

Fondazione Icona

Evaluation Of HIV Transmission Clusters Among Natives And Foreigners Living In Italy

Maria Mercedes Santoro¹, Lavinia Fabeni², Patrizia Lorenzini², Stefano Rusconi³, Nicola Gianotti⁴, Andrea Costantini⁵, Loredana Sarmati⁶, Andrea Antinori², Francesca Ceccherini-Silberstein¹, Antonella d'Arminio Monforte⁷, Annalisa Saracino⁸, Enrico Girardi², on behalf of the Icona Foundation Study Cohort

¹University of Rome «Tor Vergata», Rome, Italy, ²National Institute for Infectious Diseases «Lazzaro Spallanzani» - IRCCS, Rome, Italy, ³Luigi Sacco University Hospital, Milan, Italy, ¹University Hospital, Milan, Italy, ¹University, Hospital, Milan, ¹University, Hospital, Milan, Italy, ¹University, Hospital, Milan, Italy, ¹University, Hospital, Milan, Hospital, Milan, ¹University, Hospital, Milan, ¹University, ¹Uni ⁴San Raffaele Scientific Institute, Milan, Italy, ⁵Marche Polytechnic University, Ancona, Italy, ⁷University of Bari, Bari, Italy, ⁷University of Bari, Bari, Italy, ⁷University of Bari, Bari, Italy, ⁸University of Bari, Bari, Italy, ⁸University of Bari, Bari, Italy, ⁹University of Bari, Bari, Italy, ⁹University of Bari, Bari, Italy, ⁹University of Bari, Bari, Italy, ⁴San Raffaele Scientific Institute, Milan, Italy, ⁹University of Bari, Bari, Italy, ⁹University, Ancona, Italy, ⁹University, Ancon, ⁹University, Ancon, ⁹University, Ancon, ⁹University, Ancon, ⁹Universi

BACKGROUND

Migration is today a new global phenomenon, with a total of 272 million of international migrants, according to the UNDESA (United Nations Department of Economic and Social Affairs) data of the year 2019 (1).

Among the HIV-1 diagnosed individuals in the EU/EEA in 2018, 42% were migrants, defined as originating from outside of the country in which they were diagnosed (2). In Italy, migrants accounted for nearly 30% of all newly diagnosis of HIV infection in the last years (2).

Phylogenetic analysis has been used successfully to identify and dissect HIV-1 transmission clusters (TCs). When combined with epidemiological and clinical data, the results of such analysis can be of public health relevance, for example by identifying how virus lineages are restricted to, or mix among, different demographic and behavioural subgroups (3,4).

Aim of this study was to evaluate the characteristics of HIV-1 molecular transmission clusters (MTCs) among natives and foreign individuals diagnosed between 1998 and 2018 enrolled in the ICONA cohort.

METHODS

- Phylogenetic analyses were performed on HIV-1 pol sequences to characterise subtypes (Neighbor Joining method, 1000 replicates) and identify MTCs, divided into small (SMTCs, 2-3 sequences), medium (MMTCs, 4–9 sequences) and large (LMTCs, ≥ 10 sequences).
- MTCs were first deduced by the HIV-TRACE tool (5) (genetic distance ≤0.01). Pairwise genetic distances were obtained by MEGA 6 under the Tamura-Nei 93 (TN93) nucleotide substitution model.
- The robustness of MTCs was further tested using the Maximum Likelihood method, using MEGA6 software.
- Factors associated with MTCs were evaluated using logistic regression analysis.

REFERENCES

1- https://publications.iom.int/books/world-migration-report-2020

https://www.ecdc.europa.eu/en/publications-data/hivaids-surveillance-europe-2019-2018-data

4- Brenner B, et al., phylogenetic inferences on HIV-1 transmission: implications for the design of prevention and treatment interventions. AIDS 2013; 27:1045–1057. 5- http://hivtrace.datamonkey.org/hivtrace

<=200

RESULTS

Among 3,499 drug-naïve participants in the ICONA cohort (2,804 natives; 695 migrants), 726 (20.8%; 644 natives, 82 migrants) were involved in 228 Molecular Transmission Clusters (MTCs).

Table 1. Patient's characteristics and factors associated with HIV-1 molecular transmission clusters.

ables	Overall	Out of cluster	In cluster	P-value ^a	Adjusted model ^b		
	N=3499	2773 (79.3%)	726 (20.7%)	r-value	OR	(95% CI)	P-value
e gender, n (%)	2872 (82.1%)	2187 (78.9%)	685 (94.3%)	<0.001	-	-	-
years, median (IQR)	37 (30-45)	38 (31-46)	32 (27-40)	< 0.001	0,65	0.59-0.72	<0.001
e of HIV transmission							
erosexual	553 (15.8%)	513 (18.5%)	40 (5.5%)	<0.001	1,00	-	-
U	32 (0.9%)	31 (1.1%)	1 (0.1%)		0,49	0.06-3.80	0,497
eterosexual	713 (20.4%)	628 (22.7%)	85 (11.7%)		1,82	1.19-2.78	0,006
DU	161 (4.6%)	145 (5.2%)	16 (2.2%)		1,52	0.80-2.90	0,204
SM	1789 (51.1%)	1247 (45.0%)	542 (74.7%)		3,46	2.39-5.03	<0.001
er/unknown	251 (7.2%)	209 (7.5%)	42 (5.8%)		2,73	1.66-4.48	<0.001
on of birth, n (%)							
	2804 (80.1%)	2160 (77.8%)	644 (88.7%)	< 0.001	1,00	-	-
а	219 (6.3%)	212 (7.7%)	7 (0.9%)		0,18	0.08-0.39	<0.001
ral and South America	241 (6.9%)	201 (7.3%)	40 (5.5%)		0,49	0.33-0.71	0,001
ре	187 (5.3%)	159 (5.7%)	28 (3.9%)		, 0,29	0.08-0.97	0,045
	38 (1.1%)	35 (1.3%)	3 (0.4%)		, 0,62	0.40-0.97	<i>0,</i> 035
r	10 (0.3%)	6 (0.2%)	4 (0.6%)			0.62-10.97	, 0,189
cation, n (%)	. ,	- /	. ,		-		·
ary school	169 (4.8%)	158 (5.7%)	11 (1.5%)	<0.001	0,87	0.45-1.71	0,691
ndary school	585 (16.7%)	505 (18.2%)	80 (11.0%)		0,91	0.68-1.21	0,518
ege/University	1762 (50.4%)	1329 (47.9%)	433 (59.6%)		1,00	-	, -
nown	983 (28.1%)	781 (28.2%)	202 (27.8%)		1,03	0.83-1.28	0,773
loyment, n (%)	· · · · · · /	· · · · /	· /		,		,
loyed	1476 (42.2%)	1148 (41.4%)	328 (45.2%)	<0.001	1,00	_	-
nployed	461 (13.2%)	389 (14.0%)	72 (9.9%)		0,91	0.67-1.25	0,565
employed	526 (15.0%)	413 (14.9%)	113 (15.6)		0,97	0.75-1.26	0,840
ent	146 (4.2%)	93 (3.4%)	53 (7.3%)		0,83	0.56-1.24	0,360
sewife	94 (2.7%)	88 (3.2%)	6 (0.8%)		1,18	0.47-2.94	0,723
r	278 (7.9%)	244 (8.8%)	34 (4.7%)		0,69	0.46-1.05	0,083
iown	518 (14.8%)	398 (14.3%)	120 (16.5%)		0,99	0.75-1.30	0,929
RNA, copies/mL	010 (1		(,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,		0,00		0)0 =0
0	122 (3.5%)	99 (3.6%)	23 (3.2%)	0,005	0,66	0.39-1.12	0,127
0/10.000	559 (16.0%)	445 (16.1%)	114 (15.7%)	0,000	0,81	0.61-1.08	0,127
00/100.000	1470 (42.0%)	1126 (40.6%)	344 (47.4%)		0,94	0.75-1.17	0,562
0.000	1118 (32.0%)	905 (32.6%)	213 (29.3%)		1,00	-	0,302
onwn	230 (6.6%)	198 (7.1%)	32 (4.4%)		0,76	0.38-1.55	0,451
cells/mm ³ , n (%)			<u> </u>		5,70	5.55 I.JJ	ਹ)ਜਹ⊥
	701 (22 60/)	771 (76 00/)	70 (0 60/)	<u>~0 001</u>	1 00		
10 500	791 (22.6%) 1485 (42.4%)	721 (26.0%)	70 (9.6%) 320 (44 1%)	<0.001	1,00 2 2 2 2	-	- -0 001
500	1485 (42.4%)	1165 (42.0%)	320 (44.1%)		2,22	1.64-2.99	<0.001
	1003 (28.7%)	703 (25.4%)	300 (41.3%)		3,01	2.20-4.13	< 0.001
nown	220 (6.3%)	184 (6.6%)	36 (5.0%)	<u>~0 001</u>	1,90	0.93-3.90	0,078
of diagnosis, median (IQR)	2011 (2008-2014)	2011 (2007-2014) 2012 (2009-2014)	<0.001	1,09	1.06-1.11	<0.001
уре	104 (2.00/)		10 (2 00/)	<u>~0 001</u>			
	104 (3.0%)	85 (3.1%)	19 (2.6%)	<0.001	-	-	-
	2556 (73.1%)	2038 (73.5%)	518 (71.4%)		-	-	-
	148 (4.2%)	119 (4.3%)	29 (4.0%)		-	-	-
02_AG	187 (5.3%)	141 (5.1%)	46 (6.3%)		-	-	-
60_BC	64 (1.8%)	12 (0.4%)	52 (7.2%)		-	-	-
	179 (5.1%)	157 (5.7%)	22 (3.0%)		-	-	-
er	261 (7.5%)	221 (8.0%)	40(5.5%)		-	-	-

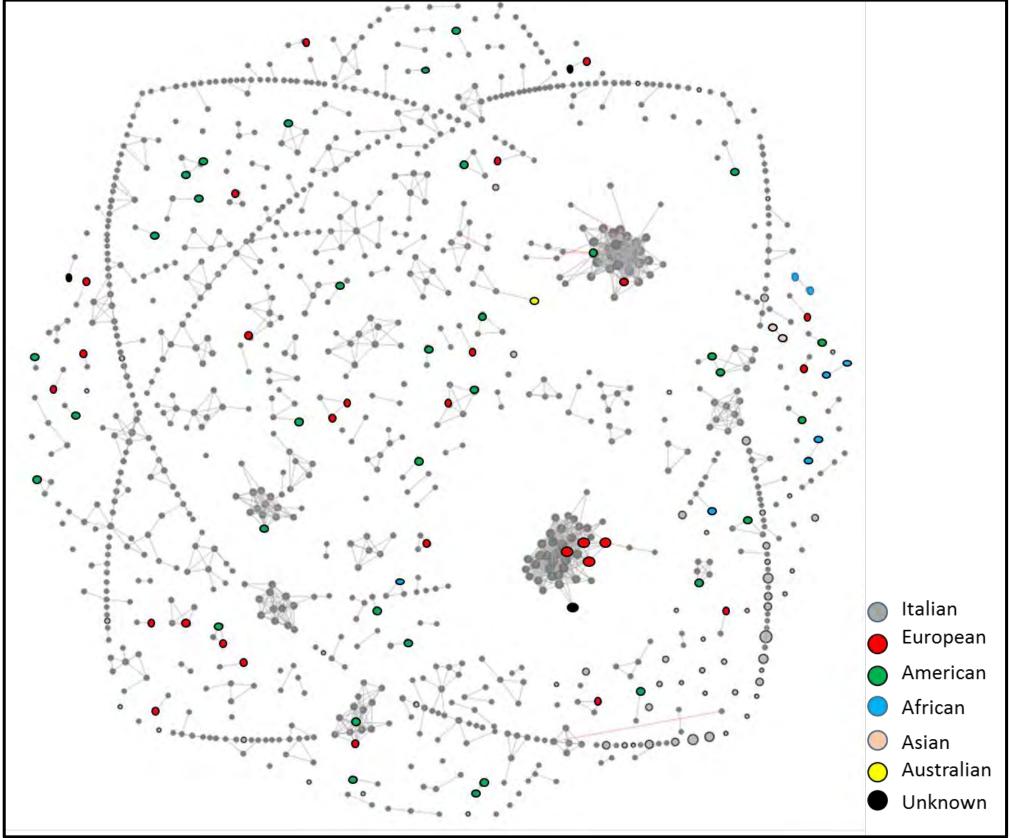
^aBy Mann-Whitney test (for quantitative variables) and x2 test or Fisher's exact test (for categorical variables), as appropriate. ^bAdjusted for: Sex, age, mode of HIV transmission, nation of birth, education, employment, plasma HIV-RNA, CD4 cell count, year of diagnosis Variables that were significant in univariable analysis (p<0.05) were considered for the multiviriable model. P values <0.05 were considered statistically significant and were reported in bold. Acronyms: F, female; IVDU, intravenous drug user; M, male; MSM, men who have sex with men.

•Subjects involved in MTCs were more frequently native, male and MSM, younger, more recently diagnosed, and with higher CD4 count compared to subjects out of MTCs (median [IQR]: cells/mm3: 459 [322–624] vs 353 [177–523], p<0.001) (Table 1).

 Logistic regression confirmed that Italian origin, being MSM, younger age, more recent diagnosis and higher CD4 count were significantly associated with MTCs (Table 1).

•HIV-1 non-B subtype was found in 51 MTCs (22.4%); of note, non-B infections involved in MTCs were more commonly found in natives (N=47, 92.2%) than in foreigners (N=4, 7.8%).

HIV-1 newly diagnosed subjects are involved in Among the **228 MTCs** identified, 6 were Large MTCs (N=140 subjects), 36 were Medium MTCs (N=184) and 186 were several MTCs in the past two decades in Italy. **Small MTCs** (N=402). Clustered transmission, especially for large clusters, is prevalently driven by natives, mainly Figure 1. Clusters' population by HIV-TRACE. MSM and frequently infected with HIV-1 non-B subtype.





The colored balls identify the nationality of the 3,499 individuals involved in the study.

Migrants contributed for 14.4% to SMTCs, 7.6% to MMTCs and 7.1% to LMTCs, respectively. The presence of both natives and migrants was found in 66.7% (n=4) of LMTCs, 33.3% (n=12) of MMTCs and 23.1% (n=43) of SMTCs. Only six pairs included exclusively migrants. Whereas, 163/288 (56.6%) MTCs included exclusively natives: 137 SMTCs, 24 MMTCs and 2 LMTCs.

Table 2. Characteristics of the medium/large molecular transmission clusters stratified according to subtypes/CRFs

		Cluster Size ^a	Sampling Interval	Migrants⁵	Cs (4-9 sequence Nationality	Age, years	Risk Factor	Genetic distar
ID	Subtype	n	Year	n (%)	n	Median (IQR)	n	Mean (SE)
1	В	4	2006-2007	0 (0.0)	-	46 (44-46)	4 MSM	0.008 (0.002
2	В	4	2007-2012	0 (0.0)	-	46 (42-50)	3 Het, 1 Unk	0.010 (0.002
3	В	4	2008-2014	0 (0.0)	-	52 (50-53)	4 MSM	0.008 (0.002
4	В	4	2008-2016	0 (0.0)	-	39 (37-41)	3 MSM, 1 Unk	0.006 (0.002
5	В	4	2009-2012	0 (0.0)	-	54 (51-56)	3 MSM, 1 Het	0.009 (0.002
6	В	4	2009-2016	0 (0.0)	-	36 (33-41)	3 MSM, 1 Unk	0.009 (0.002
7	В	4	2010-2011	1 (25.0)	1 NA	50 (46-52)	4 MSM	0.004 (0.002
8	В	4	2011-2013	0 (0.0)	-	37 (35-38)	4 MSM	0.008 (0.002
9	В	4	2011-2017	0 (0.0)	-	53 (48-56)	4 MSM	0.007 (0.002
10	В	4	2013-2014	0 (0.0)	-	41 (34-48)	4 MSM	0.006 (0.002
11	В	4	2013-2018	1 (25.0)	1 EE	41 (37-43)	3 MSM, 1 Het	0.008 (0.002
12	В	4	2016	0 (0.0)	_	38 (28-49)	4 MSM	0.004 (0.001
13	В	5	2007-2012	1 (20.0)	1 NA	38 (37-45)	5 MSM	0.006 (0.001
14	В	5	2008-2014	0 (0.0)		36 (36-37)	5 MSM	0.011 (0.002
15	В	5	2010-2012	2 (40.0)	1 CA, 1 EE	41 (37-43)	5 MSM	0.008 (0.002
16	В	5	2011-2017	0 (0.0)	-	38 (37-45)	4 MSM, 1 Het	0.009 (0.002
17	В	5	2011-2017	0 (0.0)	_	33 (32-35)	5 MSM	0.009 (0.002
18	В	5	2013-2018	1 (20.0)	1 SA	38 (36-43)	3 MSM, 2 Het	0.011 (0.002
19	B	6	2013 2018	0 (0.0)	-	41 (36-48)	6 MSM	0.010 (0.002
20	B	6	2007-2011	0 (0.0)	_	42 (37-45)	5 MSM, 1 Unk	0.011 (0.002
20	B	6	2010-2014	0 (0.0)	_	37 (35-43)	5 MSM, 1 Het	0.011 (0.002
22	B	7	2006-2016	1 (14.3)	1 SA	43 (39-48)	7 MSM	0.010 (0.002
23	B	7	2009-2014	2 (28.6)	2 SA	51 (40-53)	7 MSM	0.011 (0.002
23	B	9	2010-2016		ZJA	40 (34-52)	7 MSM, 1 Het, 1 Unk	0.009 (0.002
		-		0 (0.0)	-		8 MSM, 1 Unk	•
25	B	9	2017-2018	0 (0.0)	-	34 (31-41)	•	0.006 (0.002
26	A1	4	2013-2015	0 (0.0)	-	47 (45-50)	4 MSM	0.010 (0.002
27	A1	8	2014-2016	1 (12.5)	1 WE	37 (33-39)	8 MSM	0.008 (0.002
28	C C	4	2007-2011	1 (25.0)	1 SA	46 (44-47)	3 MSM, 1 Het	0.007 (0.002
29		4	2012-2016	0 (0.0)	-	50 (45-52)	3 Het, 1 MSM	0.009 (0.002
30	CRF02_AG	4	2009-2013	0 (0.0)	-	35 (35-37)	4 MSM	0.007 (0.002
31	CRF02_AG	4	2009-2013	0 (0.0)	-	38 (38-40)	2 MSM, 1 Het, 1 Unk	0.004 (0.001
32	CRF02_AG	4	2014	1 (25.0)	1 EE	34 (30-39)	3 MSM, 1 Het	0.009 (0.002
33	CRF02_AG	5	2013-2014	0 (0.0)	-	34 (33-35)	4 MSM, 1 Unk	0.006 (0.002
34	CRF02_AG	/	2010-2017	0 (0.0)	-	41 (36-51)	6 MSM, 1 Het	0.005 (0.001
35	CRF12_BF	5	2014-2015	1 (20.0)	1 SA	34 (27-34)	4 Het, 1 Unk	0.010 (0.002
36	CRF20_BG	7	2013-2017	1 (14.3)	1 Aus	33 (32-37)	7 MSM	0.005 (0.002
				Large MTCs	(≥10 sequence	s)		
1	В	14	2008-2016	0 (0.0)	-	40 (34-49)	11 MSM, 2 Het, 1 IDU	0.010 (0.00
2	В	19	2007-2015	2 (10.5)	1 EE, 1 SA	37 (32-43)	18 MSM, 1 Unk	0.016 (0.002
3	В	35	2009-2017	2 (5.7)	1 WE, 1 SA	34 (33-43)	33 MSM, 1 Het, 1 Unk	0.013 (0.002
4	С	10	2011-2016	0 (0.0)	-	39 (35-42)	8 MSM, 1 Het, 1 Unk	0.009 (0.001
5	CRF02_AG	10	2006-2016	1 (10.0)	1 CA	42 (35-46)	9 MSM, 1 Het	0.011 (0.002
6	CRF60 BC	52	2008-2018	5 (9.6)	4 EE, 1 Unk	34 (31-37)	41 MSM, 5 Het, 6 Unk	0.012 (0.002

*: Number of Individuals involved in a specific 10. *: Number of migrants individuals involved in a specific 10. Here resexual, inside Men who have sex with Men. Unk: Unknown, Aus: Australian, CA: Central American; EE: East European; NA: North American; SA: South American; WE: West European.

The 24 migrants involved in LMTCs and MMTCs were mainly from Central/South America or other European countries.



CROI 2020 Boston, March 8–11, 2020

00920

CONCLUSIONS

These results reinforce the fact that **phylogeny** represents one of the most important tools to better describe and monitor local HIV epidemics, by correlating the genetic relationship of the viruses with information on demographics, transmission mode and new infections.

Overall, our findings can contribute to monitoring of the HIV epidemic and guiding the public health response in Italy.

Our study shows that clustered transmission in Italy is prevalently driven by MSM with very limited contribution of migrants.

FUNDING

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

ACKNOWLEDGMENTS

Icona Fundation Study Group

OARD 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, 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

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 lalungo (Viterbo).

AUTHOR CONTACT INFORMATION

Author Contact Information: lavinia.fabeni@gmail.com

³⁻ Frost SD, et al., Understanding drivers of phylogenetic clustering in molecular epidemiological studies of HIV. J Infect Dis 2015; 211:856–858.