Non-B Subtypes HIV-1 Infections in Germany Before and After the European Migrant Crisis

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Background

- About 3,200 new HIV infections are reported annually in Germany, which makes the identification of transmission networks of central importance for targeted interventions in health care [1].
- HIV-1 subtype B is predominant in high-resource countries, and accounts for >80% of HIV-1 infections in Western Europe [2].
- However, the presence of HIV-1 non-B subtypes has increased in Western Europe and Germany in recent years [3,4].
- These changes are commonly attributed to migration, as non-B subtypes are mostly found among people from non-European origin [3,4].
- We combined molecular epidemiology and geospatial data to assess potential relationships between migratory events and spread of HIV-1 non-B subtypes before and after 2015, the beginning of the European migrant crisis.

Objective

Explore the dynamics of HIV-1 non-B subtypes before and after the German border opening for relief of the European migrant crisis

Methods

Data:

- Sociodemographic, geographic, and HIV-1 *pol* sequence data were collected from individuals, who received care in seven metropolitan cities across Germany (Bonn, Cologne, Frankfurt, Freiburg, Hamburg, Hannover, and Munich) between 2000 and 2018.
- Individuals' origins were grouped into six regions: Western Europe and other high resource countries; Eastern Europe; North Africa and the Middle East; sub-Saharan Africa; Latin America and the Caribbean; and Asia.

Sequence analyses and Network inferences:

- Partial HIV-1 *pol* sequences were subtyped, using the Subtype Classification Evolutionary Algorithms (SCUEAL) program [5].
- Genetic-distance based network analyses were performed to infer putative relationships between HIV-1 partial *pol* sequences using the HIV-TRACE software (HIV TRAnsmission Cluster Engine: www.hivtrace.org) to infer transmission links between sequences with a genetic distance ≤1.5% [6].
- The number and origin of HIV-1 subtype B and non-B introductions in Germany was evaluated with TreeTime [7] for ancestral sequence reconstruction, combining HIV-1 sequences from Germany (B: n= 2,242 and non-B: n= 868) with publicly available HIV-1 *pol* sequences from the Los Alamos National Laboratory HIV sequence database (B: n= 40,054 and non-B: n= 10,277) [7, 8].

Results

- Study population characteristics are displayed in Table 1. HIV-1 subtype B was predominant (2,242/3,110; 72.1%) and non-B subtypes accounted for 27.9% (868/3,110).
- We identified an increase in non-B subtypes, particularly in 2017 (Figure 1 & 2).
- There were only three new non-B diagnoses after 2015 among individuals from the top 5 countries of origin of the migrant crisis 2015 (i.e. Syria, Kosovo, Afghanistan, Albania, Iraq).

Figure 1. The increase in non-B subtypes was particularly observed in 2017, when they accounted for 39.4% of new HIV-1 diagnoses.

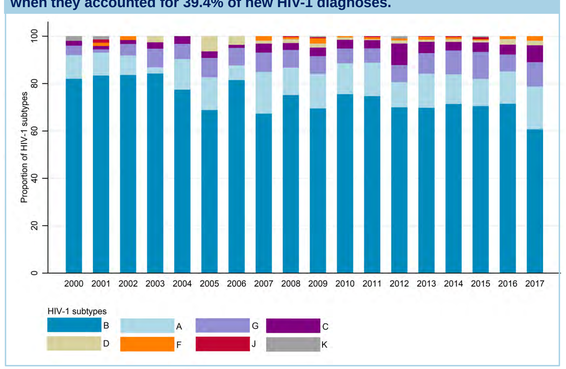
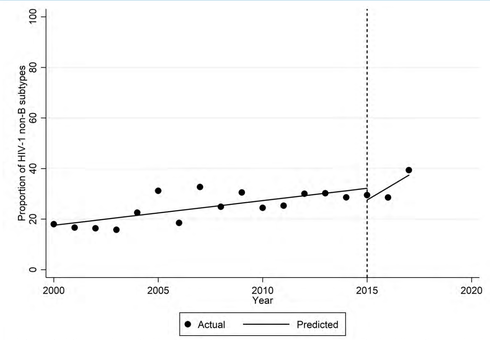


Figure 2. The proportion of HIV-1 non-B subtypes increased annually by 4.9% (95% CI 1.6-8.3) after 2015.



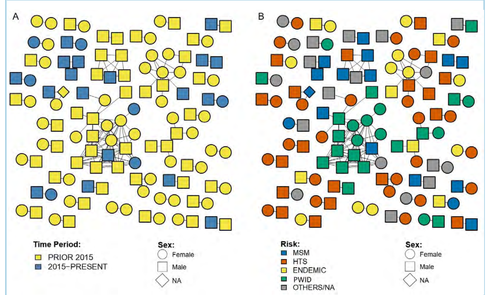
Legend. Interrupted time series with Newey-West standard errors and one lag. Dashed-line: time-series before and after 2015. Line: predicted trend.

Table 1. Characteristics of non-B Subtypes prior and after 2015.

	Study population	Non-B subtypes		
	n (%)	Prior 2015	After 2015	
Total N	3,110 (100)	673 (100)	195 (100)	p-value***
Age				**<0.001**
<30	129 (4.1)	15 (2.3)	28 (14.4)	
30-45	1,022 (32.9)	236 (35.7)	90 (46.2)	
>45	1,959 (63.0)	422 (62.7)	77 (39.5)	
Gender				**<0.001**
Female	653 (21.0)	351 (52.2)	94 (48.2)	
Male	2,446 (78.7)	318 (47.3)	99 (50.8)	
Missing	11 (0.3)	4 (0.6)	2 (1.0)	
Risk*				**<0.001**
HTS	591 (19.1)	220 (32.8)	42 (21.8)	
MSM	1,548 (49.9)	101 (15.1)	37 (19.2)	
ENDEMIC	338 (10.9)	207 (30.9)	46 (23.8)	
PWID	177 (5.7)	61 (9.1)	21 (10.9)	
Others/Unknown	437 (14.1)	82 (12.2)	47 (24.4)	
Country of origin				**<0.001**
Western Europe**	2,198 (70.7)	255 (37.9)	60 (30.8)	
Eastern Europe	177 (5.7)	46 (6.8)	22 (11.3)	
North Africa & Middle East	33 (1.1)	7 (1.0)	9 (4.6)	
Sub-Saharan Africa	393 (12.6)	300 (44.6)	75 (38.5)	
Latin America & Carribean	45 (1.5)	4 (0.6)	2 (1.0)	
Asia & Oceanien	147 (4.7)	45 (6.7)	9 (4.6)	
Unknown	117 (3.8)	16 (2.4)	18 (9.2)	

Legend. Baseline sociodemographic and clinical characteristics. *HTS, heterosexual; MSM, men who have sex with men; ENDEMIC, recent immigration from a country with a HIV prevalence >1%, PWID, people with injection drug use. **Western Europe and comparable developed countries.***Chi-square test or Fisher`s exact test as appropriate. P-values given in bold depict significant results (p<0.05).

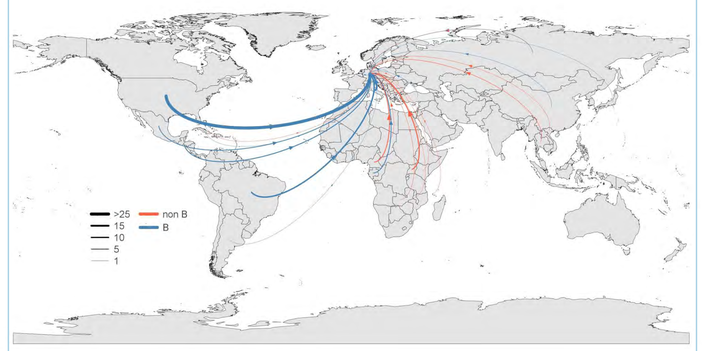
Figure 3. HIV-1 non-B clusters comprising mainly sequences from heterosexuals (HTS) and persons who inject drugs (PWID).



Legend. Transmission network of HIV-1 non-B subtypes in Germany. All edges represent a genetic distance of ≤1.5%. A) Color indicates the period prior 2015 (yellow) and after 2015 (blue). B) Color indicates the risk group: men having sex with men (MSM) in blue, heterosexuals (HTS) in red, people originating from an endemic country (ENDEMIC) in yellow, people who inject drugs (PWID) in green, and others or unknown in grey.

- Of the 868 non-B HIV infected individuals, 119 (13.7%) were genetically linked, forming 42 transmission clusters (size 2-19 sequences) with heterosexual risk (36.1%; 43/119) and injection drug use (20.1%; 24/119) being predominant (Figure 3).
- There was an increase in genetically linked men, with two male only clusters before 2015 and the emergence of six new male-only clusters after 2015 (Figure 3).
- Multiplicity and origin of HIV-1 introductions are displayed in Figure 4.

Figure 4. The majority (>2/3) of subtype B introductions come from the United States. Eighty unique introductions of HIV-1 non-B subtypes from abroad have been identified, mostly small clusters originating from Sub-Saharan Africa.



Legend. HIV introductions of HIV-1 subtype non-B (red) and B (blue) in Germany. The number and origin of introductions was obtained after combining the HIV-1 B (n= 2,242) and non-B (n= 868) dataset from Germany with all publicly available Los Alamos National Laboratory HIV-1 B (n=40,054) and non-B (n=10,277) sequences Analyses using TreeTime for ancestral sequence reconstruction [8]. The thickness of the lines represents the number of HIV-1 introductions in Germany.

Conclusion

- The proportion of HIV-1 non-B diagnoses increased after 2015, particularly driven by subtypes A and G.
- Individuals infected with non-B subtypes are mainly originating from Eastern Europe, North Africa, and Middle East.
- However, the number of new diagnoses among migrants from the top 5 countries of the European migrant crisis was minimal in our analysis.
- We have not found a link between the European migrant crisis and the spread of HIV-1 non-B subtypes in Germany.
- The HIV-1 epidemic in Germany is changing from predominately involving MSM with subtype B to being more diverse regarding risk groups and subtypes.

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References:
[1] Robert-Koch-Institut. Epidemiologisches Bulletin 46, 2019. Available at: https://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2019/Ausgaben/46_19.pdf?__blob=publicationFile. Accessed January 2020.
[2] Beloukas A, Psarris A, Giannelou P, Kostaki E, Hatzakis A, Paraskevis D. Molecular epidemiology of HIV-1 infection in Europe: An overview. Infect Genet Evol. 2016;46:180-9. doi:10.1016/j.meegid.2016.06.033.
[3] Hanke K, Faria NR, Kuhnert D, Yousef KP, Hauser A, Meixenberger K et al. Reconstruction of the Genetic History and the Current Spread of HIV-1 Subtype A in Germany. J Virol. 2019;93(12). doi:10.1128/jvi.02238-18.
[4] von Wyl V, Kouyos RD, Yerly S, Boni J, Shah C, Burgisser P et al. The role of migration and domestic transmission in the spread of HIV-1 non-B subtypes in Switzerland. J Infect Dis. 2011;204(7):1095-103. doi:10.1093/infdis/jir491.
[5] Kosakovsky Pond SL, Posada D, Stawiski E, Chappey C, Poon AF, Hughes G, et al. An evolutionary model-based algorithm for accurate phylogenetic breakpoint mapping and subtype prediction in HIV-1. PLoS Comput Biol. 2009;5(11):e1000581.
[6] Kosakovsky Pond SL, Weaver S, Leigh Brown AJ, Wertheim JO. HIV-TRACE (TRAnsmission Cluster Engine): a Tool for Large Scale Molecular Epidemiology of HIV-1 and Other Rapidly Evolving Pathogens. Molecular biology and evolution. 2018;35(7):1812-9.
[7] Kulkem, C., Korber, B. & Shafer, R. W. HIV sequence databases. AIDS Rev. 5, 52–61 (2003).
[8] Sagulenko P, Puller V, Neher RA. TreeTime: Maximum-likelihood phylodynamic analysis. Virus Evol. 2018;4(1):vex042. doi:10.1093/ve/vex042.
[9] Hadfield J, Megill C, Bell SM, Huddleston J, Potter B, Callender C et al. Nextstrain: real-time tracking of pathogen evolution. Bioinformatics. 2018;34(23):4121-3. doi:10.1093/bioinformatics/bty407.

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