EFFECT OF PAST VIROLOGICAL FAILURE ON DOLUTEGRAVIR + LAMIVUDINE AS MAINTENANCE REGIMEN

0486

Roberta Gagliardini[1], Patrizia Lorenzini [1], Alessandro Cozzi-Lepri [2], Alessandro Tavelli[3], Vanni Borghi [4], Laura Galli [5], Gianmarco Tagliaferri[6], Franco Maggiolo[7], Cristina Mussini[4], Antonella Castagna[5], Antonella D'Arminio Monforte[6], Andrea Antinori[1], for the Icona Foundation Study Group

1 IRCCS Lazzaro Spallanzani, Rome, Italy; 2 University College London, London, UK; 3 Icona Foundation, Milan, Italy; 4 Azienda Ospedaliera Universitaria Policlinico di Modena, Modena, Italy; 5 IRCCS San Raffaele Scientific Institute, University Vita-Salute San Raffaele, Milan, Italy; 6 ASST Santi Paolo e Carlo, University of Milan, Milan, Italy; 7 ASST Papa Giovanni XXIII, Bergamo, Italy

CROI 2020 Boston, March 8–11, 2020

BACKGROUND

- 2DR with DTG+3TC resulted effective as maintenance therapy in RCT (Tango, Aspire), in pts with no prior VF and no documented NRTI or INSTI resistance
- The high virological efficacy of DTG+3TC has been extensively showed also in unselected real-life cohorts[1]
- Real-life data showed also that up to 40% of all 2DR prescriptions are in pts with prior VF, 14% of DTG+3TC [2]
- Few data about the use of DTG+3TC in the context of previous VF are available:
  - o Dolulam study: pilot study, 27 HTE pts with tolerability issues, 67% of pts at least 1 RAM, 52% at least resistant to one drug [3]
  - o ART-PRO pilot study: 21 pts with historical resistance to 3TC, no VF at 48w[4]

AIMS

- Compare virological efficacy of 2DR DTG+3TC in patients with and without prior VF
- Analyze the impact of previous VF on virological efficacy of 2DR DTG+3TC

METHODS

Study population:
- PLWH >18 years old
- Enrolled in Icona Foundation Study cohort or in 5 Italian monocentric Cohorts (L.Spallanzani, Rome; Modena Hospital; San Raffaele Institute, Milan; San Paolo Hospital, Milan; Papa Giovanni XXIII Hospital, Bergamo)
- Starting DTG+3TC with HIV-RNA < 50 cp/mL from any ART

Endpoints:
- Viral rebound (VR, confirmed HIV-RNA ≥ 50 c/mL)
- Viral blip (VB, HIV-RNA ≥ 50 c/mL not confirmed by the following measurement)

Definitions:
- Previous VF (Def 1): single HIV-RNA ≥ 1000 c/mL or confirmed HIV-RNA ≥ 50 c/mL on any ART
- Previous VF (Def 2): single HIV-RNA ≥ 1000 c/mL or confirmed HIV-RNA ≥ 50 c/mL on a NRTI or INSTI-containing regimen and VR as confirmed HIV-RNA ≥ 50 c/mL or a single HIV-RNA ≥ 50 c/ml followed by change of ART

Statistical analysis:
- Standard survival analysis (Kaplan-Meier curves and Log-rank)
- Weighted Cox regression model to estimate causal HR of VR and VB, after controlling for confounding variables

Sensitivity analysis: excluding pts with incomplete history of viral load data (>1 year gap in measurements)

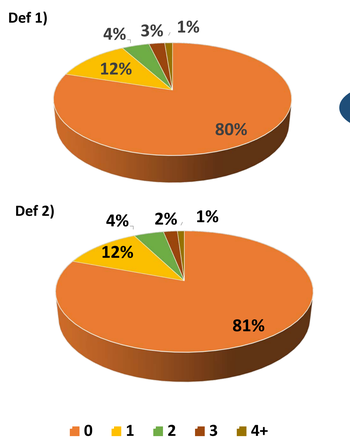
RESULTS

A total of 966 patients were included in this study. Median observation time was 15 months (IQR 6-32).

Table 1 – Patients baseline characteristics

	Overall population N=966	No previous VF N=772	≥1 previous VF N=194	p-value
Female gender, n(%)	248 (25.7%)	189 (24.5%)	59 (30.4%)	0.091
Age, median (IQR)	51 (44-57)	50 (42-57)	53 (49- 58)	<0.001
Mode of HIV transmission, n(%)				<0.001
heterosexual	340 (35.2%)	274 (35.5%)	66 (34.0%)	
IVDU	146 (15.1%)	94 (12.2%)	52 (26.8%)	
MSM	356 (36.9%)	307 (39.8%)	49 (25.3%)	
Other/unknown	124 (12.8%)	97 (12.6%)	27 (13.9%)	
CDC stage C, n(%)	150 (15.5%)	107 (13.9%)	43 (22.2%)	0.017
HCV Ab, n(%)				<0.001
negative	753 (78.0%)	623 (80.7%)	130 (67.0%)	
positive	172 (17.8%)	111 (14.4%)	61 (31.4%)	
missing	41 (4.2%)	38 (4.9%)	3 (1.6%)	
HBsAg, n(%)				0.008
negative	834 (87.7%)	653 (86.3%)	181 (93.3%)	
positive	15 (1.6%)	11 (1.4%)	4 (2.1%)	
missing	102 (10.7%)	93 (12.3%)	9 (4.6%)	
Nadir CD4, cell/mmc, median (IQR)	247 (98-372)	268 (126-400)	165 (44-270)	<0.001
CD4 at switch, cell/mmc, median (IQR)	699 (541-888)	695 (545-898)	714 (525-864)	0.870
Years of HIV Infection, median (IQR)	12 (6-21)	9 (5-17)	22 (19-27)	<0.001
Years of ART, median (IQR)	8.4 (4.0-17.5)	6.6 (3.3-12.1)	18.9 (16.5-20.7)	<0.001
Years of viral suppression, median (IQR)	7.0 (3.4-12.0)	5.9 (2.9-10.6)	12.0 (8.4-14.3)	<0.001

Number of previous VF according to definition

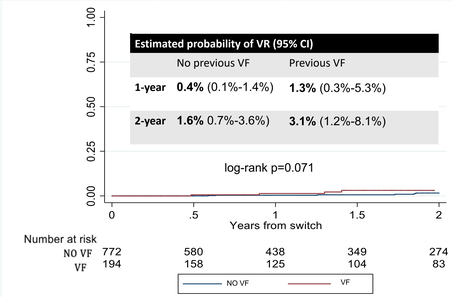


Virological Rebound by previous VF definition

Def 1

Virological rebound: **11** events over 1555 PYFU
IR=0.7 x 100 PYFU (95% CI 0.4-1.3)
- ➢0.5 x 100 PYFU (95% CI 0.2-1.1) in pts w/o previous VF
- ➢1.4 x 100 PYFU (95% CI 0.6-3.4) in pts w/ ≥ 1 previous VF

Estimated probability of VR according to the presence of previous VF

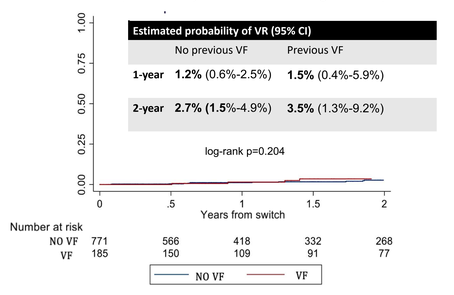


At sensitivity analysis
Virological rebound: 8 over 1051 PYFU.
IR=0.7 x 100 PYFU (95% CI 0.4-1.5)
- 0.6 x 100 PYFU (0.2-1.4) in pts w/o previous VF
- 1.6 x 100 PYFU (0.6-4.8) in pts w/ ≥ 1 previous VF

Def 2

Virological rebound: **18** events over 1505 PYFU
IR=1.2 x 100 PYFU (95% CI 0.7-1.9)
- ➢1.0 x 100 PYFU (95% CI 0.6-1.8) in pts w/o previous VF
- ➢1.9 x 100 PYFU (95% CI 0.8-4.2) in pts w/ ≥ 1 previous VF

Estimated probability of VR according to the presence of previous VF



At sensitivity analysis
Virological rebound: 12 over 1018 PYFU.
IR=1.2 x 100 PYFU (95% CI 0.7-2.1)
- 1.1 x 100 PYFU (0.5-2-0) in pts w/o previous VF
- 1.8 x 100 PYFU (0.6-5.5) in pts w/ ≥ 1 previous VF

Risk of Virological Rebound by VF definition

Viral Rebound [Def 1]	HR 95%CI	p-value	AHR 95%CI	p-value	AHR 95% CI (sensitivity analysis)	p-value
Previous VF 1 vs 0	2.81 (0.70-11.25)	0.144	2.87 (0.65-12.74)	0.166	3.71 (0.53-25.75)	0.185
Previous VF ≥ 1 vs 0	2.88 (0.74-11.13)	0.125	3.39 (0.77-14.90)	0.106	5.39 (0.99-29.30)	0.051

Viral Rebound [Def 2]	HR 95%CI	p-value	AHR 95%CI	p-value	AHR 95% CI (sensitivity analysis)	p-value
Previous VF 1 vs 0	2.62 (0.93-7.42)	0.069	2.37 (0.75-7.51)	0.142	2.69 (0.53-13.60)	0.231
Previous VF ≥1 vs 0	1.88 (0.71-4.99)	0.204	2.36 (0.73-7.63)	0.152	4.32 (1.00-18.53)	0.049

Crude and adjusted hazard ratios (95%CI) of the risk of VR from fitting a weighted Cox regression model according to presence and number of previous virological failures and by standard and modified definitions [Def 2]. Sensitivity analysis excluded pts with uncomplete data about past viral loads. AHR are adjusted for nadir CD4 (</>350 cell/mmc) and total time of virological suppression.

Virological Blips

IR=4.3 x 100 PYFU (95%CI 3.5-5.5)
- ➢4.0 x 100 PYFU (95% CI 3.0-5.2) in pts w/o previous VF
- ➢5.7 x 100 PYFU (95% CI 2.7-10.3) in pts w/ ≥ 1 previous VF

Estimated probability of viral blips at 1 year: log-rank p=0.124
- No previous VF: 2.7% (95% CI 1.7%-4.4%)
- Previous VF: 3.8% (95% CI 1.7%-8.3%)

CONCLUSIONS

Limitations
- ✓Short follow-up
- ✓Few number of events
- ✓Lack of information on resistance

Conclusions
- ✓In real-life, DTG+3TC is prescribed also in patients with **history of previous VF** (~**20%** of cases)
- ✓The **risk** of **viral rebound** and viral blip is **increased** in pts with previous VF, especially in those with ≥ 1 VF in comparison to those without previous VF
- ✓1-year **probability** of **VR** was **very low** throughout all the analyses and comparable to the one found in a recent meta-analysis of DTG-based 2DR[1]
- ✓DTG+3TC should be cautiously used in pts with current viral suppression but a history of VF
- ✓Further studies are necessary to evaluate how historical/archived genotypic resistance could help to discriminate patients at higher risk of virological failure

REFERENCES

1- Wandeler G, F1000Res, 2018; 2- Allavena C, P0493, CROI 2019; 3- Charpentier C, JAC 2017; 5-De Miguel Buckley R, EACS 2019

FUNDING

ICONA Foundation is supported by unrestricted grants from Gilead Sciences, Janssen, MSD and ViiV Healthcare

ACKNOWLEDGMENTS

Icona Fundation Study Group
BOARD OF DIRECTORS: A d'Arminio Monforte (President), A Antinori (Vice-President), M Andreoni, A Castagna, F Castelli, R Cauda, G Di Perri, M Galli, R Iardino, G Ippolito, A Lazzarin, GC Marchetti, G Rezza, F von Schloesser, P Viale.
SCIENTIFIC SECRETARY: A d'Arminio Monforte, A Antinori, A Castagna, F Ceccherini-Silberstein, A Cozzi-Lepri, E Girardi, A Gori, S Lo Caputo, F Maggiolo, C Mussini, M Puoti, CF Perno. **STEERING COMMITTEE:** A Antinori, F Bai, A Bandera, S Bonora, M Borderi, A Calcagno, MR Capobianchi, A Castagna, F Ceccherini-Silberstein, S Cicalini, A Cingolani, P Cinque, A Cozzi-Lepri, A d'Arminio Monforte, A Di Biagio, R Gagliardini, E Girardi, N Gianotti, A Gori, G Guaraldi, G Lapadula, M Lichtner, A Lai, S Lo Caputo, G Madeddu, F Maggiolo, G Marchetti, E Merlini, C Mussini, S Nozza, CF Perno, S Piconi, C Pinnetti, M Puoti, E Quiros Roldan, R Rossotti, S Rusconi, MM Santoro, A Saracino, L Sarmati, V Spagnuolo, V Svicher, L Taramasso.
STATISTICAL AND MONITORING TEAM: A Cozzi-Lepri, I Fanti, L Galli, P Lorenzini, A Rodano', M Macchia, A Tavelli.
COMMUNITY ADVISORY BOARD: A Bove, A Camposeragna, M Errico, M Manfredini, A Perziano, V Calvino.**BIOLOGICAL BANK INMI:** F Carletti, S Carrara, A Di Caro, S Graziano, F Petroni, G Prota, S Truffa. **PARTICIPATING PHYSICIANS AND CENTERS:** Italy A Giacometti, A Costantini, V Barocci (Ancona); G Angarano, L Monno, E Milano (Bari); F Maggiolo, C Suardi (Bergamo); P Viale, V Donati, G Verucchi (Bologna); F Castelnuovo, C Minardi, E Quiros Roldan (Brescia); B Menzaghi, C Abeli (Busto Arsizio); L Chessa, F Pes (Cagliarti); B Cacopardo, B Celesia (Catania); J Vecchiet, K Falasca (Chieti); A Pan, S Lorenzotti (Cremona); L Sighinolfi, D Segala (Ferrara); P Blanc, F Vichi (Firenze); G Cassola, M Bassetti, A Alessandrini, N Bobbio, G Mazzarello (Genova); M Lichtner, L Fondaco, (Latina); P Bonfanti, C Molteni (Lecco); A Chiodera, P Milini (Macerata); G Nunnari, G Pellicanò (Messina); A d'Arminio Monforte, M Galli, A Lazzarin, G Rizzardini, M Puoti, A Castagna, ES Cannizzo, MC Moioli, R Piolini, D Bernacchia, A Poli, C Tincati, (Milano); C Mussini, C Puzzolante (Modena); C Migliorino, G Lapadula (Monza); V Sangiovanni, G Borgia, V Esposito, G Di Flumeri, I Gentile, V Rizzo (Napoli); AM Cattelan, S Marinello (Padova); A Cascio, M Trizzino (Palermo); D Francisci, E Schiaroli (Perugia); G Parruti, F Sozio (Pescara); C Lazzaretti, R Corsini (Reggio Emilia); M Andreoni, A Antinori, R Cauda, A Cristaudo, V Vullo, R Acinapura, S Lamonica, M Capozzi, A Mondi, A Cingolani, M Rivano Capparuccia, G Iaiani, A Latini, G Onnelli, MM Plazzi, G De Girolamo, A Vergori (Roma); M Cecchetto, F Viviani (Rovigo); G Madeddu, A De Vito(Sassari); B Rossetti, F Montagnani (Siena); A Franco, R Fontana Del Vecchio (Siracusa); C Di Giuli (Terni); P Caramello, G Di Perri, S Bonora, GC Orofino, M Sciandra (Torino); A Londero (Udine); V Manfrin, G Battagin (Vicenza); G Starnini, A Ialungo (Viterbo).

AUTHOR CONTACT INFORMATION

Roberta Gagliardini, MD, Lazzaro Spallanzani National Institute for Infectious Diseases IRCCS, Rome, Italy, roberta.gagliardini@inmi.it