castagna[1,2], V. Spagnuolo[2]

[1]Vita-Salute San Raffaele University, Milan, Italy; [2]Infectious Diseases, IRCCS San Raffaele Scientific Institute, Milan, Italy; [3]University Department of Infectious and Tropical Diseases, University of Brescia and ASST Spedali Civili, Brescia, Italy; [4]Unit of Infectious Diseases, IRCCS Ospedale Policlinico San Martino, Genoa, Italy; [5]Infectious Diseases Unit, Santa Maria Annunziata Hospital, Bagno a Ripoli, Italy; [6]Infectious Disease Unit, Sanremo Hospital, Sanremo, Italy; [7]Clinic of Infectious Diseases, Department of Clinical and Surgical Sciences, University of Foggia, Foggia, Italy; [8]Infective Diseases, AOU Ospedali Riuniti, Ancona, Italy; [9]III Division of Infectious Diseases, ASST Fatebenefratelli Sacco, Luigi Sacco Hospital, Milan, Italy

P284

Introduction

- Major adverse cardiovascular events (MACEs) may contribute to the high morbidity in people with 4-class drug-resistant HIV (4DR-PWH) [1].
- Aim of this study was to explore the probability of MACEs in 4DR-PWH compared with non-4DR controls.

Study design

- Retrospective, propensity score-matched cohort study on 4DR- (cases) and non-4DR-PWH (controls), on antiretroviral therapy (ART), without previous MACEs.
- Cases were individuals with 4DR HIV from the PRESTIGIO Registry with ≥1 matched control [2].
- Controls were individuals who never developed resistance to >2 drug classes and were matched to cases in a 4:1 ratio for age (±3 years), sex-assigned-at-birth, and ART duration (±3 years).
- An index date [baseline (BL)] was assigned to each case and control: for cases, this was the date of first evidence of 4-class drug resistance; for controls, this was the index date of the corresponding case.

Methods

- The primary outcome was the probability of first MACE (cardiovascular death, myocardial infarction, unstable angina, stroke, transient ischemic attack, peripheral arterial ischemia, or revascularization).
- Poisson regression modelled incidence rates (IRs), 95% confidence intervals (95%CIs), and incidence rate ratios (IRRs); follow-up accrued from BL until last visit (censoring date: 12th April, 2024).
- Kaplan-Meier curves estimated cumulative probabilities of first MACE, compared using log-rank test. Predictors of first MACE assessed by multivariable stepwise Cox model, including fixed (at BL) and time-dependent covariates (with univariable p<0.100). Follow-up accrued from BL until first event or last visit.

Results

- Overall, 223 4DR- and 797 non-4DR-PWH included (Table 1).
- During a median follow-up of 8.2 (interquartile range=5.4-11.1) years [1833 person-years-of-follow-up (PY)], 23/223 (10.3%) 4DR-PWH developed 29 incident MACEs: IR=1.6 (95%CI=1.1-2.3)/100 PY.
- During a median follow-up of 8.4 (5.2-11.0) years (6450 PY), 42/797 (5.3%) non-4DR controls developed 45 incident MACEs: IR=0.7 (95%CI=0.5-0.9)/100 PY; IRR (4DR/non-4DR)=2.3 (95%CI=1.4-3.6); p<0.001.
- Cumulative probabilities of first incident MACE were higher in 4DR- compared to non-4DR-PWH (Figure 1).
- After adjusting for confounders, a higher risk of MACEs was associated with 4DR status (Table 2).

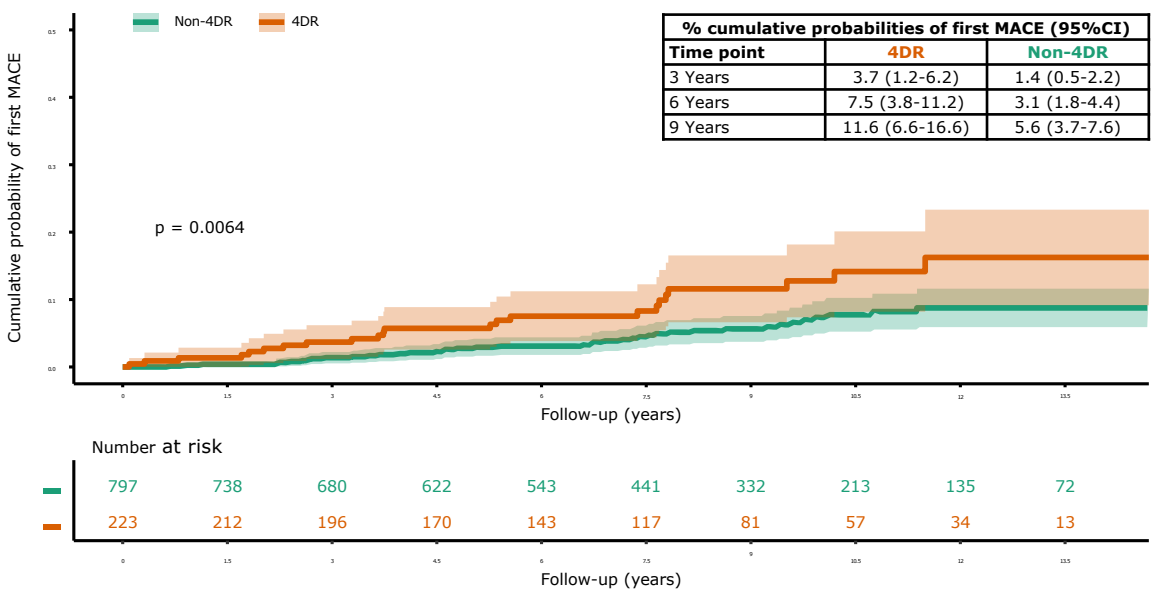
Table 1. Characteristics of 4DR- and non-4DR-PWH included in the analysis.

	Overall (n=1020)	4DR-PWH (n=223)	Non-4DR-PWH (n=797)	p
Age at BL (years)	50.1 (45.4-54.5)	50.0 (44.4-54.9)	50.3 (45.6-54.5)	0.590
Male sex-assigned-at-birth	754 (73.9%)	163 (73.1%)	591 (74.2%)	0.816
ART duration at BL (years)	17.8 (14.5-21.3)	18.2 (14.5-21.2)	17.7 (14.5-21.3)	0.517
BL HIV load (copies/mL)	<20 (<1-85)	1512 (133-19802)	<1 (<1-39)	**<0.001**
BL CD4+/CD8+ ratio	0.64 (0.39-0.97)	0.37 (0.21-0.62)	0.71 (0.46-1.04)	**<0.001**
CD4+ T-cell nadir (cells/mm3)	188 (74-307)	96 (23-187)	216 (102-333)	**<0.001**
Current or former smoking at BL	653 (64.0%)	136 (61.0%)	517 (64.9%)	0.323
BL diabetes mellitus	101 (9.9%)	17 (7.6%)	84 (10.5%)	0.245
BL arterial hypertension	228 (22.4%)	44 (19.7%)	184 (23.1%)	0.331
BL dyslipidaemia	694 (68.0%)	148 (66.4%)	546 (68.5%)	0.600
BL chronic kidney disease	51 (5.0%)	10 (4.5%)	41 (5.1%)	0.816
Positive HCV serostatus at BL	391 (38.3%)	71 (31.8%)	320 (40.2%)	**0.029**
Positive HBsAg at BL	73 (7.2%)	15 (6.7%)	58 (7.3%)	0.871

Table 2. Cox time-dependent multivariable analysis for first MACE

Characteristics	Category	Adjusted HR of first MACE (95%CI)	p
4DR status	Yes vs no	1.8 (1.0-3.3)	**0.039**
Age (time-dependent)	Per 5-year higher	1.2 (1.0-1.4)	0.054
Sex-assigned-at-birth	Male vs female	2.2 (0.9-5.0)	0.070
HIV load (time-dependent)	≥50 vs <50 copies/mL	2.2 (1.2-3.9)	**0.011**
CD4+ nadir	Per 100-cell/mm3 higher	1.0 (0.9-1.1)	0.956
BL smoking habit	Yes vs no	1.7 (1.0-3.0)	0.070
BL diabetes mellitus	Yes vs no	2.1 (1.2-4.0)	**0.015**
BL dyslipidaemia	Yes vs no	2.0 (1.0-3.9)	**0.037**
BL chronic kidney disease	Yes vs no	2.5 (0.8-7.8)	0.101
BL HCV serostatus	Positive vs negative	1.8 (1.1-3.1)	**0.030**

Figure 1. Kaplan-Meier curves for probabilities of the first MACE in 4DR- (orange line) and non-4DR-PWH (green line).



% cumulative probabilities of first MACE (95%CI)		
Time point	4DR	Non-4DR
3 Years	3.7 (1.2-6.2)	1.4 (0.5-2.2)
6 Years	7.5 (3.8-11.2)	3.1 (1.8-4.4)
9 Years	11.6 (6.6-16.6)	5.6 (3.7-7.6)

Conclusions

- In PWH, multidrug resistance is significantly associated with a higher incidence and risk of cardiovascular events.
- Prompt implementation of prevention strategies is mandatory in this fragile population.

Contact Information
Tommaso Clemente, MD
Vita-Salute San Raffaele University, Milan, Italy
Infectious Diseases, IRCCS San Raffaele Scientific Institute, Milan, Italy
phone: +39 0226437907; e-mail: clemente.tommaso@hsr.it

Acknowledgements

PRESTIGIO STUDY GROUP STEERING COMMITTEE: Antonella Castagna (Coordinator), Vincenzo Spagnuolo (Operative Coordinator), Daniele Armenia, Stefano Bonora, Leonardo Calza, Anna Maria Cattelan, Giovanni Cenderello, Adriana Cervo, Laura Comi, Antonio Di Biagio, Emanuele Focà, Roberta Gagliardini, Andrea Giacomelli, Filippo Lagi, Giulia Marchetti, Stefano Rusconi, Francesco Saladini, Maria Santoro, Maurizio Zazzi. VIROLOGY TEAM AND BIOLOGICAL BANK: Maurizio Zazzi, Maria Santoro, Francesco Saladini, Daniele Armenia, Andrea Galli; BioRepSRL. STUDY COORDINATORS: Elisabetta Carini, Sabrina Bagaglio, Girolamo Piromalli. STATISTICAL AND MONITORING TEAM: Riccardo Lolatto. ENROLLING CENTERS: ANCONA: Marcello Tavio, Alessandra Mataloni Paggi; AVIANO: Ornella Schioppa, Valentina Da Ros; BARI: Annalisa Saracino, Flavia Balena; BERGAMO: Laura Comi, Daniela Valenti, Claudia Suardi; BOLOGNA: Pierluigi Viale, Leonardo Calza, Federica Malerba, Silvia Cretella, Riccardo Riccardi; BRESCIA: Francesco Castelli, Emanuele Focà, Davide Minisci, Francesca Pennati; BUSTO ARSIZIO: Barbara Menzaghi, Maddalena Farinazzo; CATANIA: Bruno Cacopardo, Maurizio Celesia, Michele Salvatore Paternò Raddusa, Carmen Giarratana; CATANZARO: Paolo Fusco, Vincenzo Olivadese; CREMONA: Angelo Pan, Chiara Fornabaio, Paola Brambilla; FIRENZE: Alessandro Bartoloni, Filippo Lagi, Paola Corsi, SebleTekle Kiros, Filippo Ducci, Susanna Giachè, Cecilia Costa, Alessio Bellucci, Elisa Mirabelli; FOGGIA: Teresa Santantonio, Sergio Lo Caputo, Sergio Ferrara, Arianna Narducci; GENOVA: Emanuele Pontali, Marcello Feasi, Antonio Sarà, Matteo Bassetti, Antonio Di Biagio, Sabrina Bianchi; MILANO: Antonella Castagna, Vincenzo Spagnuolo, Camilla Muccini, Elisabetta Carini, Sabrina Bagaglio, Riccardo Lolatto, Andrea Galli, Rebecka Papaioannu, Tommaso Clemente, Girolamo Piromalli, Spinello Antinori, Andrea Giacomelli, Tiziana Formenti, Fabiola Schiavo, Giulia Marchetti, Lidia Gazzola, Fabiana Trionfo Fineo, Massimo Puoti, Cristina Moioli, Federico D'Amico; MODENA: Cristina Mussini, Adriana Cervo; NAPOLI: Elio Manzillo, Amedeo Lanzardo; PADOVA: Anna Maria Cattelan, Maria Mazzitelli; PALERMO: Antonio Cascio, Marcello Trizzino; PARMA: Elisa Fronti, Diletta Laccabue, Federica Carli; PAVIA: Roberto Gulminetti, Layla Pagnucco, Mattia Demitri; PERUGIA: Daniela Francisci, Giuseppe De Socio, Elisabetta Schiaroli; REGGIO EMILIA: Elisa Garlassi, Romina Corsini; ROMA: Roberta Gagliardini, Marisa Fusto, Loredana Sarmati, Vincenzo Malagnino, Tiziana Mulas, Mirko Compagno Carlo Torti, Simona Di Giambenedetto, Silvia Lamonica, Pierluigi Francesco Salvo; SANREMO: Giovanni Cenderello, Rachele Pincino; SIENA: Mario Tumbarello, Massimiliano Fabbiani, Francesca Panza, Ilaria Rancan; TORINO: Giovanni Di Perri, Stefano Bonora, Micol Ferrara, Andrea Calcagno, Silvia Fantino; VERONA: Stefano Nardi, Marta Fiscon. SUPPORTED BY: ViiV Healthcare, Gilead Sciences, MSD, Janssen-Cilag

References

1. Galli L, et al. **Burden of Disease in PWH Harboring a Multidrug-Resistant Virus: Data From the PRESTIGIO Registry.** Open Forum Infect Dis, 2020.
2. Clemente T, et al. **Cohort profile: PRESTIGIO, an Italian prospective registry-based cohort of people with HIV-1 resistant to reverse transcriptase, protease and integrase inhibitors.** BMJ Open, 2024.