SIGNS OF LATE HIV DIAGNOSIS AND OUTBREAKS IN TRANSMISSION NETWORKS IN JAPAN

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BACKGROUND

In Japan, approximately 30% of individuals newly diagnosed with HIV infection are identified after the onset of the symptoms of AIDS, suggesting that many people living with HIV (PLHIV) remain undiagnosed. Understanding the factors associated with late HIV diagnosis (LHD), which is a major concern worldwide, is essential for achieving the 95-95-95 goal in Japan. Recently, we have found that LHD in Japan was associated with a transmission clustering pattern. Herein, we present the possibility of identifying clusters involving LHD through transmission-network analysis using our large-scale monitoring of domestic transmission clusters (dTCs) in Japan.

METHODS

The dynamics of dTCs and the network structure of newly diagnosed cases collected by the Japanese HIV Drug Resistance Surveillance Network were monitored by our search program for HIV nationwide clusters by sequence (SPHNCS), which identifies the transmission link by the genetic distance estimated by the protease-reverse transcriptase sequences (Fig 1). In 2021, 566 subtype B and 105 CRF01_AE dTCs were registered in SPHNCS. Consequently, 9,722 newly diagnosed cases between 2003 and 2021 were recruited in this study. We identified their dTC affiliation, network structure, and chronological tree. The relationship of the transmission network patterns to LHD and outbreak involvements, which were recognized by the CD4 count and chronological phylogeny, were investigated.

Fig 1. Overview of SPHNCS
SPHNCS estimates the genetic distance of the polymerase region between a query and the cases collected by Japanese drug resistance surveillance and identifies the domestic transmission cluster (dTC) of the query as the most closely linked neighbor (distance of <1.5%).

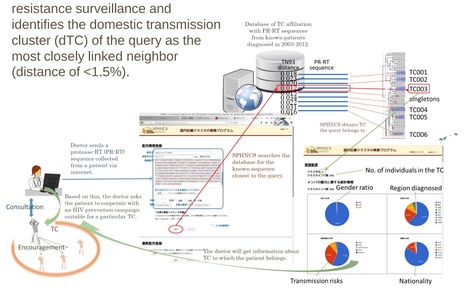




Fig 2. The location of Japanese geographic blocks and the colors that represent them

A decrease in **the transitivity index** in an HIV transmission network **suggests late diagnosis. Furthermore, network density** and the resulting inversion of the degree **distribution indicates an outbreak**. Sequence-based monitoring of transmission clusters, such as SPHNCS, may *efficiently detect these signs*.

RESULTS

We identified seven cases of LHD involving dTCs and seven cases of outbreak that constituted dTCs or subclusters within a dTC. The LHD clusters had lower means of CD4 counts and viral loads than did other patient groups (Tables 1 and 2). While mature transmission networks usually follow the power law, with the lower degree being more frequent (Fig 3A), the outbreak clusters were characterized by the opposite degree distribution and a dense structure of the network (Fig 3B). These were a relatively high ratio of the individuals diagnosed during the acute stage (Table 3). In contrast, networks of the LHD clusters showed star-like structures (Fig 3C). These signs of the presence of untreated LHDs were characterized by a decrease in the transitivity index of the network (Fig 4).

Table 1. Tukey multiple comparisons of mean CD4+ T-cell counts of specific dTCs with remarkable network structure compared to the outliers

Cluster	Cluster's feature	Mean CD4	diff	lwr	upr	p
TC026	Late presenter	228.2	-205.37	-321.98	-88.76	0.000*
TC032	Late presenter	208.5	-154.94	-256.84	-53.04	0.000*
TC034	Late presenter	242.1	-161.02	-270.70	-51.34	0.000*
TC039	Late presenter	244.0	-140.41	-273.18	-7.64	0.026*
TC047	Late presenter	239.6	-232.54	-308.68	-156.39	0.000*
TC165	Late presenter	221.3	-161.71	-271.39	-52.04	0.000*
TC316	Late presenter	192.6	-84.77	-172.17	2.63	0.069#
TC002-subcluster3	Outbreak	287.5	-59.94	-234.98	115.09	0.998
TC003-subcluster2	Outbreak	317.8	-73.23	-316.19	169.72	1.000
TC013	Outbreak	238.4	-39.38	-181.51	102.74	1.000
TC021-subcluster_L	Outbreak	252.5	27.21	-147.83	202.24	1.000
TC021-subcluster_S	Outbreak	290.7	-74.68	-235.50	86.13	0.964
TC340	Outbreak	348.0	-16.05	-194.42	162.31	1.000
AETC2	Outbreak	375.6	-76.27	-201.33	48.79	0.756

* 95% family-wise confidence level, # 90% family-wise confidence level

Table 2. Tukey multiple comparisons of mean viral loads of specific dTCs with remarkable network structure compared to the outliers

Cluster	Cluster's feature	Mean VL	diff	lwr	upr	P
TC026	Late presenter	2.28.E+05	-599.49	-889.07	-309.92	0.000*
TC032	Late presenter	3.31.E+05	-473.10	-726.15	-220.04	0.000*
TC034	Late presenter	1.96.E+06	-491.60	-763.96	-219.24	0.000*
TC039	Late presenter	2.64.E+05	-638.73	-968.44	-309.02	0.000*
TC047	Late presenter	2.67.E+05	-723.18	-912.28	-534.09	0.000*
TC165	Late presenter	6.33.E+05	-430.02	-702.38	-157.66	0.000*
TC316	Late presenter	2.70.E+05	-487.10	-704.14	-270.06	0.000*
TC002-subcluster3	Outbreak	1.50.E+05	-297.52	-732.19	137.14	0.574
TC003-subcluster2	Outbreak	9.51.E+05	-167.35	-770.67	435.98	1.000
TC013	Outbreak	1.89.E+06	-124.49	-477.42	228.44	0.997
TC021-subcluster_L	Outbreak	2.49.E+05	-71.71	-506.37	362.96	1.000
TC021-subcluster_S	Outbreak	6.07.E+05	5.94	-393.41	405.29	1.000
TC340	Outbreak	2.89.E+06	-108.60	-551.53	334.33	1.000
AETC2	Outbreak	5.19.E+05	119.96	-190.61	430.52	0.993

* 95% family-wise confidence level, # 90% family-wise confidence level

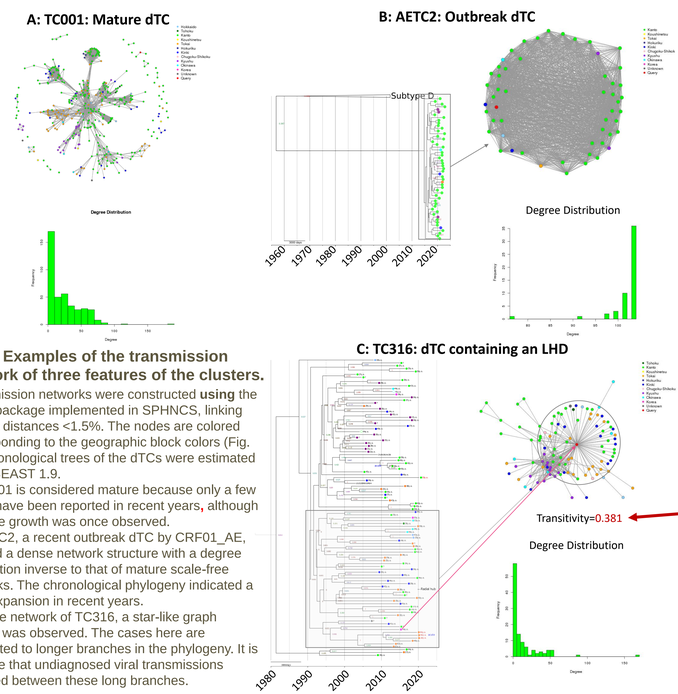


Fig 3. Examples of the transmission network of three features of the clusters.
Transmission networks were constructed **using** the R/sna package implemented in SPHNCS, linking genetic distances <1.5%. The nodes are colored corresponding to the geographic block colors (Fig. 2). Chronological trees of the dTCs were estimated using BEAST 1.9.
A: TC001 is considered mature because only a few cases have been reported in recent years, although massive growth was once observed.
B: AETC2, a recent outbreak dTC by CRF01_AE, showed a dense network structure with a degree distribution inverse to that of mature scale-free networks. The chronological phylogeny indicated a clear expansion in recent years.
C: In the network of TC316, a star-like graph section was observed. The cases here are connected to longer branches in the phylogeny. It is possible that undiagnosed viral transmissions occurred between these long branches.

CONCLUSIONS

Our results indicate that network indices of the HIV transmission clusters may imply involvements in LHD and outbreaks. A decrease in transitivity suggests a late diagnosis and a reversal of the degree distribution is an indicator of an outbreak. This suggests that to promote preventive measures, monitoring the dynamics of dTCs using network analysis may quickly identify a local population where an outbreak occurred, or testing was delayed.

ADDITIONAL KEY INFORMATION

SPHNCS web-site: *https://sphncs.nih.go.jp/*
Access is only available from authorized facilities.

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Acknowledgements:
We are grateful to all the patients who participated in our surveillance project and to all medical staff for the time and effort that they expended in surveillance. We would like to thank the members of the Japanese Drug Resistance HIV-1 Surveillance Network, and Editage (www.editage.com) for English language editing.

Table 3. Transmission network indices of specific dTCs with remarkable network structure

Cluster	Network feature	Density	Degree Centrality	Betweenness Centrality	Transitivity
TC026	Late presenter	0.163	0.314	0.338	0.657
TC032	Late presenter	0.123	0.640	0.500	0.460
TC034	Late presenter	0.222	0.392	0.301	0.659
TC039	Late presenter	0.366	0.457	0.281	0.722
TC047	Late presenter	0.132	0.617	0.231	0.499
TC165	Late presenter	0.151	0.435	0.418	0.602
TC316	Late presenter	0.066	0.734	0.742	0.381
TC002-subcluster3	Outbreak	0.350	0.369	0.252	0.664
TC003-subcluster2	Outbreak	0.238	0.702	0.836	0.590
TC013	Outbreak	0.247	0.524	0.133	0.594
TC021-large_subcluster	Outbreak	0.633	0.363	0.051	0.811
TC021-small_subcluster	Outbreak	0.493	0.370	0.078	0.727
TC340	Outbreak	0.791	0.183	0.026	0.876
AETC2	Outbreak	0.985	0.016	0.000	0.987

t=-3.166, p=0.015*; t=-1.494, p=0.164; t=-1.585, p=0.145; t=-2.480, p=0.030*

* 95% confidence level by Welch's two sample t-test

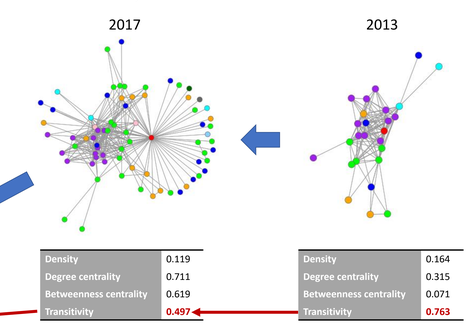


Fig 4. Changes in the network structure and its indices during the growth process of TC316
In 2013, TC316 appeared to have a small outbreak. In 2017, we observed a star-like structure of the network. During this period, there must have been a viral spread involving LHDs. Along **with** this undetected spread, the network showed a decrease in transitivity, which is a measure of the star-like structure; the decrease in **transitivity continues** even now.