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

Maria Mercedes Santoro[1], **Lavinia Fabeni**[2], Patrizia Lorenzini[2], Stefano Rusconi[3], Nicola Gianotti[4], Andrea Costantini[5], Loredana Sarmati[6], Andrea Antinori[2], Francesca Ceccherini-Silberstein[1], Antonella d'Arminio Monforte[7], Annalisa Saracino[8], Enrico Girardi[2], on behalf of the Icona Foundation Study Cohort

[1]University of Rome «Tor Vergata», Rome, Italy, [2]National Institute for Infectious Diseases «Lazzaro Spallanzani» - IRCCS, Rome, Italy, [3]Luigi Sacco University Hospital, Milan, Italy, [4]San Raffaele Scientific Institute, Milan, Italy, [5]Marche Polytechnic University, Ancona, Italy, [6]Hospital of Rome «Tor Vergata», Rome, Italy, [7]University of Milan, Milan, Italy, [8]University of Bari, Bari, Italy

CROI 2020 Boston, March 8–11, 2020

00920

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
2- https://www.ecdc.europa.eu/en/publications-data/hivaids-surveillance-europe-2019-2018-data
3- Frost SD, *et al.*, Understanding drivers of phylogenetic clustering in molecular epidemiological studies of HIV. J Infect Dis 2015; 211:856–858.
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

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.

Variables	Overall N=3499	Out of cluster 2773 (79.3%)	In cluster 726 (20.7%)	P-value[a]	OR	(95% CI)	P-value
					Adjusted model[b]		
Male gender, n (%)	2872 (82.1%)	2187 (78.9%)	685 (94.3%)	<0.001			
Age, years, median (IQR)	37 (30-45)	38 (31-46)	32 (27-40)	<0.001	0,65	0.59-0.72	<0.001
Mode of HIV transmission							
F heterosexual	553 (15.8%)	513 (18.5%)	40 (5.5%)	<0.001	1,00	-	-
F IVDU	32 (0.9%)	31 (1.1%)	1 (0.1%)		0,49	0.06-3.80	0,497
M heterosexual	713 (20.4%)	628 (22.7%)	85 (11.7%)		1,82	1.19-2.78	0,006
M IVDU	161 (4.6%)	145 (5.2%)	16 (2.2%)		1,52	0.80-2.90	0,204
M MSM	1789 (51.1%)	1247 (45.0%)	542 (74.7%)		3,46	2.39-5.03	<0.001
Other/unknown	251 (7.2%)	209 (7.5%)	42 (5.8%)		2,73	1.66-4.48	<0.001
Nation of birth, n (%)							
Italy	2804 (80.1%)	2160 (77.8%)	644 (88.7%)	<0.001	1,00	-	-
Africa	219 (6.3%)	212 (7.7%)	7 (0.9%)		0,18	0.08-0.39	<0.001
Central and South America	241 (6.9%)	201 (7.3%)	40 (5.5%)		0,49	0.33-0.71	0,001
Europe	187 (5.3%)	159 (5.7%)	28 (3.9%)		0,29	0.08-0.97	0,045
Asia	38 (1.1%)	35 (1.3%)	3 (0.4%)		0,62	0.40-0.97	0,035
Other	10 (0.3%)	6 (0.2%)	4 (0.6%)		2,61	0.62-10.97	0,189
Education, n (%)							
Primary school	169 (4.8%)	158 (5.7%)	11 (1.5%)	<0.001	0,87	0.45-1.71	0,691
Secondary school	585 (16.7%)	505 (18.2%)	80 (11.0%)		0,91	0.68-1.21	0,518
College/University	1762 (50.4%)	1329 (47.9%)	433 (59.6%)		1,00	-	-
Unknown	983 (28.1%)	781 (28.2%)	202 (27.8%)		1,03	0.83-1.28	0,773
Employment, n (%)							
Employed	1476 (42.2%)	1148 (41.4%)	328 (45.2%)	<0.001	1,00	-	-
Unemployed	461 (13.2%)	389 (14.0%)	72 (9.9%)		0,91	0.67-1.25	0,565
Self-employed	526 (15.0%)	413 (14.9%)	113 (15.6)		0,97	0.75-1.26	0,840
Student	146 (4.2%)	93 (3.4%)	53 (7.3%)		0,83	0.56-1.24	0,360
Housewife	94 (2.7%)	88 (3.2%)	6 (0.8%)		1,18	0.47-2.94	0,723
Other	278 (7.9%)	244 (8.8%)	34 (4.7%)		0,69	0.46-1.05	0,083
Unknown	518 (14.8%)	398 (14.3%)	120 (16.5%)		0,99	0.75-1.30	0,929
HIV RNA, copies/mL							
<1000	122 (3.5%)	99 (3.6%)	23 (3.2%)	0,005	0,66	0.39-1.12	0,127
1.000/10.000	559 (16.0%)	445 (16.1%)	114 (15.7%)		0,81	0.61-1.08	0,147
10.000/100.000	1470 (42.0%)	1126 (40.6%)	344 (47.4%)		0,94	0.75-1.17	0,562
>100.000	1118 (32.0%)	905 (32.6%)	213 (29.3%)		1,00	-	-
Unknown	230 (6.6%)	198 (7.1%)	32 (4.4%)		0,76	0.38-1.55	0,451
CD4, cells/mm³, n (%)							
<=200	791 (22.6%)	721 (26.0%)	70 (9.6%)	<0.001	1,00	-	-
201-500	1485 (42.4%)	1165 (42.0%)	320 (44.1%)		2,22	1.64-2.99	<0.001
>500	1003 (28.7%)	703 (25.4%)	300 (41.3%)		3,01	2.20-4.13	<0.001
Unknown	220 (6.3%)	184 (6.6%)	36 (5.0%)		1,90	0.93-3.90	0,078
Year of diagnosis, median (IQR)	2011 (2008-2014)	2011 (2007-2014)	2012 (2009-2014)	<0.001	1,09	1.06-1.11	<0.001
Subtype							
A1	104 (3.0%)	85 (3.1%)	19 (2.6%)	<0.001	-	-	-
B	2556 (73.1%)	2038 (73.5%)	518 (71.4%)		-	-	-
C	148 (4.2%)	119 (4.3%)	29 (4.0%)		-	-	-
CRF02_AG	187 (5.3%)	141 (5.1%)	46 (6.3%)		-	-	-
CRF60_BC	64 (1.8%)	12 (0.4%)	52 (7.2%)		-	-	-
F1	179 (5.1%)	157 (5.7%)	22 (3.0%)		-	-	-
Other	261 (7.5%)	221 (8.0%)	40(5.5%)		-	-	-

[a]By Mann-Whitney test (for quantitative variables) and χ2 test or Fisher's exact test (for categorical variables), as appropriate. [b]Adjusted 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 multivariable 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%).

Among the **228 MTCs** identified, 6 were **Large MTCs** (N=140 subjects), **36 were Medium MTCs** (N=184) and **186 were Small MTCs** (N=402).

Figure 1. Clusters' population by HIV-TRACE.
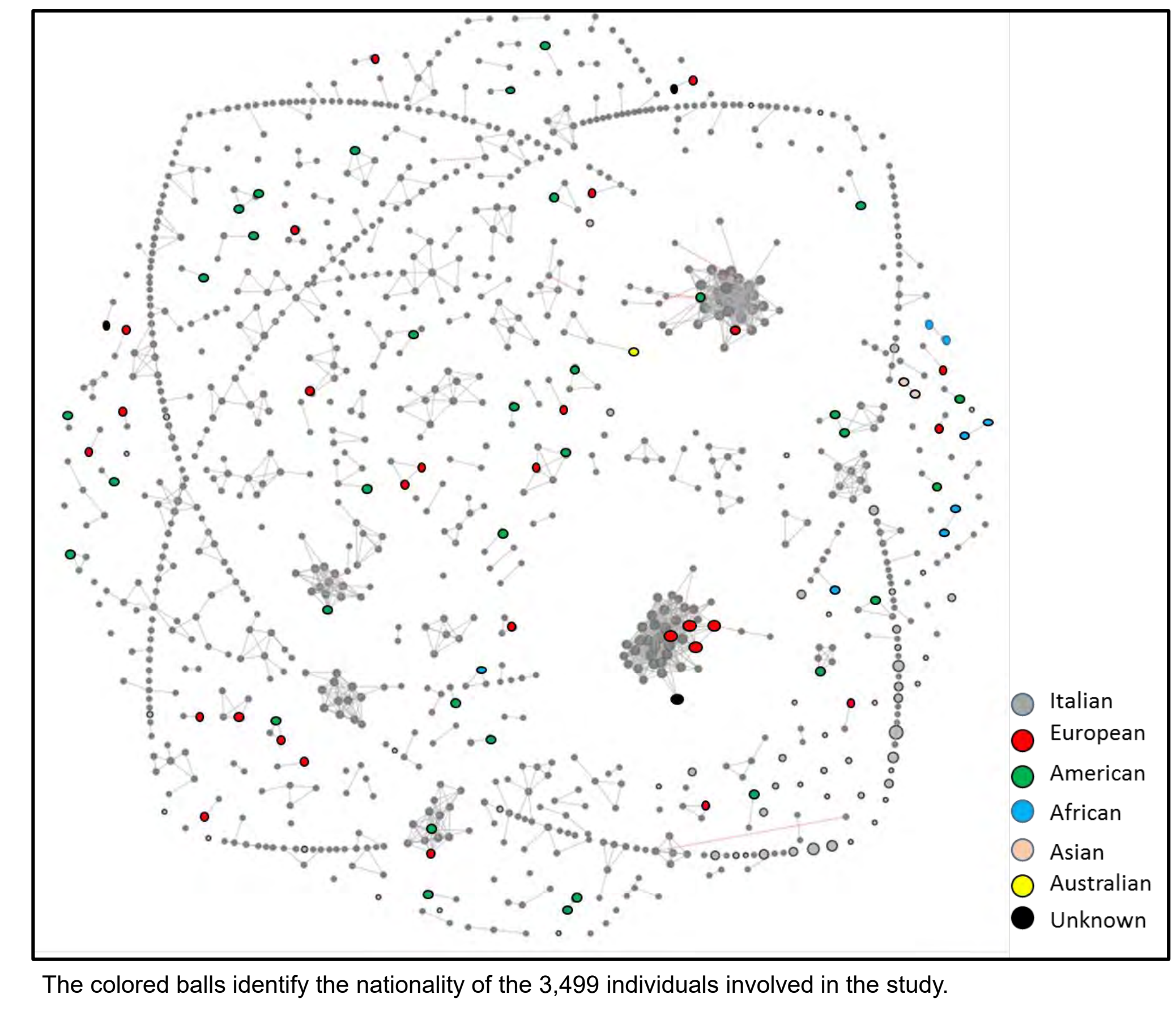
The colored balls identify the nationality of the 3,499 individuals involved in the study.

Legend: Italian, European, American, African, Asian, Australian, Unknown

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

Medium MTCs (4-9 sequences)

ID	Subtype	Cluster Size[a] n	Sampling Interval Year	Migrants[b] n (%)	Nationality n	Age, years Median (IQR)	Risk Factor n	Genetic distance Mean (SE)
1	B	4	2006-2007	0 (0.0)	-	46 (44-46)	4 MSM	0.008 (0.002)
2	B	4	2007-2012	0 (0.0)	-	46 (42-50)	3 Het, 1 Unk	0.010 (0.002)
3	B	4	2008-2014	0 (0.0)	-	52 (50-53)	4 MSM	0.008 (0.002)
4	B	4	2008-2016	0 (0.0)	-	39 (37-41)	3 MSM, 1 Unk	0.006 (0.002)
5	B	4	2009-2012	0 (0.0)	-	54 (51-56)	3 MSM, 1 Het	0.009 (0.002)
6	B	4	2009-2016	0 (0.0)	-	36 (33-41)	3 MSM, 1 Unk	0.009 (0.002)
7	B	4	2010-2011	1 (25.0)	1 NA	50 (46-52)	4 MSM	0.004 (0.002)
8	B	4	2011-2013	0 (0.0)	-	37 (35-38)	4 MSM	0.008 (0.002)
9	B	4	2011-2017	0 (0.0)	-	53 (48-56)	4 MSM	0.007 (0.002)
10	B	4	2013-2014	0 (0.0)	-	41 (34-48)	4 MSM	0.006 (0.002)
11	B	4	2013-2018	1 (25.0)	1 EE	41 (37-43)	3 MSM, 1 Het	0.010 (0.002)
12	B	4	2016	0 (0.0)	-	38 (28-49)	4 MSM	0.004 (0.001)
13	B	5	2007-2012	1 (20.0)	1 NA	38 (37-45)	5 MSM	0.006 (0.001)
14	B	5	2008-2014	0 (0.0)	-	36 (36-37)	5 MSM	0.011 (0.002)
15	B	5	2010-2012	2 (40.0)	1 CA, 1 EE	41 (37-43)	5 MSM	0.008 (0.002)
16	B	5	2011-2017	0 (0.0)	-	38 (37-45)	4 MSM, 1 Het	0.007 (0.002)
17	B	5	2011-2017	0 (0.0)	-	33 (32-35)	5 MSM	0.009 (0.002)
18	B	5	2013-2018	1 (20.0)	1 SA	38 (36-43)	3 MSM, 2 Het	0.011 (0.002)
19	B	6	2007-2011	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)
21	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)
24	B	9	2010-2016	0 (0.0)	-	40 (34-52)	7 MSM, 1 Het, 1 Unk	0.011 (0.002)
25	B	9	2017-2018	0 (0.0)	-	34 (31-41)	8 MSM, 1 Unk	0.006 (0.001)
26	A1	4	2013-2015	0 (0.0)	-	47 (45-50)	4 MSM	0.005 (0.002)
27	A1	4	2014-2016	1 (12.5)	1 WE	37 (33-39)	8 MSM	0.007 (0.002)
28	C	4	2007-2011	1 (25.0)	1 SA	46 (44-47)	3 MSM, 1 Het	0.007 (0.002)
29	C	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 (0.001)
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	0.003 (0.001)
33	CRF02_AG	5	2013-2014	0 (0.0)	-	34 (33-35)	4 MSM, 1 Unk	0.008 (0.002)
34	CRF02_AG	7	2010-2017	0 (0.0)	-	41 (36-51)	6 MSM, 1 Het	0.005 (0.001)
35	CRF12_BF	5	2014-2016	1 (20.0)	1 SA	34 (27-34)	4 Het, 1 Unk	0.010 (0.002)
36	CRF60_BG	7	2013-2017	1 (14.3)	1 Aus	33 (32-37)	7 MSM	0.005 (0.001)

Large MTCs (≥10 sequences)

ID	Subtype	Cluster Size[a] n	Sampling Interval Year	Migrants[b] n (%)	Nationality n	Age, years Median (IQR)	Risk Factor n	Genetic distance Mean (SE)
1	B	14	2008-2016	0 (0.0)	-	40 (34-49)	11 MSM, 2 Het, 1 IDU	0.010 (0.001)
2	B	19	2007-2015	2 (10.5)	1 EE, 1 SA	37 (32-43)	18 MSM, 1 Unk	0.013 (0.002)
3	B	35	2009-2017	2 (5.7)	1 WE, 1 SA	34 (30-43)	33 MSM, 1 Het, 1 Unk	0.013 (0.002)
4	C	10	2011-2016	0 (0.0)	-	39 (35-42)	8 MSM, 1 Het, 1 Unk	0.010 (0.002)
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)

[a]: Number of individuals involved in a specific TC; [b]: Number of migrants individuals involved in a specific TC. Het: Heterosexual, MSM: 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**.

CONCLUSIONS

HIV-1 newly diagnosed subjects are **involved in several MTCs in the past two decades in Italy**. **Clustered transmission**, especially for large clusters, is prevalently **driven by natives, mainly MSM** and **frequently infected** with **HIV-1 non-B subtype**.

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

ACKNOWLEDGMENTS

AUTHOR CONTACT INFORMATION

Author Contact Information: lavinia.fabeni@gmail.com