Estimation of Recent HIV Infections in Japan Using a Novel Testing Algorithm With Chronological Tree

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BACKGROUND

In Japan, approximately 30% of individuals newly diagnosed with HIV are identified after the onset of AIDS symptoms (Fig 1), suggesting that the diagnosis of people living with HIV is delayed. The lack of a serological avidity assay in Japan's surveillance system makes it difficult to accurately estimate HIV incidence. Therefore, we developed a recent infection testing algorithm (RITA) using the viral sequence-based time of the most recent common ancestor (tMRCA), based on information from our drug resistance surveillance instead of the avidity assay, and investigated the recency of some major domestic transmission clusters (dTCs) in Japan.

METHODS

The Japanese HIV Drug Resistance Surveillance Network has monitored the dTC dynamics of newly diagnosed HIV-1 cases in Japan using our search program for HIV nationwide clusters by sequence (SPHNCS; Fig 2), which stored 10,445 newly diagnosed cases between 2003 and 2022. We extracted the viral sequences and clinical information of three subtype B and one CRF01_AE dTCs prevalent during 2018–2022 (Fig 3) and the singleton cases from SPHNCS and inferred their chronological phylogeny using BEAST1. Based on the tMRCAs between neighboring cases in the phylogeny, CD4+ T-cell count, viral copy number, and possibility of an acute infection, we constructed a RITA estimating the probability of recent or late diagnosis of each case (Fig 4).

We developed a **RITA combining some clinical data with the time since the most recent common ancestor** obtained from a chronological viral gene phylogeny. Of 989 HIV-positive cases, 91 were acutely infected, and 26 and 55 had a 1/2 and 1/3 probability, respectively, of having been infected within 1 year. **The recency of large dTCs from 2018 to 2022 ranged from 23.4% to 28.9%,** while the recency of singleton cases was 10.0%. When **a regional outbreak occurred in a dTC, an increase in the recency was observed**. Until 2019, HIV testing in Japan was used to rapidly diagnosed ongoing local HIV transmission, but this was not the case after 2020. Our results suggest that decreased HIV testing opportunities during **the COVID-19 pandemic caused the decline in diagnoses of recent infections**.

RESULTS

All four targeted dTCs showed men who have sex with men as a major risk factor. Of the 541 cases in the major dTCs and the 448 singleton cases, 91 were acutely infected. A total of 740 chronic cases met the CD4/VL criteria, and the phylogenetic tree suggested that 26 and 55 of these cases had a 1/2 and 1/3 likelihood, respectively, of having been infected within the last year (Fig 4). We counted these cases as recent infections. The recency of major dTCs in 2018–2022 ranged from 23.4 to 28.9%, and the recency of singleton cases was 10.0%. The estimated overall recency was 20.3%. The annual recency for each dTC was typically less than 25%; however, it was >30% in 2018 for B-TC21 and in 2018–2019 for AE-TC2, when outbreaks were observed in a region. The annual recency estimates for the total population consistently decreased from 24.3% in 2018 to 15.7% in 2022 (Fig 5).

CONCLUSIONS

Our results show that before 2019, HIV testing in Japan was used to rapidly diagnose ongoing HIV transmission in some local at-risk populations, but this was not the case after 2020. As the number of positive cases decreased, HIV testing opportunities also decreased during the COVID-19 pandemic, which may have been a barrier to early detection. The decline in diagnoses of recent infections suggests a problem with the testing system in Japan.

ADDITIONAL KEY INFORMATION

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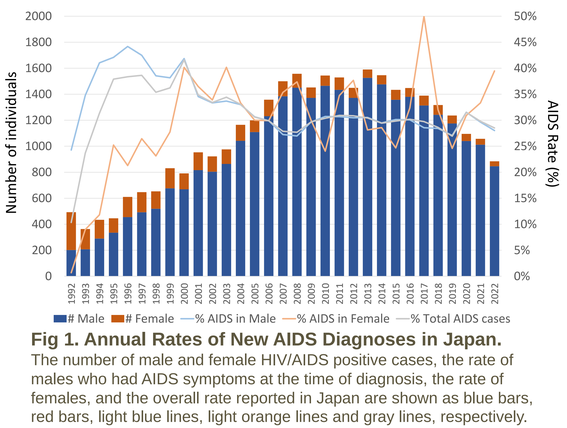


Fig 1. Annual Rates of New AIDS Diagnoses in Japan.
The number of male and female HIV/AIDS positive cases, the rate of males who had AIDS symptoms at the time of diagnosis, the rate of females, and the overall rate reported in Japan are shown as blue bars, red bars, light blue lines, light orange lines and gray lines, respectively.

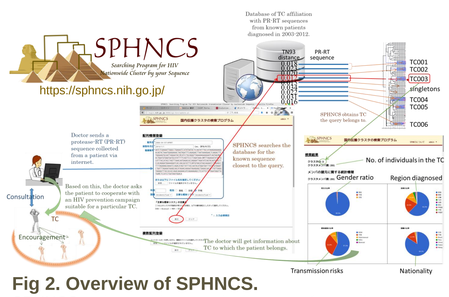


Fig 2. Overview of SPHNCS.
SPHNCS estimates the genetic distance of the polymerase region between a query and the cases collected by Japanese drug resistance surveillance and identifies the domestic transmission cluster (dTC) of the query as the most closely linked neighbor (distance of <1.5%).

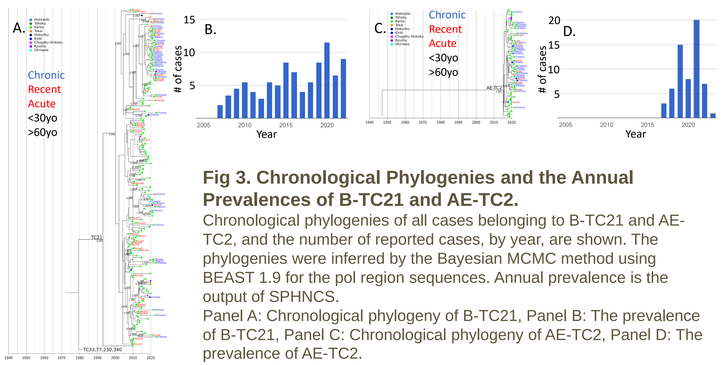


Fig 3. Chronological Phylogenies and the Annual Prevalences of B-TC21 and AE-TC2.
Chronological phylogenies of all cases belonging to B-TC21 and AE-TC2, and the number of reported cases, by year, are shown. The phylogenies were inferred by the Bayesian MCMC method using BEAST 1.9 for the pol region sequences. Annual prevalence is the output of SPHNCS.
Panel A: Chronological phylogeny of B-TC21, Panel B: The prevalence of B-TC21, Panel C: Chronological phylogeny of AE-TC2, Panel D: The prevalence of AE-TC2.

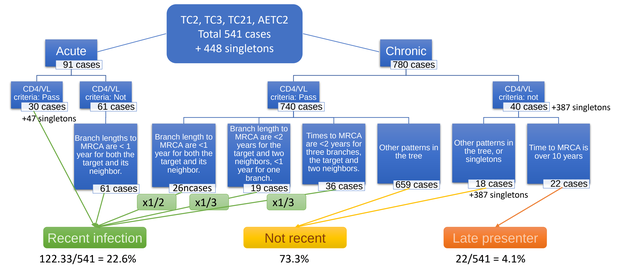


Fig 4. Flowchart of the RITA using tMRCA and the Clinical Data.
Our RITA first considers the presence of the acute infection, then considers CD4/VL criteria where CD4+ T cell > 200 /μl and viral load > 1,000. Finally branch lengths from a target case or its neighbors to the recent node (MRCA), which is collected from the chronological phylogeny, are evaluated. In some categories, it is unknow which targets and neighbors are 'recent', so the values are weighted, which are shown in the green boxes, according to their posterior probability of a target recency.

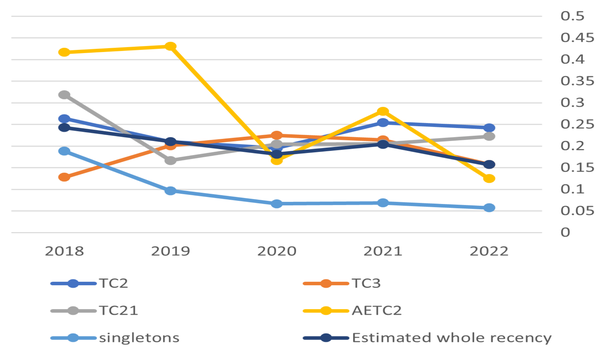


Fig 5. Annual Recency of Major Four dTCs and Singleton Cases in Japan.
Rates of the recent infection cases, which were computed using our RITA, of four dTCs and singleton cases are shown by the colored lines. Whole recency was estimated by taking the unbiased mean of the four dTCs as the recent rate of the other dTCs and then weighting the recent rates of the dTCs and singletons by their occupancies.