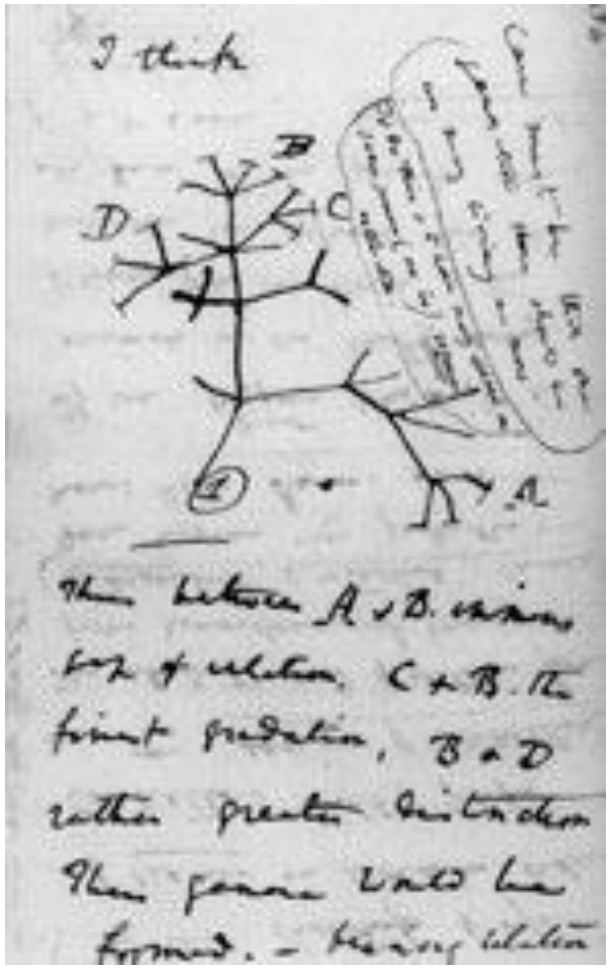
Od sieci transmisji do oporności w HIV/HCV: czy leczenie HCV u zakażonych HIV powinno być priorytetem ze wskazań epidemiologicznych?

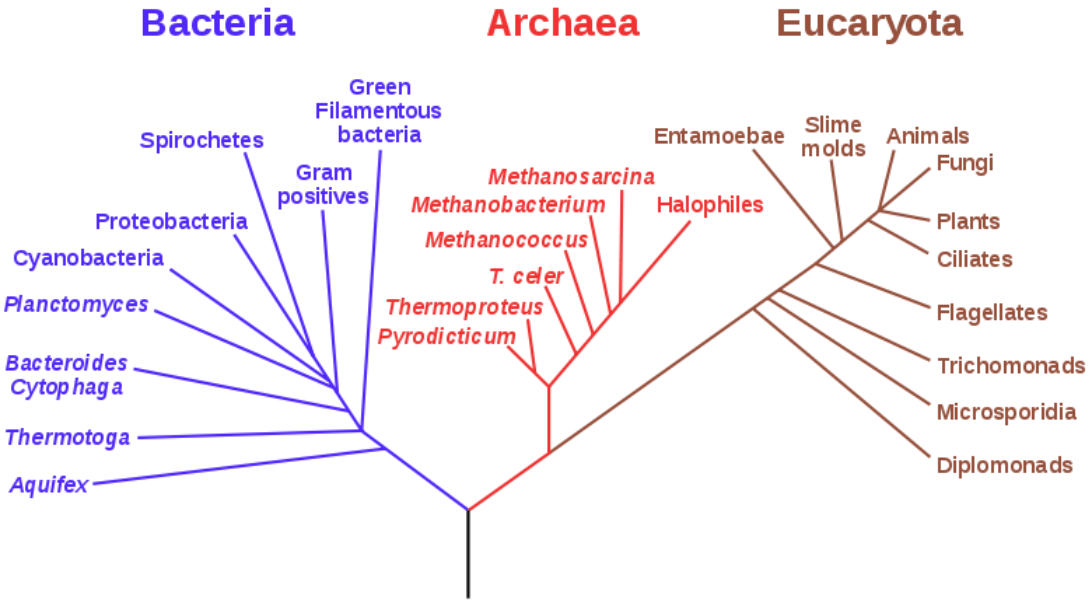
Miłosz Parczewski
Klinika Chorób Zakaźnych, Tropikalnych i Nabytych Niedoborów Immunologicznych PUM w Szczecinie

Wykład sponsorowany przez firmę Abbvie Polska

Zacznijmy od Darwina



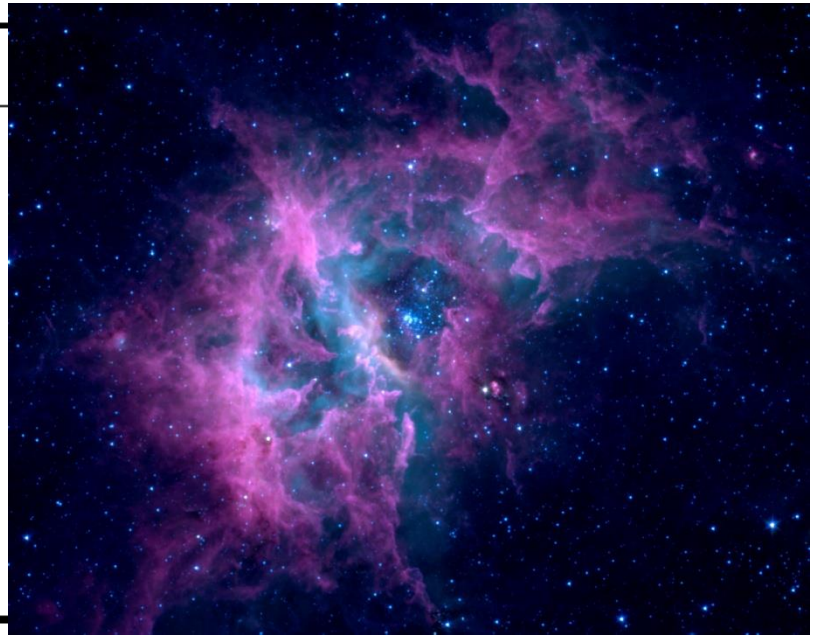
Drzewo życia - filogenetycznie



Darwin_tree_of_life.jpg
Bioinformatics **23** (1): 127–8.
doi:10.1093/bioinformatics/btl529

Liczba kombinacji

Number of OTUs	Number of rooted trees
2	1
3	3
4	15
5	105
6	954
7	10,395
8	135,135
9	2,027,025
10	34,459,425



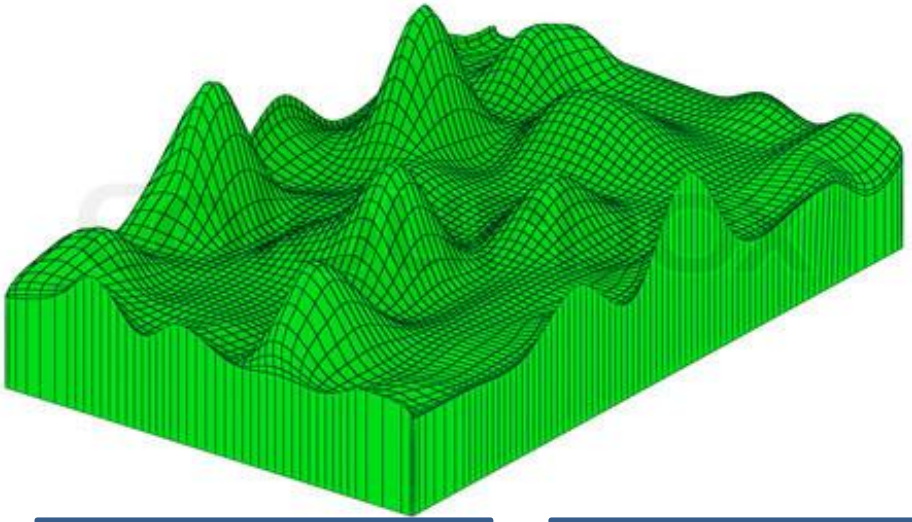
„chmura drzew”

Lemey, Salemi, Vandamme, The Phylognetic handbook

Thomas Bayes

$$P(A|B) = \frac{P(B|A)\ P(A)}{P(B)}$$

Modelowanie Bayesowskie

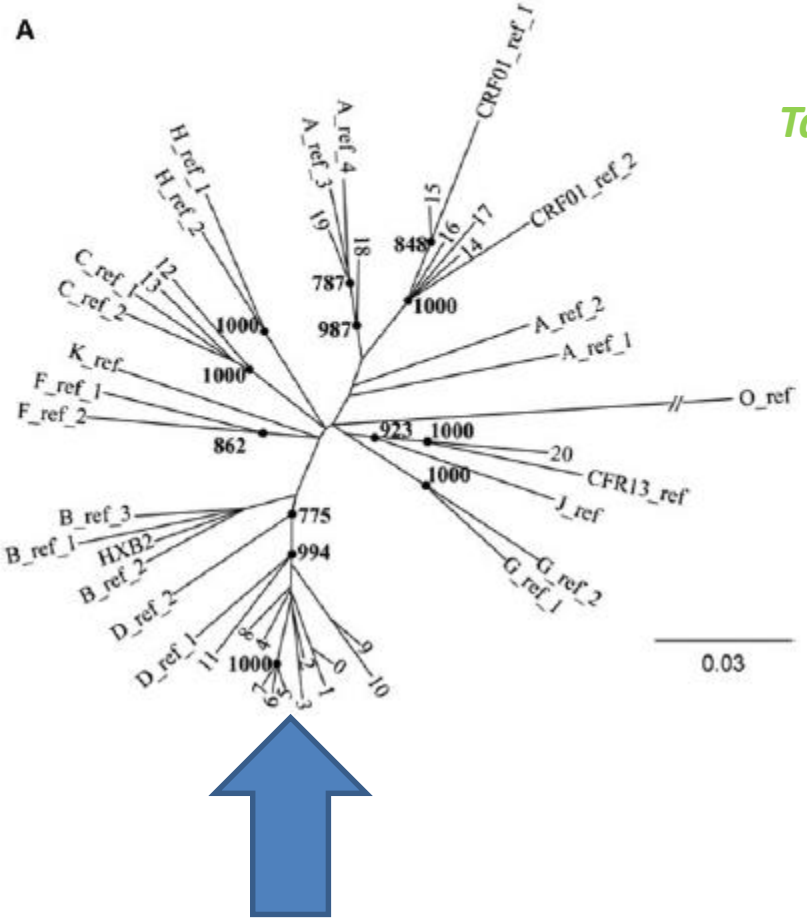


Modele „neighbour joining”

Modele największego prawdopodobieństwa

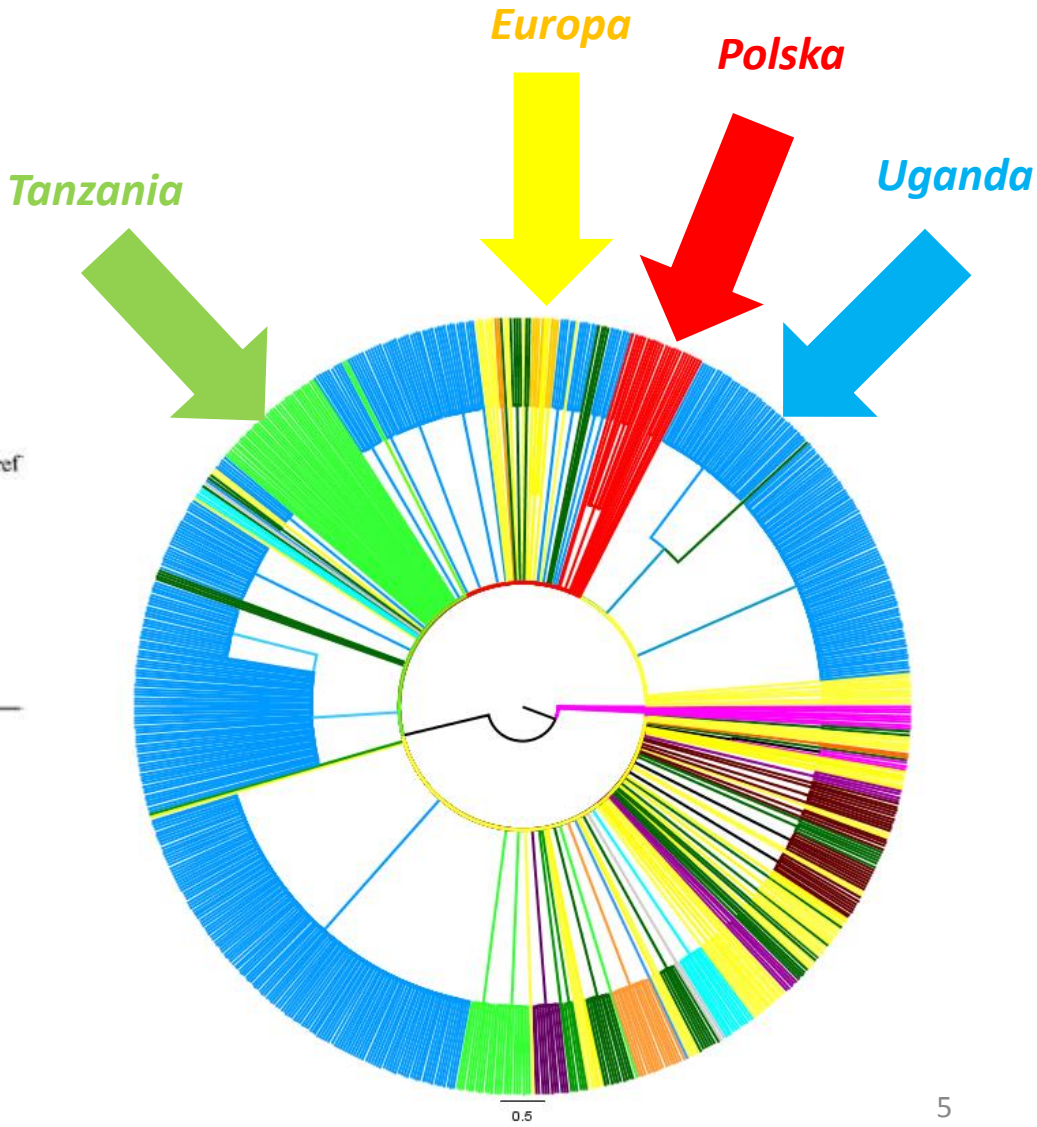
16 Bioinformatics workshop, Rockville, 2010.

Subtypowanie i pochodzenie



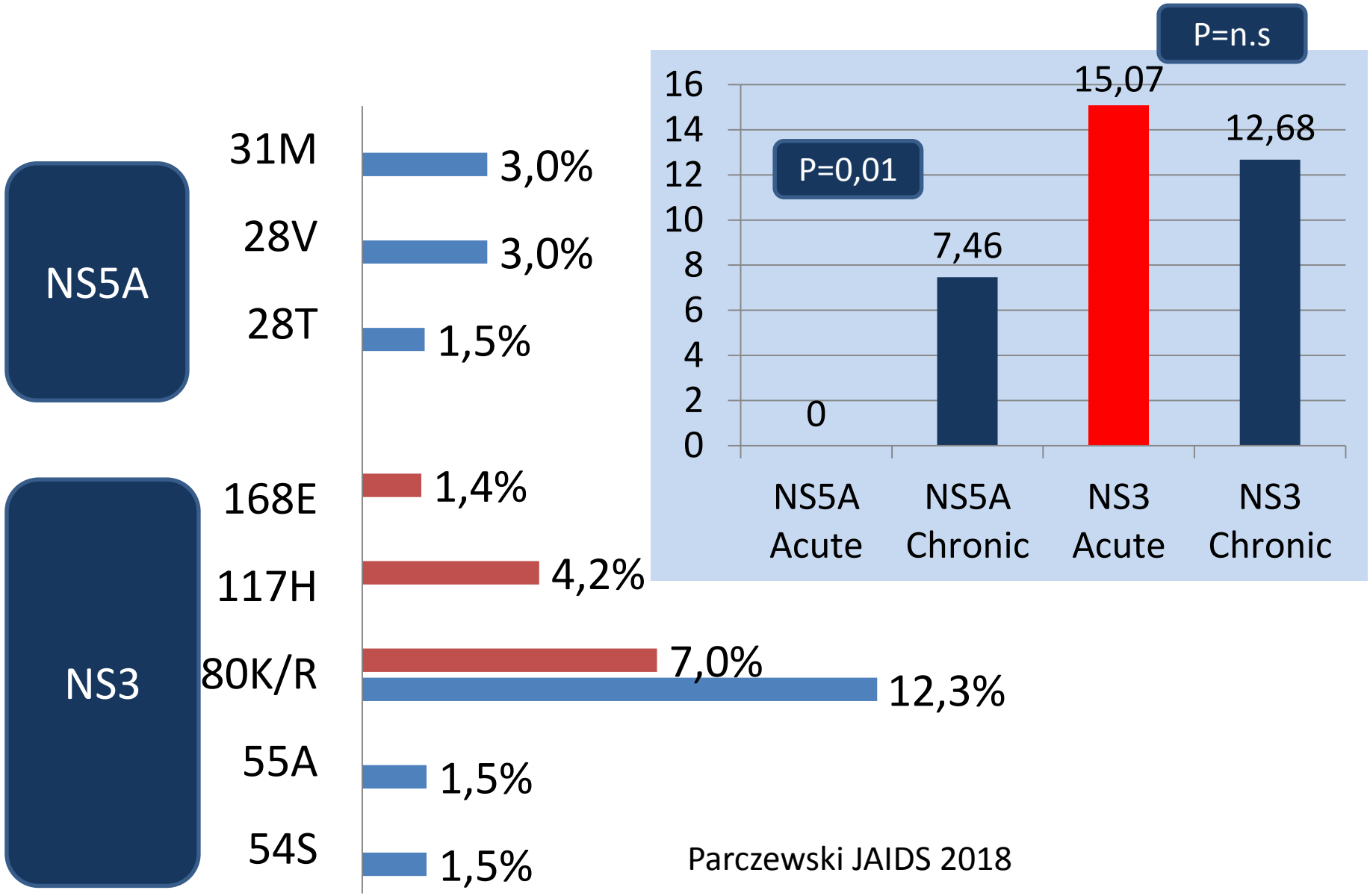
Subtypy D

Journal of Medical Virology 82:1306–1313 (2010)



PLoS ONE 7(2): e31674. doi:10.1371/journal.pone.0031674

Częstości RASs NS3/NS5A



Parczewski JAIDS 2018

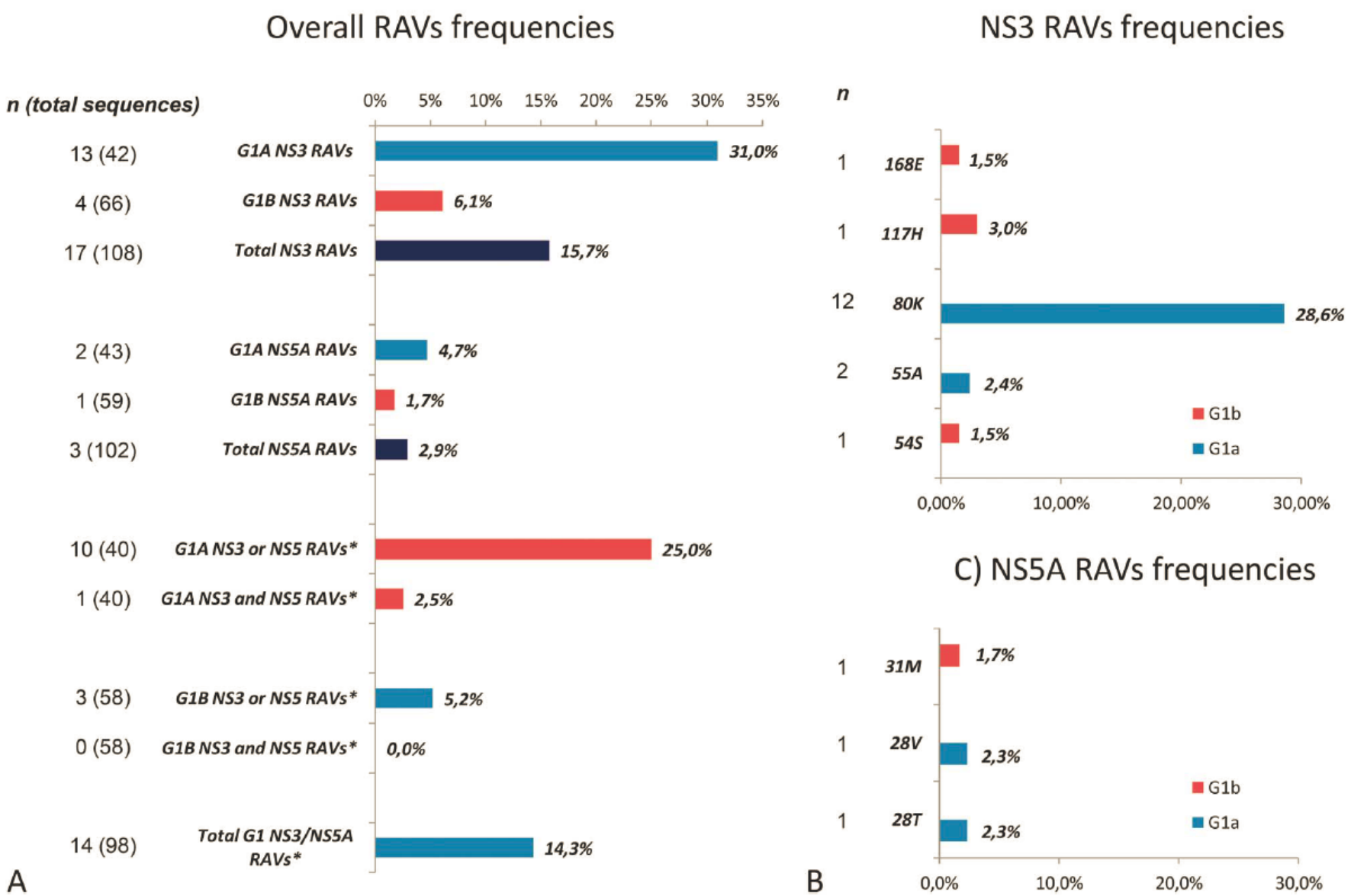


FIGURE 1. Total RAV frequencies shown per HCV subtype (A), for the HCV NS3 region (B), and NS5A region (C). RAVs are listed separately for NS3, NS5A, and for the sequences used to construct the concatenated NS3/NS5A alignments. Sample size/the total number of sequences included in each category and subtype is indicated on the left. For G1a, the observed prevalence of RAV is indicated in light blue, for G1b in red, and for the total of both subtypes in dark blue. *Frequencies calculated only for the paired NS3/NS5A sequences (n = 40 for G1A, n = 58 for G1B).

Parczewski JAIDS 2018

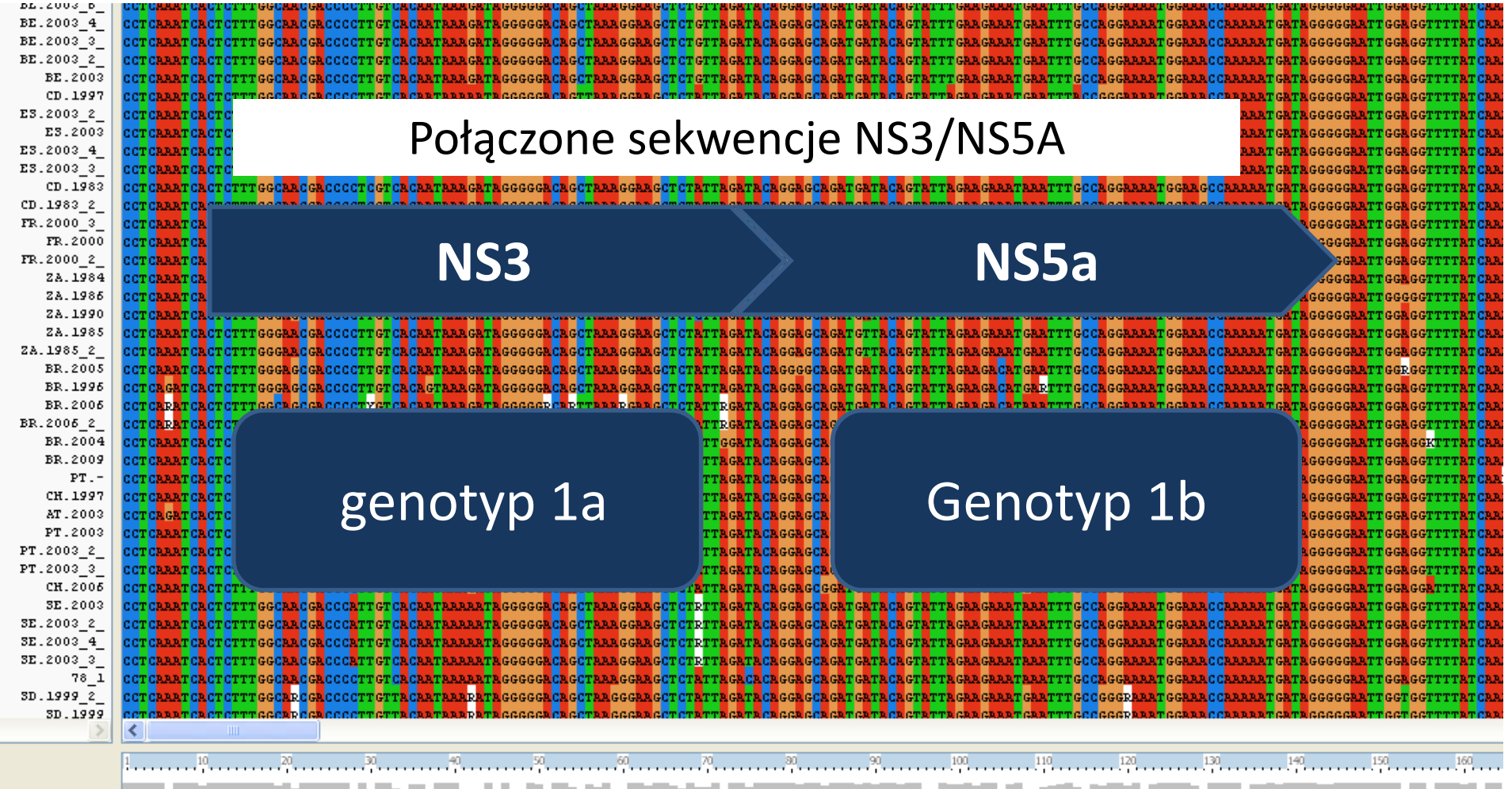
Leczenie osób z wysokim ryzykiem transmisji jako priorytet?

Treatment should be considered without delay in patients with significant fibrosis or cirrhosis (METAVIR score F2, F3 or F4), including decompensated (Child-Pugh B or C) cirrhosis, in patients with clinically significant extra-hepatic manifestations (e.g. symptomatic vasculitis associated with HCV-related mixed cryoglobulinaemia, HCV immune complex-related nephropathy and non-Hodgkin B cell lymphoma), in patients with HCV recurrence after liver transplantation, and in individuals at risk of transmitting HCV (active injection drug users, men who have sex with men with high-risk sexual practices, women of child-bearing age who wish to get pregnant, haemodialysis patients, incarcerated individuals) (**A1**).

EASL guidelines 2016

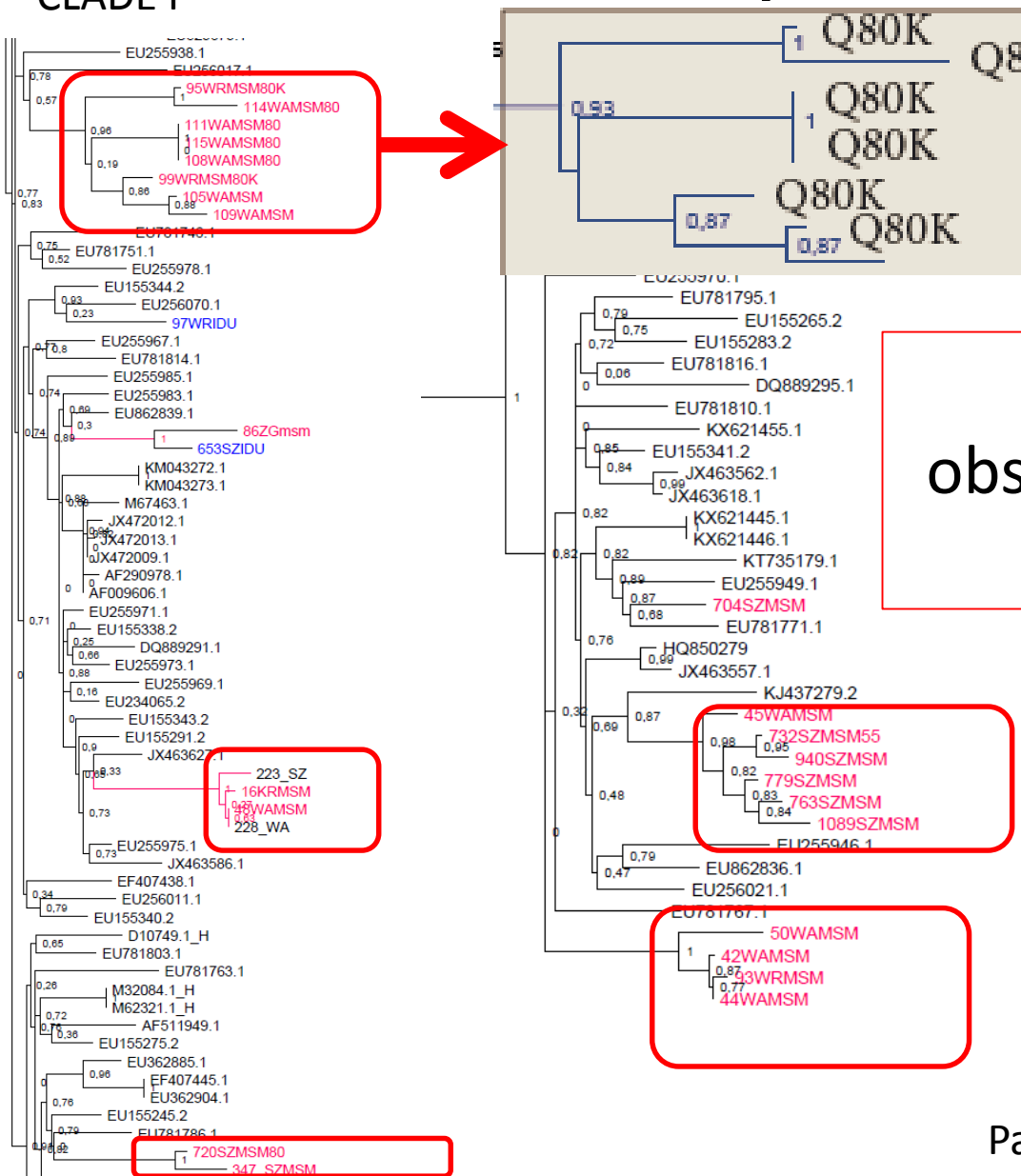
Jak wnioskujemy filogenetycznie?

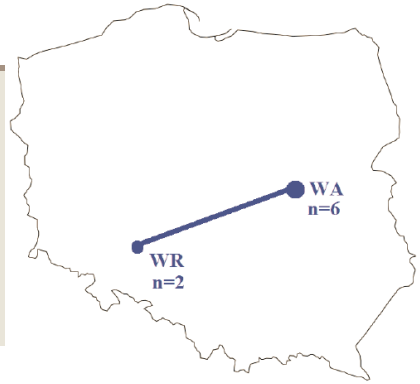
Filogenetyka przy użyciu algorytmu maximum likelihood (ML) z aLRT , parametry: bootstrap >90% , dystans: 0.08 (GTR model + γ),



Genotyp 1a klastry u osób z ostrym HCV/hiv-1

CLADE I





Transmisja Q80K obserwowana u 6 osób z G1A.

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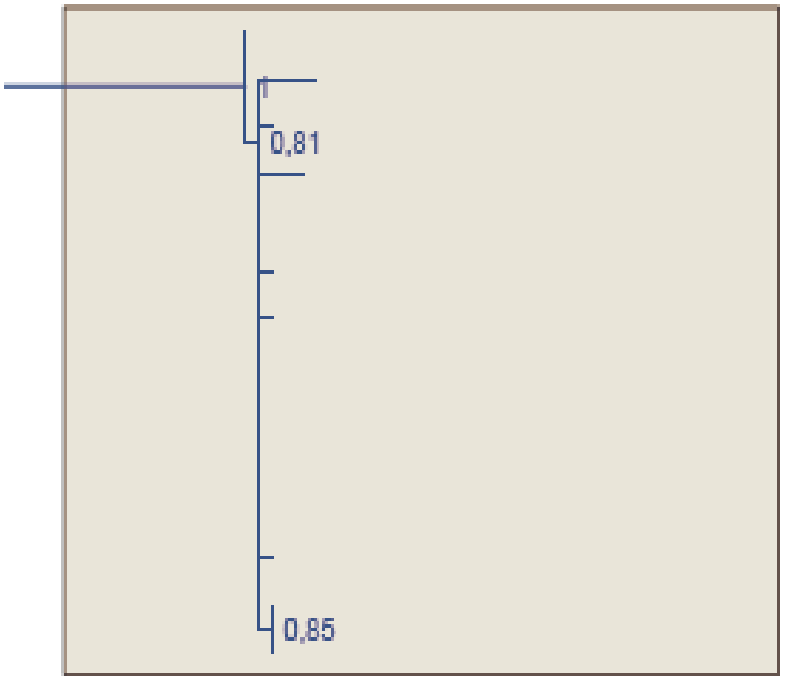
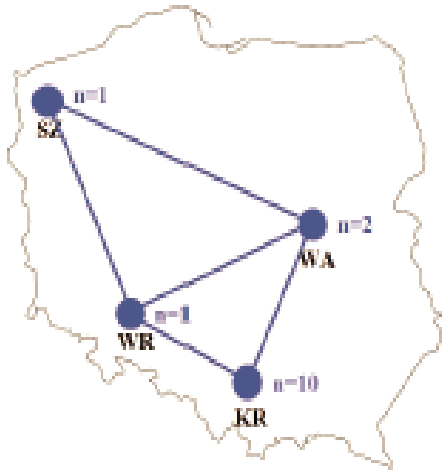
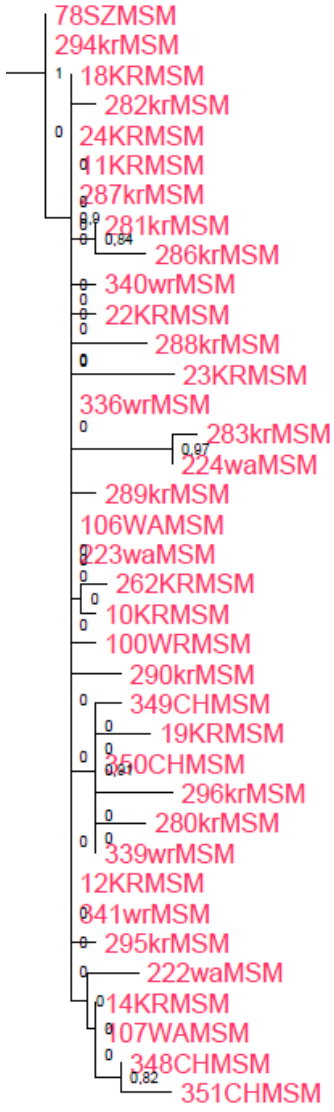
POWIĘKSZAJĄCY SIĘ klastry transmisji G1b HCV u osób z HIV-1

Part of the Genotype 1b tree







Klaster zwierający 37 sekwencji z 5 miast (średnia odległość między miastami 370 km).
(czas próby 2012-2017)

Parczewski EACS 2017

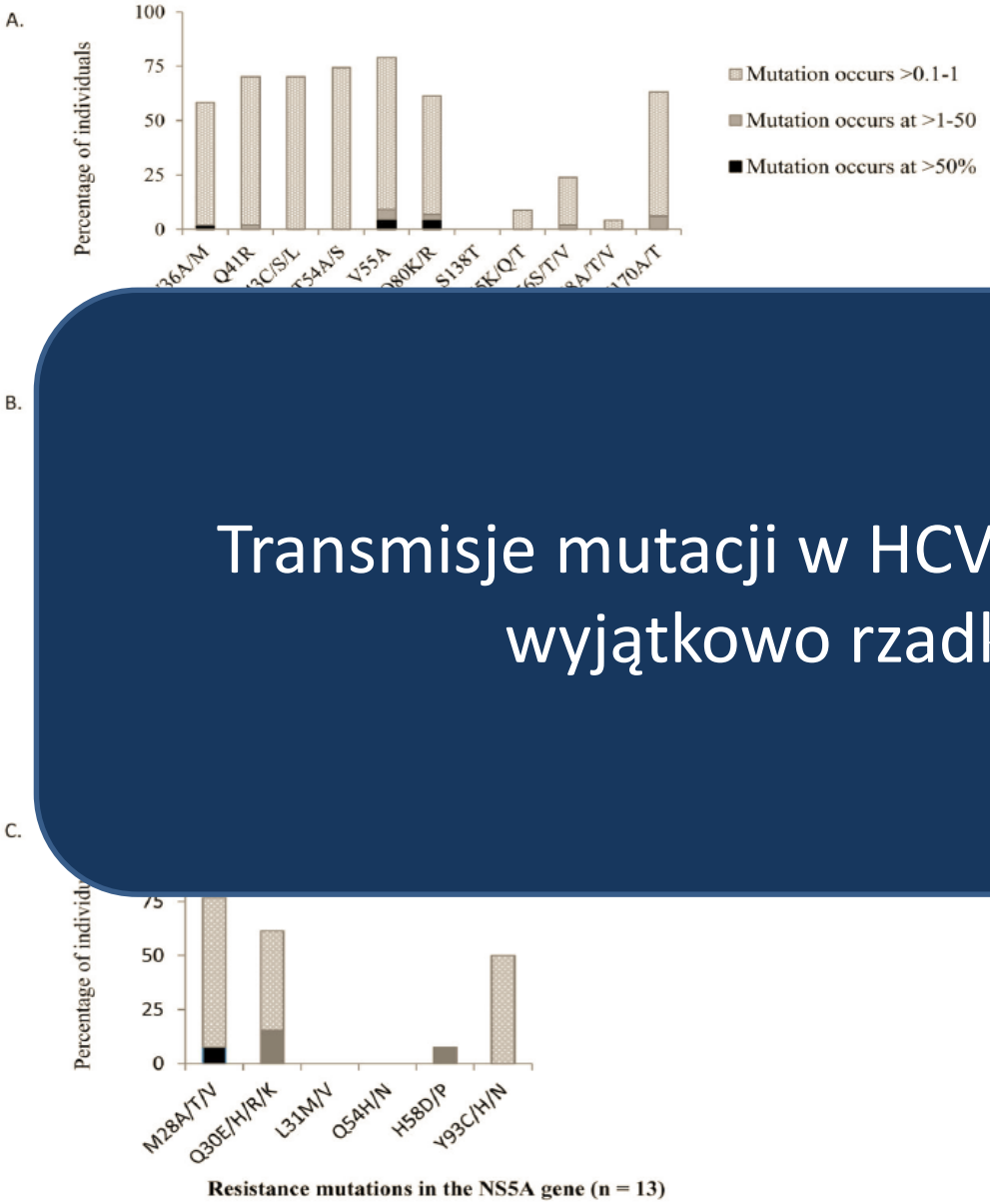
G1A częstsze niż G1B u MSM [34/52(65.38%) vs. 48/96(50.0%), p=0.07] i u osób z przebytą kiłą [18/34 (52.94%) vs. 15/56(26.79%), p=0.01].

Charakterystyka klastrów transmisji

TABLE 2. Characteristics of the Identified Transmission Clusters

Cluster ID	Cluster Size, No. of Sequences	HCV Subtype/ Clade	Observed NS3 RAVs, (%)	Observed NS5 RAVs, (%)	Transmission route (%)†	City of diagnosis‡ (%)	Documented Acute Hepatitis C, (%)	Evolutionary Distance Within the Cluster	Cluster aLRT Support
1	10	1a/I	0	28T (10%)	IDU (100%)	SZ (90%) WR (10%)	0	0.062	0.998
2	8	1a/I	Q80K (75%)	0	MSM (100%)	WA (75%) WR (25%)	100	0.137*	0.932
3	4	1a/II	0	0	MSM (100%)	WA (100%)	100	0.042	0.87
4	6	1a/II	0	0	MSM (100%)	WA (16.6%) SZ (83.4%)	83.4	0.042	0.98
5	4	1b	0	0	IDU (75%), HET (25%)	SZ (100%)	0	0.056	0.865
6	8	1b	0	0	IDU (100%)	SZ (100%)	0	0.077	0.986
7	14	1b	0	0	MSM (100%)	KR (85.7%) WA (14.3%) SZ (7.1%) WR (7.1%)	100	0.076	1
8	3	1b	0	0	IDU (66.6%) MSM (33.3%)	SZ (100%)	0	0.064	0.976
9	4	1b	0	0	IDU (75%) HET (25%)	SZ (100%)	0	0.58	0.995
10	5	1b	0	0	IDU (80%), HET (20%)	SZ (80%) WR (20%)	0	0.041	0.988

Parczewski JAIDS 2018

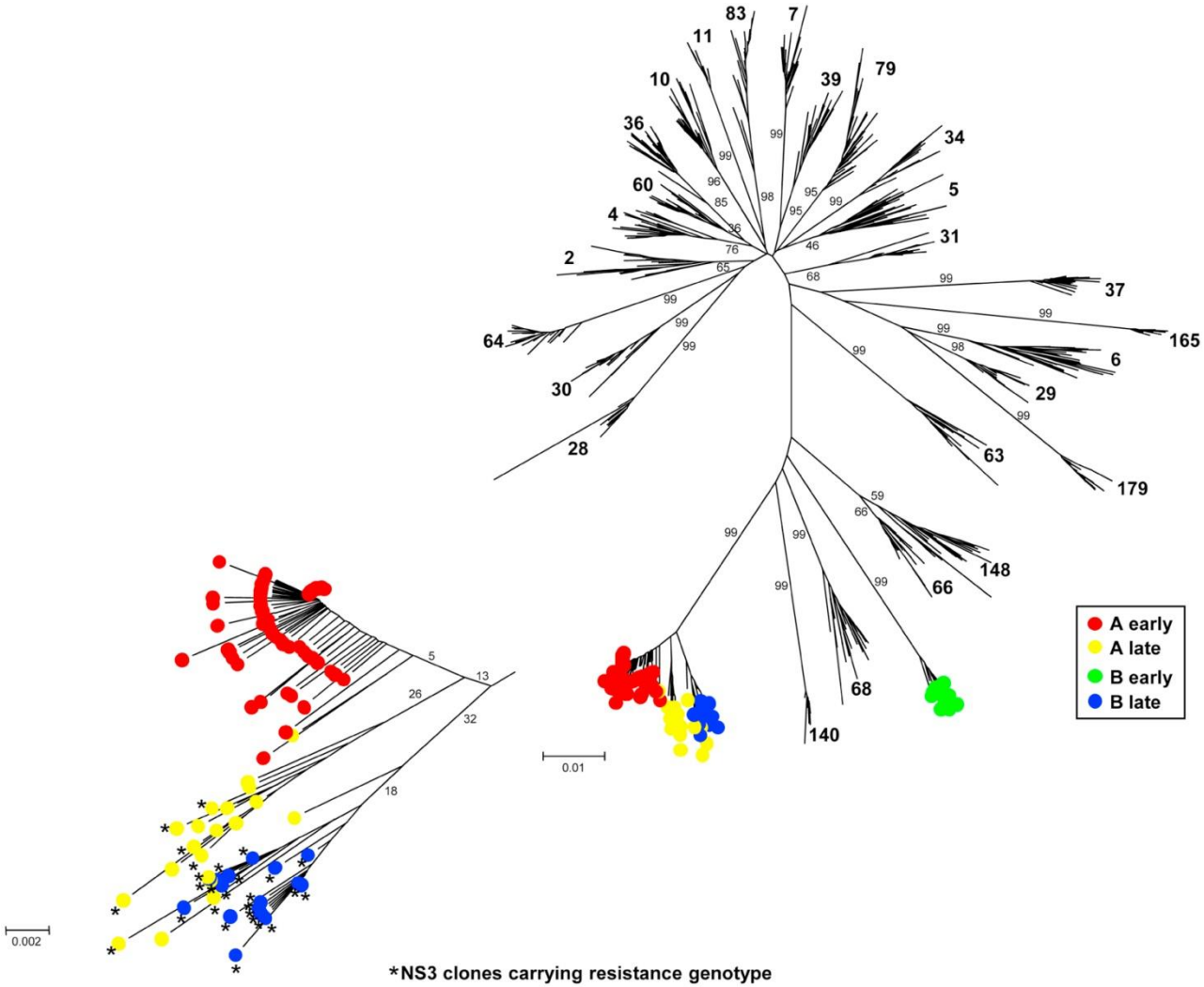


Transmisje mutacji w HCV opisywano wyjątkowo rzadko

2. Percentage of individuals with resistance mutations present in the (A) NS3 protease n=49), NS5B polymerase gene (n=49) and (C) NS5A gene (n=13)

Antivir Ther. 2015 ; 20(2): 199–208. doi:10.3851/IMP2821.

Transmisja lekoopornego HCV (V36M, telaprewir)



Podobne klastry opisują włosi

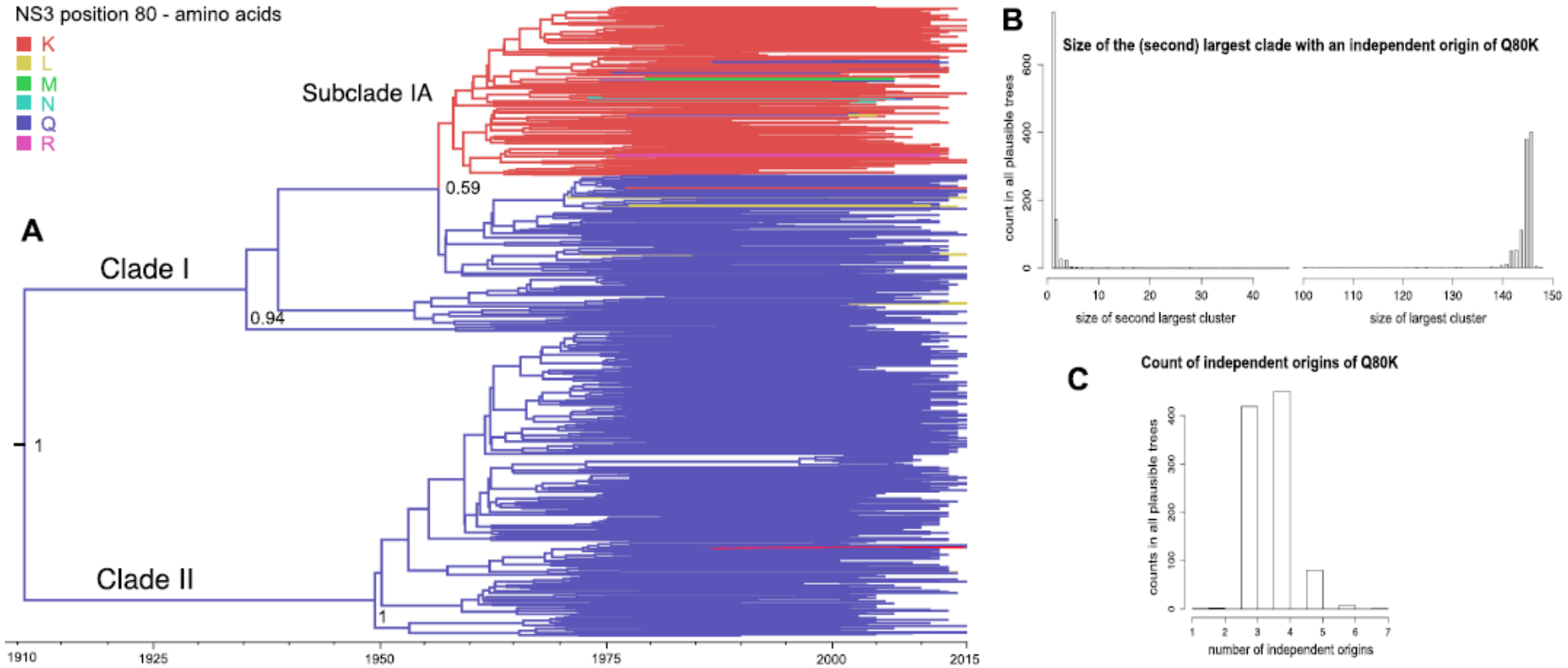


Fig. 3 a: A founder effect dominates the history of the Q80K clade. The branches in the HCV1a MCC tree are colored according to the inferred

Cuypers *et al. BMC Evolutionary Biology* (2017) 17:70
DOI 10.1186/s12862-017-0913-3

Klaster HCV 1a z UK

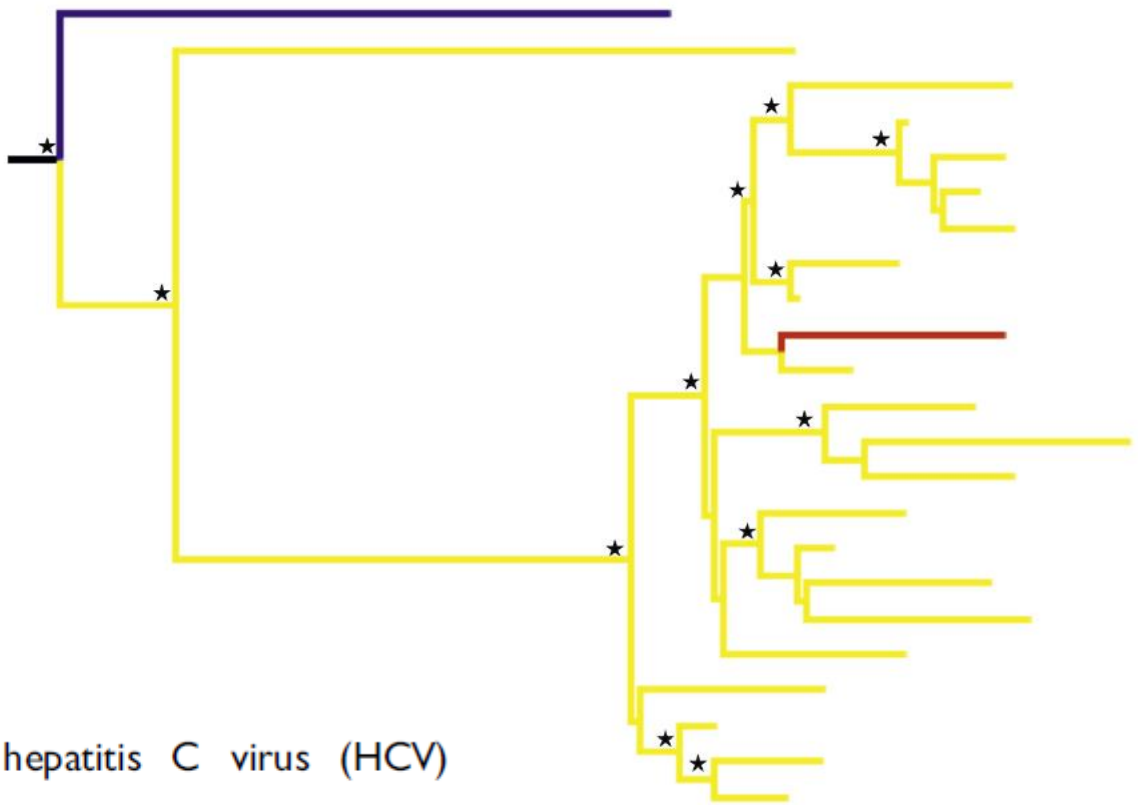


FIG. 2. A hepatitis C virus (HCV) transmission cluster in the South East region of England, comprising 20 HCV-1a

http://dx.doi.org/10.1016/j.cmi.2015.07.017

Zmniejszenie liczby ostrych HCV w Holandii

Characteristic	Patients With Acute HCV Infection		
	2014 (n = 93)	2016 (n = 49)	*P* Value
Age, mean (SD), y	42 (9)	46 (9)	.06
Receiving cART, No. (%)	84 (90)	43 (94)	.53
CD4 cell count, median (IQR), cells/μL	610 (430–810)	620 (465–763)	.86
Reinfection, No. (%)	21 (23)	12 (25)	.75
HCV genotype, No. (%)			
Genotype 1	72 (77)	27 (55)	.02
Genotype 2	2 (2)	1 (2)	
Genotype 3	0	2 (4)	
Genotype 4	18 (19)	15 (31)	
Missing	1 (1)	4 (8)	
HCV genotype 1 subtype, No. (%)			
Subtype a	68 (73)	27 (55)	.57
Subtype b	4 (4)	0	

Figure 1
(HIV)–pos
Percenta
RNA pos
2016. IRR, incidence rate ratio.

Spadek liczby nowych zakażeń HCV u MSM po wprowadzeniu leczenia

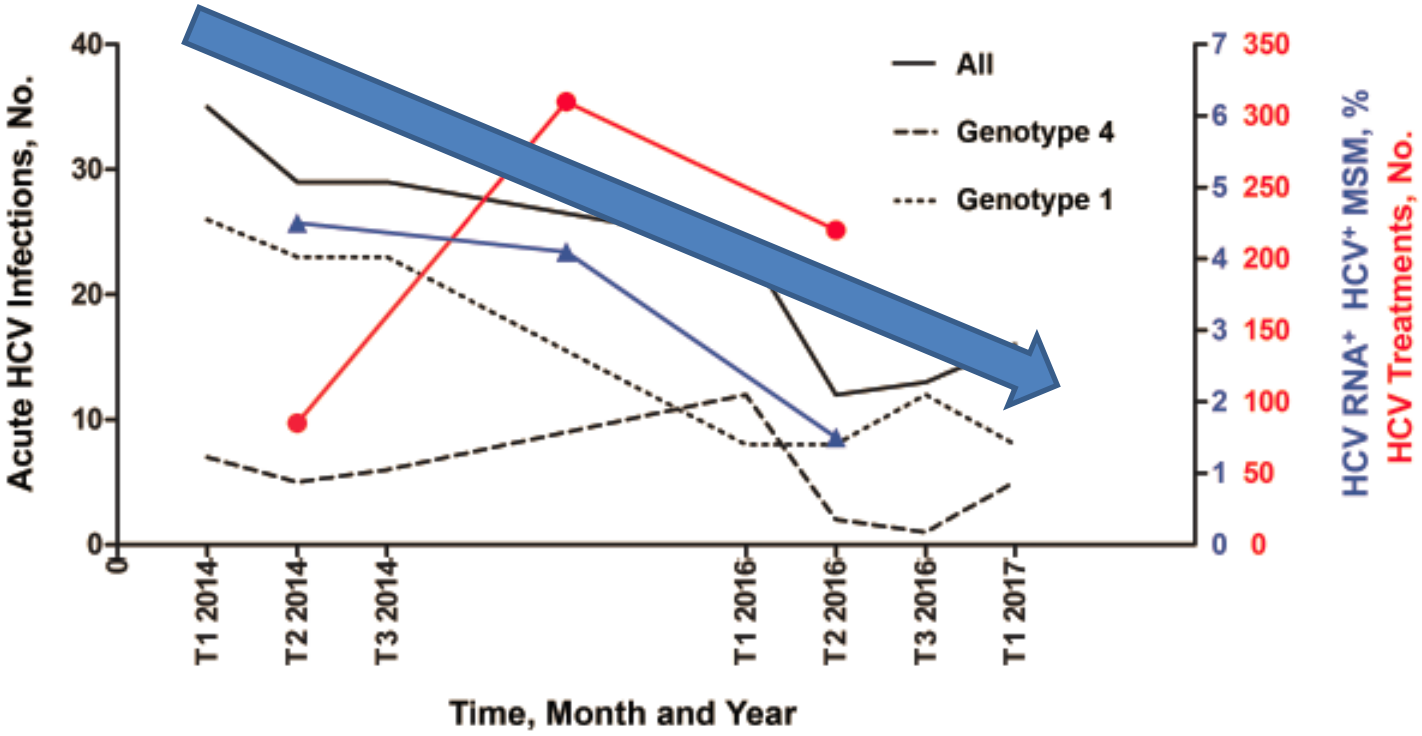
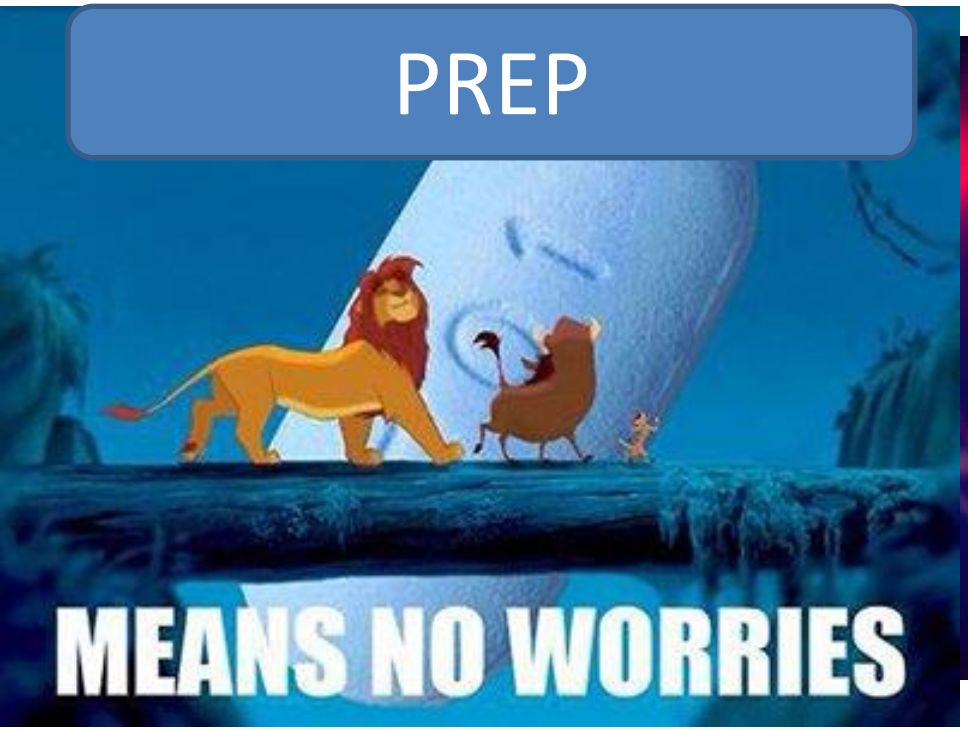
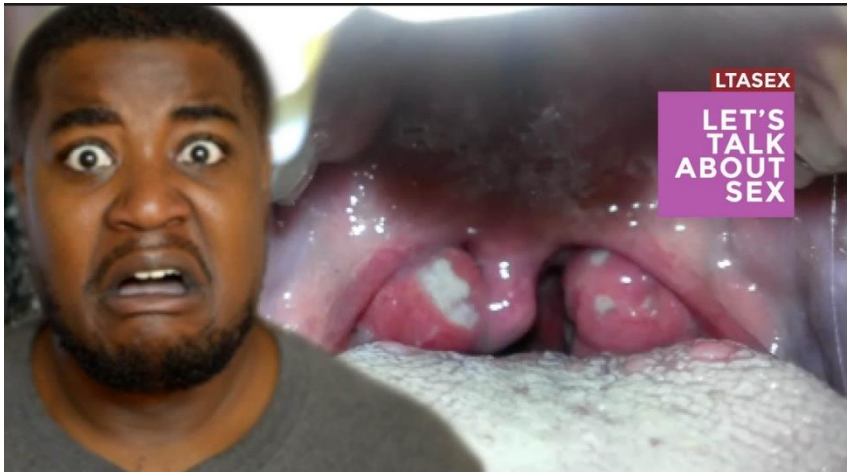


Figure 2. *Left axis,* Acute hepatitis C virus (HCV) infections per 4 months and per genotype. *Right axis,* Percentage of HCV RNA–positive human immunodeficiency virus (HIV)–positive men who have sex with men (MSM) (*blue*) and number of HCV treatments (*red*) in the Netherlands per year (data for both obtained from Stichting HIV Monitoring; personal communication). T1: Jan–Apr; T2: May–Aug; T3: Sept–Dec.



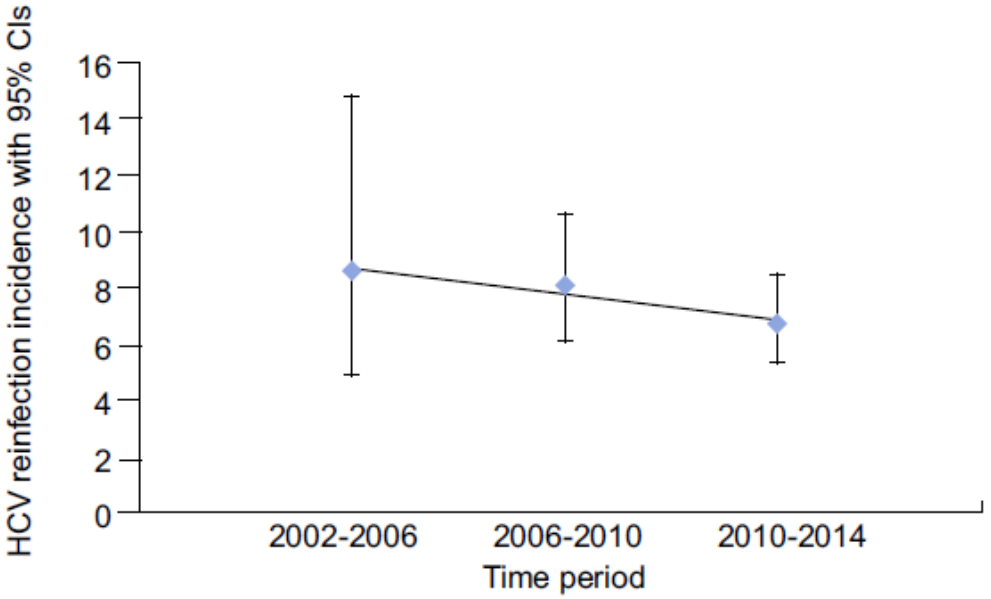


W kohorcie 375 HIV (-) MSM w Amsterdamie 18 (**4.8%, 95% CI:2.9-7.5%)** była a-HCV/HCV-RNA dodatnia; 15/18 (83%) miała wykrywalny HCV-RNA. Genotyp 1a (73%), 4d (20%), i 2b (7

How I caught oral gonorrhea - YouTube

AIDS. 2017 Jul 17;31(11):1603-1610. doi:

Reinfekcje = ostre WZW-C



Time period	Person-years follow-up	Number of reinfections	Reinfection incidence, per 100 py (95% CIs)
2002-2006	151	13	8.6 (5.0-14.8)
2006-2010	666	54	8.1 (6.2-10.6)
2010-2014	1119	76	6.8 (5.4-8.5)

Fig. 2. HCV reinfection incidence in Western Europe over time.

Journal of Hepatology **2017** vol. 66 | 282–287

Reinfekcje a wyleczenie z HCV

	Reinfection, n=41
Median Age [years (SD)]	47 (+/-8.5)
Male [n (%)]	41 (100)
Mode of HCV transmission - IVDU [n (%)] - MSM [n (%)] - MSM + IVDU [n (%)]	 5 (12) 26 (63) 10 (24)
HIV coinfection [n (%)]	34 (83)
Median time to reinfection [weeks (IQR)]	63 (16-180)

Table 2: Characteristics at reinfection

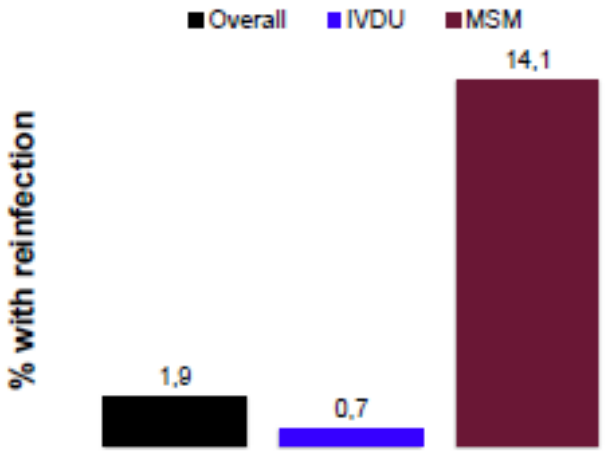


Figure 1: Prevalence of HCV reinfection according to transmission group

The overall follow-up time was 2239 person-years. The median follow-up time in IDUs was 28 weeks with 704 person-years and 73 weeks in MSM with 384 person-years. The HCV reinfection incidence rates are shown in figure 2.

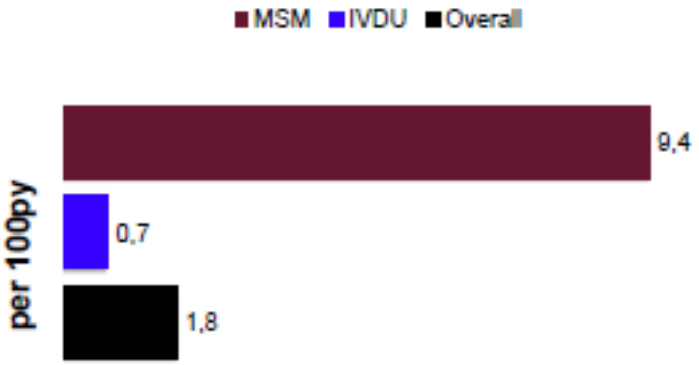
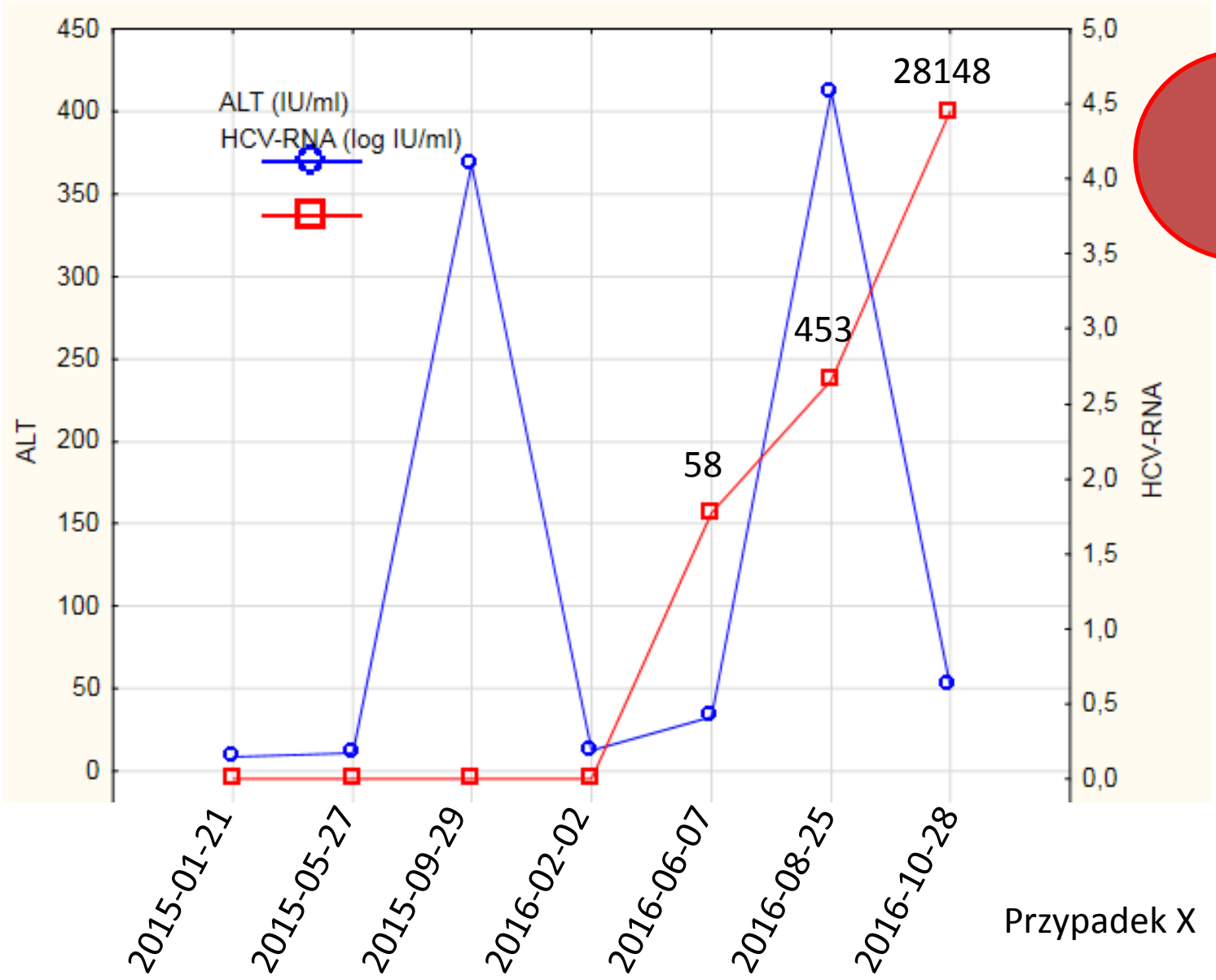


Figure 2: Incidence rate of HCV reinfection according to transmission group

http://CROI 2018, poster 612,

Czy w Polsce mamy reinfekcje? Jasne.



G1a

Przypadek X

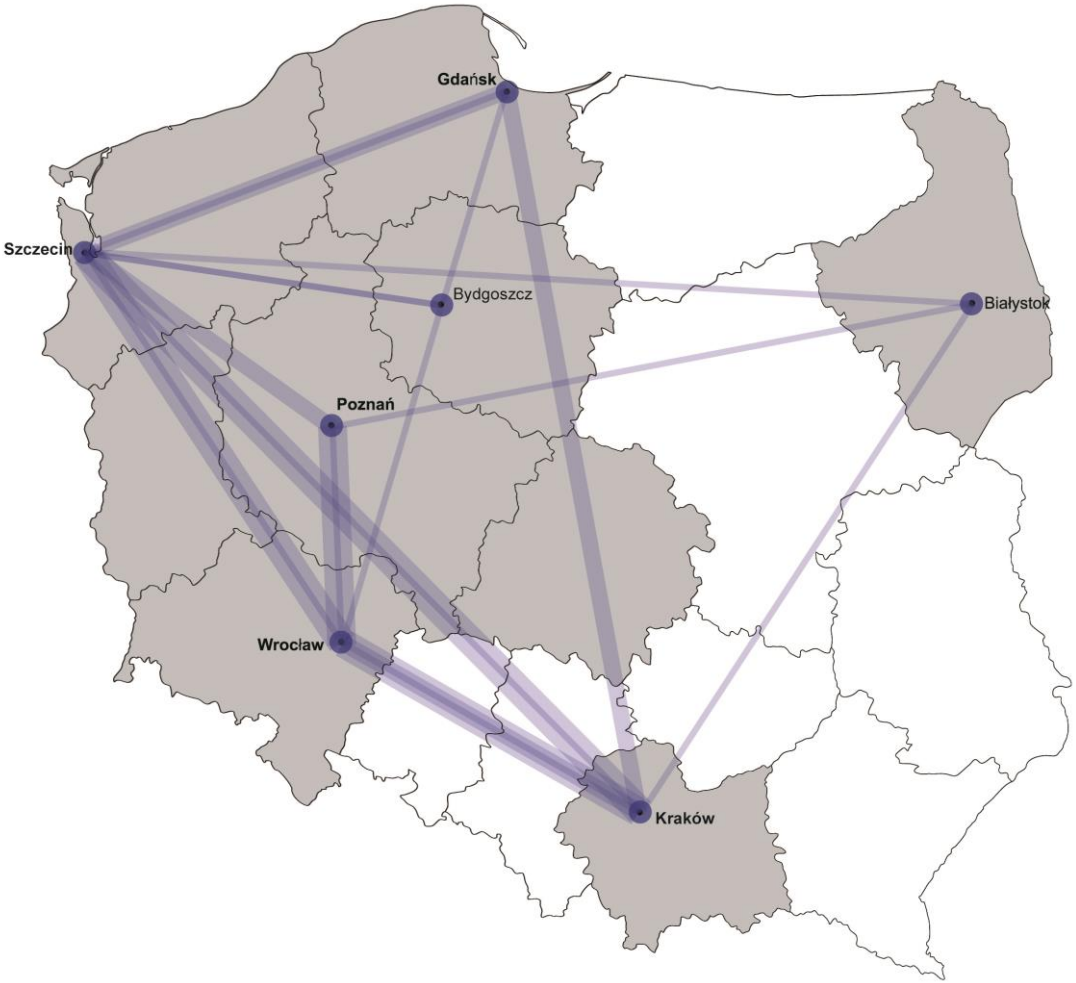
Transmisja jako priorytet

Treatment should be considered without delay in patients with significant fibrosis or cirrhosis (METAVIR score F2, F3 or F4), including decompensated (Child-Pugh B or C) cirrhosis, in patients with clinically significant extra-hepatic manifestations (e.g. symptomatic vasculitis associated with HCV-related mixed cryoglobulinaemia, HCV immune complex-related nephropathy and non-Hodgkin B cell lymphoma), in patients with HCV recurrence after liver transplantation, and in individuals at risk of transmitting HCV (active injection drug users, men who have sex with men with high-risk sexual practices, women of child-bearing age who wish to get pregnant, haemodialysis patients, incarcerated individuals) (**A1**).

EASL guidelines 2016

Filodynamika – sieci transmisji subtypu B (n=966).

Dane molekularne dla 9/15 centrów Polski

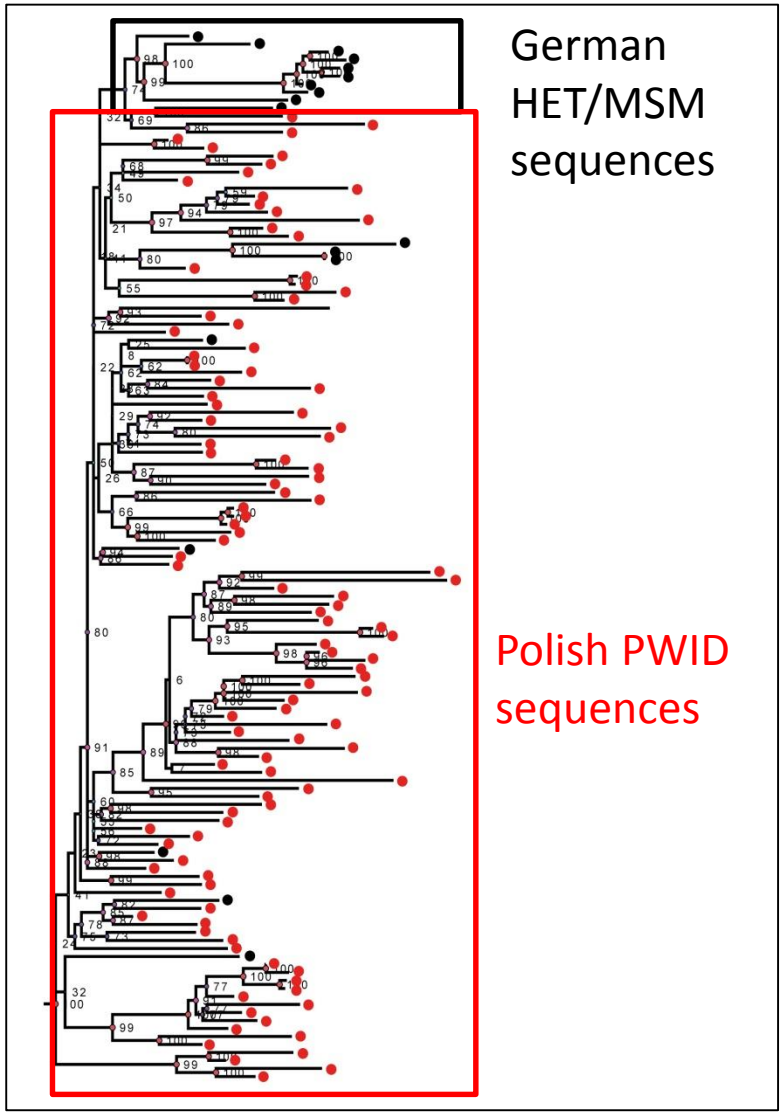


32,2% sekwencji tworzy sieci transmisji

Parczewski i et al. PlosOne 2017, doi: 10.1371/journal.pone.0172473

Dla dodatkowego smaku: Sieci HIV-1 Polsko-Niemiecke

PWID Cluster



German HET/MSM sequences

Polish PWID sequences

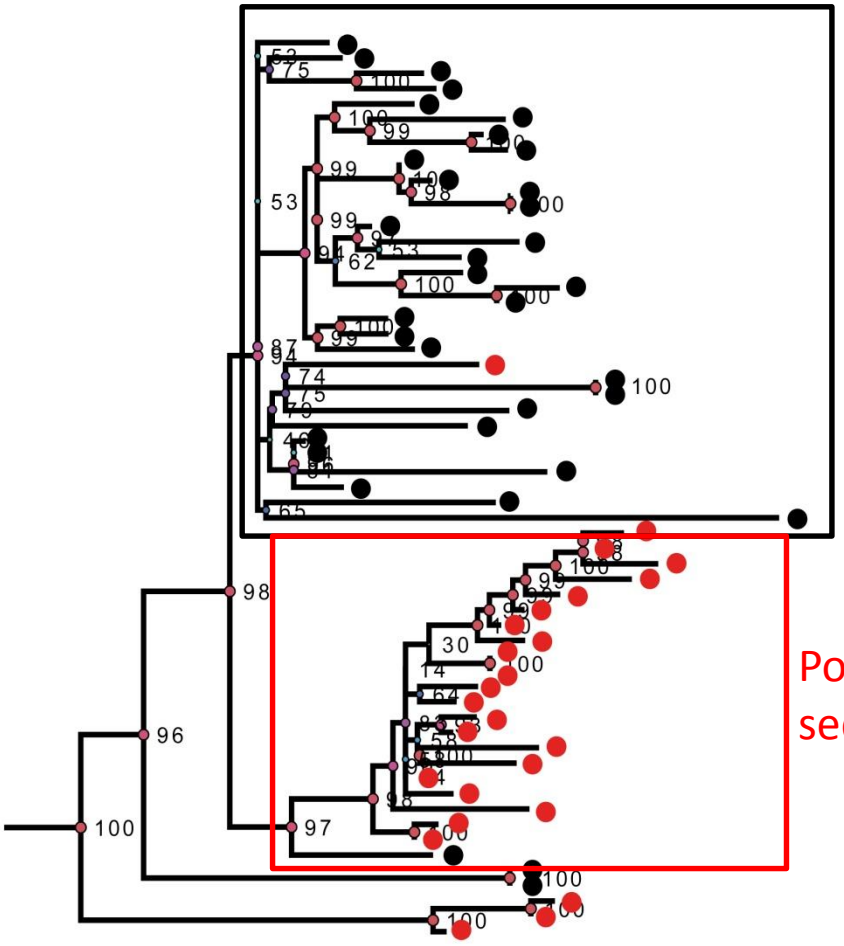
Within the largest cluster (131 taxonomical units) formed by 113 Polish sequences mostly from PWID, a sub-cluster of eight German HET/MSM was found, indicating transmissions from Poland to Germany.

German sequences

Polish sequences

Parczewski i wsp EACS 2017

Różna charakterystyka zmienności w klastrach



German MSM sequences

Polish MSM sequences

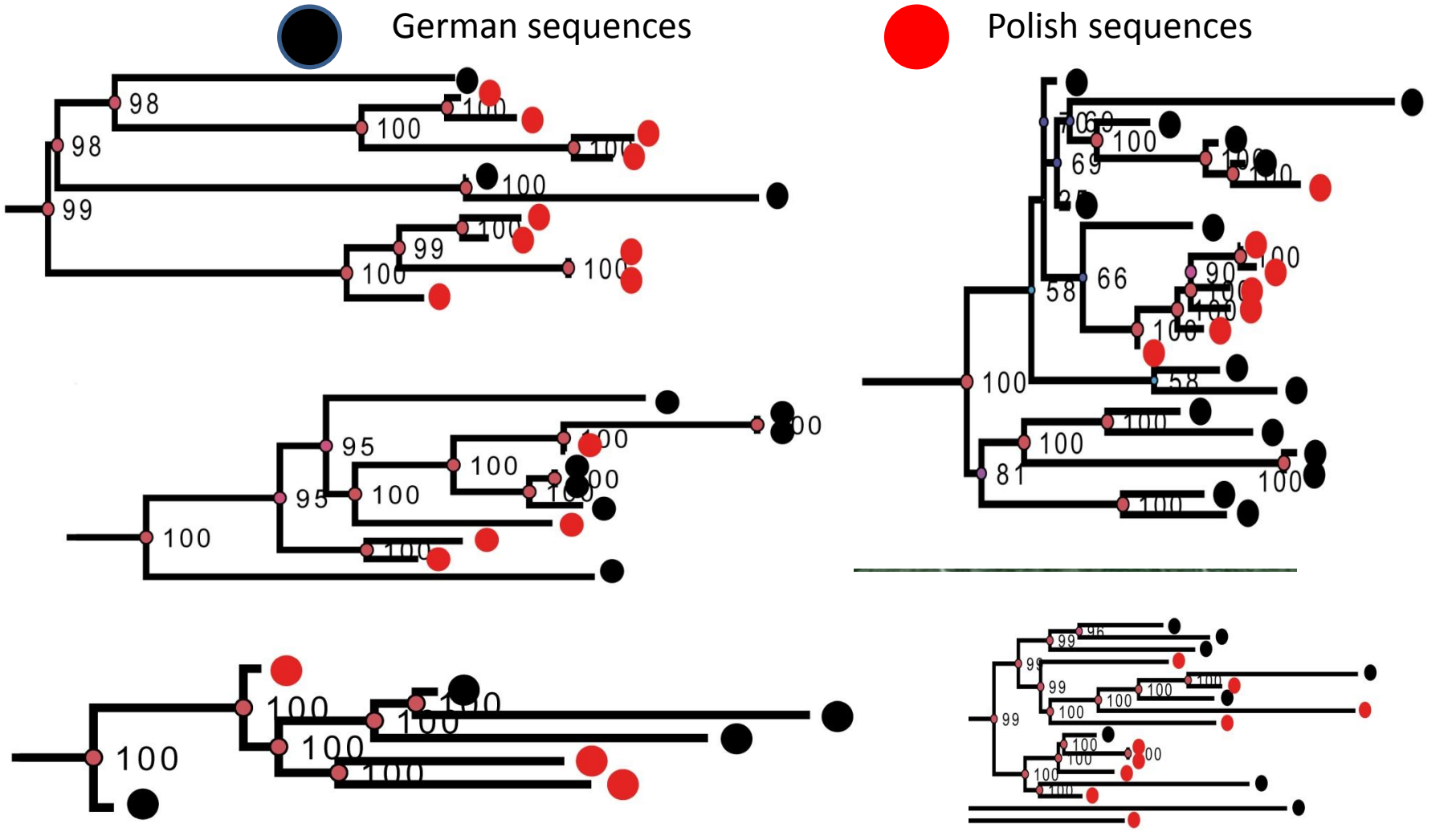
One MSM cluster of common ancestry diverged into separate German (36 sequences) and Polish (23 taxa) clades.

German sequences

Polish sequences

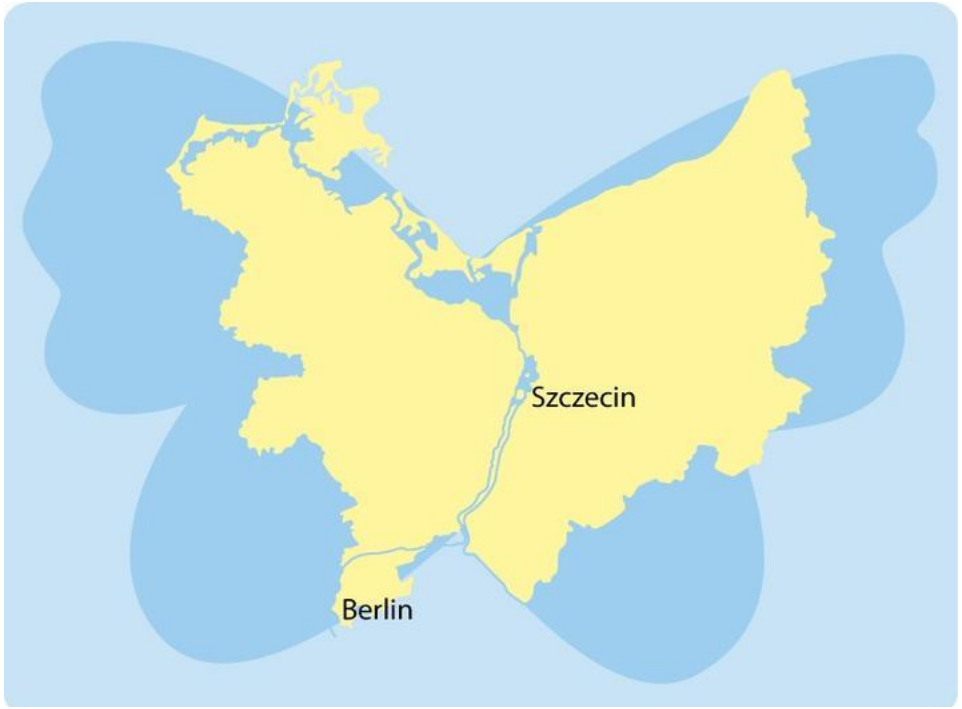
Parczewski i wsp EACS 2017

Przemieszanie sekwencji u MSM



Parczewski i wsp. EACS 2017

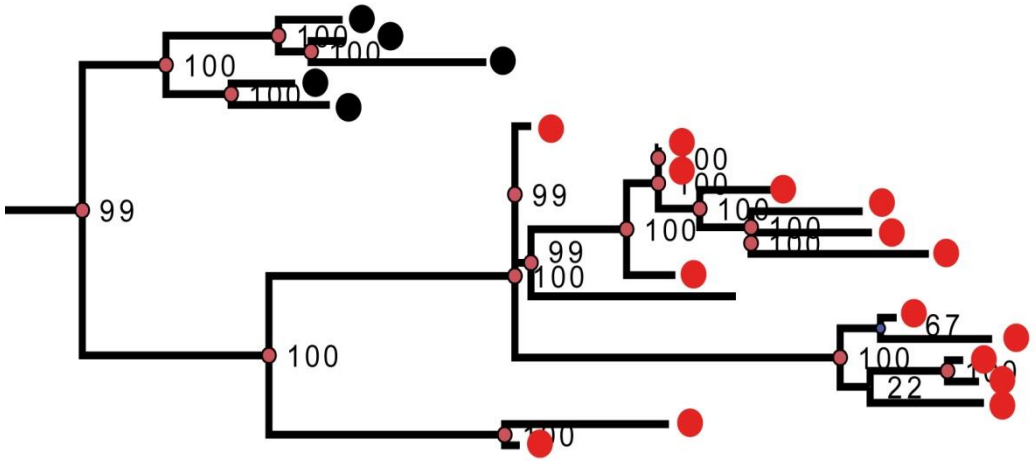
Klaster „turystyczny” Berlin-Szczecin



German sequences

Polish sequences

Oficjalny „klaster turystyczny” (dystans: 170 km)



Klaster MSM Berlin→Szczecin

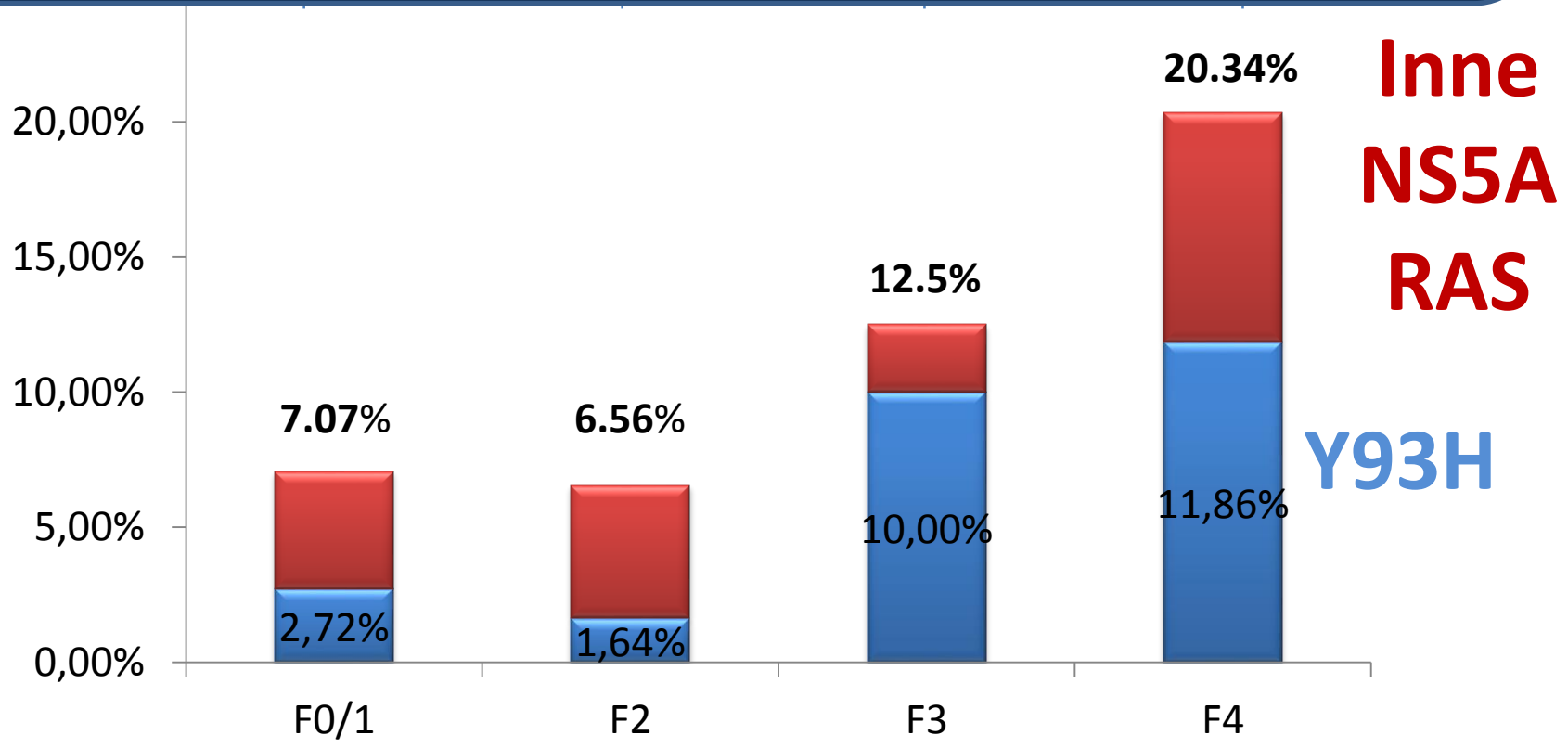
Odpowiedź na pytanie z tytułu:

- Wnioskowanie molekularne wskazuje na dynamikę ostrych HCV w Polsce
- Leczenie w trybie przyspieszonym skutkuje redukcją liczby nowych zakażeń/reinfekcji
- Ostre, seksualne HCV mogą re-introdukować wirus do populacji wyleczonej.

Nieustannie zapraszamy do filharmonii w Szczecinie.
No i do Berlina blisko….

Filharmonia Szczecin, Mies Van Der Rohe Prize for Contemporary Architecture 2015

NS5A RAS w populacji osób nieleczonych HCV w zależności od wyjściowego włóknienia, dane polskie, unpublished, n=344



	F0/1	F2	F3	F4
Present	13	4	5	12
Absent	171	57	35	47
Total	**184**	**61**	**40**	**59**