Large MSM Group and Local Heterosexual Transmission Are Major Concerns on HIV Epidemic in Japan

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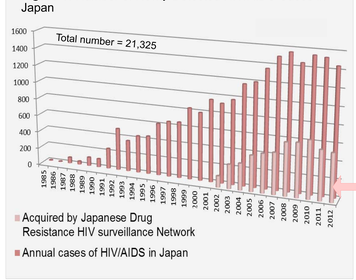
Abstract

Background:
To clarify HIV transmission dynamics from a large collection of viral sequences, a useful tool is phylodynamic analysis. We used this tool to analyze HIV pol sequence data from our nationwide surveillance network to reveal the dynamics of HIV transmission in Japan.
Methodology:
Nucleotide sequences of the protease-reverse transcriptase (RT) gene were obtained from 4393 newly diagnosed HIV patients in 2003-2011. These sequences were then aligned with subtype reference sequences retrieved from the HIV database, and subtypes belonging to each sequence segment were determined using similarity plot analysis against subtype references. Domestic transmission clusters (infection networks) were identified by combined monophyly evaluation using three different phylogenetic methods: neighbor-joining method with interior branch test, maximum likelihood method, and Bayesian Markov chain Monte Carlo (MCMC) method. Chronological phylogeny, median time of the most recent common ancestor (tMRCA), and basic reproductive number (R0) were also inferred by Bayesian MCMC coalescent analysis using BEAST1.7.4.
Results:
The predominant subtypes in Japan (with number of patients and prevalence) were subtype B (n=3899: 88.8%) and CRF01_AE (n=344: 7.8%). Other minor subtypes were found: C (n=46), CRF02_AG (n=36), G (n=15), F (n=9), CRF06_cpx (n=3), CRF07_BC (n=2), and CRF12_BF (n=2), and CRF33_01B (n=2). Subtypes D, CRF08_BC and CRF28 or 29_BF were detected in one patient. Another 32 patients had unknown forms of intra-subtype recombinants. Phylodynamic analysis yielded four major findings. 1) Although tMRCAs of a few infection networks of subtype B dated to the 1980s, many had spread between men having sex with men (MSM) from the second half of the 1990s. 2) CRF01_AE was also transmitted into Japan through heterosexual and intravenous drug user routes in the 1990s. 3) In the 1990s, minor subtypes and recombinant viruses also colonized in some groups that mingled with foreigners. 4) In the 2000s, CRF01_AE was also transmitted to MSM communities and might have generated some domestically circulated recombinants between subtypes 01_AE and B. R0 of subtypes B, C, F and CRF01_AE in Japan (3.3, 3.2, 2.1, and 3.7, respectively) did not differ significantly, but the R0s of subtypes G and CRF02_AG (7.7 and 6.9) were significantly higher than those of other subtypes.
Conclusions:
These results suggest that a large MSM community with intra-subtype recombinants and a local population network with high infectivity females are major concerns in Japan.

Background

Figure 1: Number of Newly Detected HIV/AIDS Cases in Japan



- The first HIV-1 infected case was found in Japan in 1985.
- Number of cases has reached more than 20,000 so far.
- Japan HIV drug resistance surveillance database covers nearly 40% of reported HIV cases in Japan.
- This large-scale data allowed us to use 'phylodynamics' to assess HIV transmission dynamics in Japan.

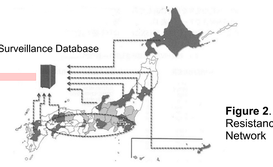


Figure 2. Japan Drug Resistance HIV Surveillance Network

Materials and Methods

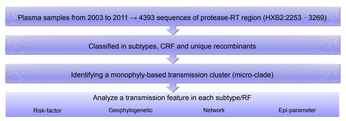


Figure 3: Chart of an analyzing process in this study

- 4,393 sequences of protease-RT region in our surveillance from 2003 to 2011 were enrolled.
- Monophyly-based transmission clusters were identified in these sequences by method described in Figure 4.
- The clusters were analyzed by Bayesian MCMC method to infer a clade-credibility trees, times of most recent common ancestor (tMRCA) and basic reproductive numbers (R0).

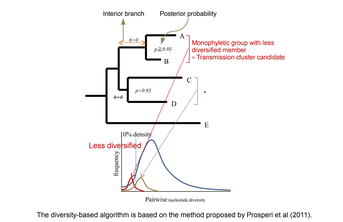


Figure 4: How did we identify a candidate for transmission cluster

Transmission cluster candidate must show monopyly and share less diversified genes, so...

1. Make a common topology from 3 different trees (NJ, ML and Bayesian MCMC).
2. Statistically significant phylogenetic clusters were searched by depth-first algorithm.
3. Test of monophyly using the interior branch test in NJ tree and a posterior probability in Bayesian MCMC.
4. The distributions of all pairwise distances in the given phylogeny were calculated, and select the median value of genetic distance between each pair of sub-tree members being lower than the 10th percentile density (see left panel).
5. A specific sub-tree fulfilling criteria 2-4 was identified as “micro-clade”.

Results

1. The predominant subtypes in Japan were subtype B and CRF01_AE.

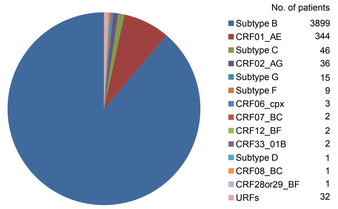


Figure 5: Prevalence of HIV-1 subtype in Japan

- The predominant subtype circulating in Japan is subtype B followed by CRF01_AE.
- These two subtypes represent 97% of circulating strains in Japan.
- Other subtypes, CRF and URF account for 3% of HIV infections.

2. tMRCAs of Transmission Cluster Candidates in Japan Showed an Introduction History of HIV-1 to Various Risk populations in the Country.

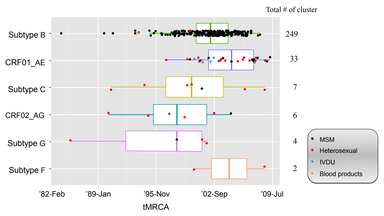


Figure 6: Distribution of tMRCA of the transmission cluster candidate detected in Japan

The graph shows the distribution of tMRCA of the transmission clusters in Japan. Dots shows a cluster's tMRCA colored by main risk factor of the cluster.

- Subtype B had mainly spread among the MSM community from the second half of the 1990s.
- CRF01_AE was transmitted in Japan through heterosexual and IVDU routes in the 1990s.
- CRF01_AE was also transmitted to MSM community in the 2000s.
- Viruses with the minor subtypes spread mainly in the heterosexual group.

3. A Number of Unique Recombinants Between B and 01_AE were Found in Japan.

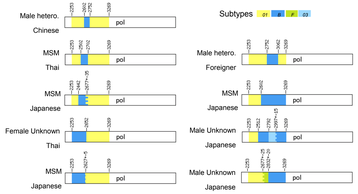


Figure 7: Recombination structures of partial pol region found in Japan

- We found at least 9 different forms of unique B-E recombinants in protease-RT region.
- These URFs indicated that there were high-risk populations which were concurrently infected by B and CRF01_AE.

See also:
P-B3-229 Hosaka, M. et.al.
CRF01_AE and Subtype B Transmission Networks Cross Over; A New AE-B Recombinant Emerges in Japan.

4. R0 of CRF02_AG and Subtype G were Significantly Higher Than Others.

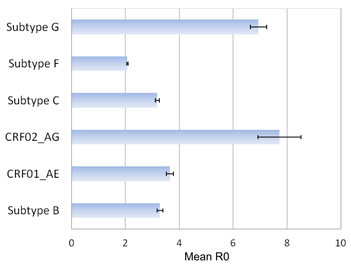


Figure 8: Mean R0 of the transmission cluster for subtypes

- Mean R0 estimates of the transmission cluster in Japan were inferred by a sequence-based inference developed by *Stadler et al* (2011).
- The R0 for subtype G and CRF02_AG were at least 3-fold higher implying that these viruses could be more easily transmitted.

4. The High-R0 Subtypes had a Biased Transmission Network toward Female.

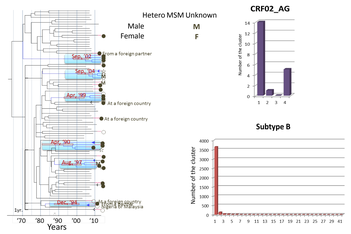


Figure 9: Maximum clade credibility tree of CRF02_AG in Japan with histograms of a number of patients in the transmission cluster

- 5/6 clusters consisted of four patients, in which female patients from a same geographic region dominated.
- The histogram showed that a transmission network of subtype B was scale-free, but 02_AG was not.
- These results implied an existence of "hyper-active" male spreaders in CRF02_AG transmission network in Japan.

5. MSM and IVDU Showed higher R0 Than Other Risk Behaviors at CRF01_AE Infection.

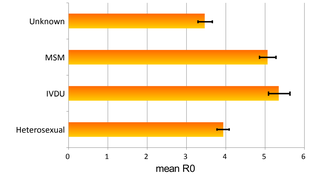


Figure 10: Mean R0 of each risk behavior

- The R0 for MSM and IVDU were higher implying that these risk groups could be more easily transmitted the CRF01_AE virus in Japan.

6. MSM Transmission Networks Varied in R0 That was Not Associated to their tMRCA, Size nor Region.

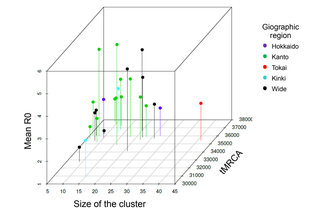


Figure 11: Relationship between mean R0, tMRCA and size in subtype B-infected MSM transmission clusters.

Color of a symbol showed a geographic region where the cluster member mainly collected.

- Mean R0 and tMRCAs of MSM transmission clusters with more than 5 male patients were estimated.
- Mean R0 estimates varied in the range from 1.14 to 5.44.
- No significant associations were found between R0 and patient's characteristics.

Summary

- Subtype B was the predominant in MSM.
- CRF01_AE was in the heterosexual and IVDU groups.
- CRF01_AE became established in the MSM community later.
- The minor subtypes were observed in some groups where the risk factor was foreign partners.
- Basic reproductive numbers (R0s) were larger in subtype G and CRF02_AE where heterosexual transmission by a few male spreaders.
- R0s were larger in IVDU group.
- Mean R0s in MSM transmission clusters varied.
- Concerns about HIV transmission in Japan are follows:
  - Large transmission clusters in MSM communities
  - Development of intra-subtype recombinants between B and CRF01_AE
  - Local heterosexual transmission enhanced by “hyper-active” male spreaders