INCIDENT INFECTION IN HIGH-PRIORITY HIV MOLECULAR TRANSMISSION CLUSTERS

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Background

- HIV-1 molecular sequence data can identify people with direct or indirect epidemiological connections in a public health surveillance setting[1]
- Molecular transmission clusters with recent and rapid growth disproportionately contribute to future cases of HIV diagnosis[2,3]
- This cluster growth can be due to:
  - **previously undiagnosed infections:** HIV transmitted prior to cluster identification, but diagnosed afterwards
  - **incident infection:** HIV transmitted after cluster identification
- **It is unclear the extent to which infections in clusters with recent and rapid growth are due to transmission from:**
  - **Diagnosed but virally unsuppressed cases, or**
  - **Previously undiagnosed cases**

Methods

- Sequences reported to U.S. National HIV Surveillance System for diagnoses occurring in 2010–2017
- Restricted to 6 jurisdictions with ≥50% genetic sequence completeness: CT, MI, NY, SC, TX, and WA

Baseline Analysis

- Using data from cases diagnosed from 2010–2012, used HIV-TRACE[4] to construct molecular transmission clusters using partial *pol* (genetic distance ≤0.005 substitutions/site)
- Identified priority clusters with recent and rapid growth: ≥3 cases diagnosed in 2012
- Determined number of unsuppressed individuals (viral load ≥200 copies/ml or no reported lab in previous year) in cluster at time of prioritization (end of 2012)

Follow-Up Analysis

- Examined cluster growth by re-running HIV-TRACE using sequences from cases diagnosed through 2017 (5 years follow-up) in these 6 jurisdictions

Phylogenetic Approach

- Constructed time-trees using BEAST[5]
- Inferred time of most recent common ancestor (TMRCA) for each cluster using a fixed substitution rate prior
- Identified clusters with post-2012 internal node ages, which are indicative of **incident infections** (**Figure 1**)

Regression Analysis

- Performed multivariate logistic regression analysis in which outcome was ≥1 inferred incident infection
- Cluster level attributes (epidemiologic, phylogenetic, and demographic) were included as covariates

Identifying Incident Infections

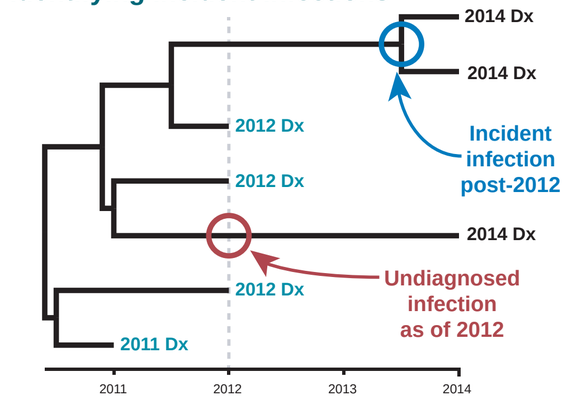


Figure 1. Phylogenetic approach for identifying clusters with new, incident infections added after identification in 2012 (dashed line). Original members of high-priority cluster (dx'd ≤2012) highlighted in green. New members added to priority cluster (dx'd ≥2013) shown in black. Internal nodes post-dating 2012 are evidence for incident infection. Branches that extend before 2012 are evidence that a new case was potentially infected, but undiagnosed in 2012.

Priority Clusters at End of 2012

- 19,511 cases diagnosed between 2010–2012 with a reported partial *pol* sequence
- 116 priority clusters, comprising 759 total cases, were identified in December 2012 (Figure 2)
- 31% clusters were majority (≥50%) Black/African American; 25% were majority Hispanic/Latino; and 27% were majority White
- 86% clusters had majority MSM (men who have sex with men)

Cluster Growth During 2013–2017

- 641 newly diagnosed cases were added to these clusters through 2017
- 91 (78%) clusters added ≥1 new case through 2017
- 73 (63%) clusters had phylogenetic evidence for a new incident case through 2017
- The number of unsuppressed cases in 2012 and the number undiagnosed in 2012 were significantly associated with incident cluster growth (**Table 1**)

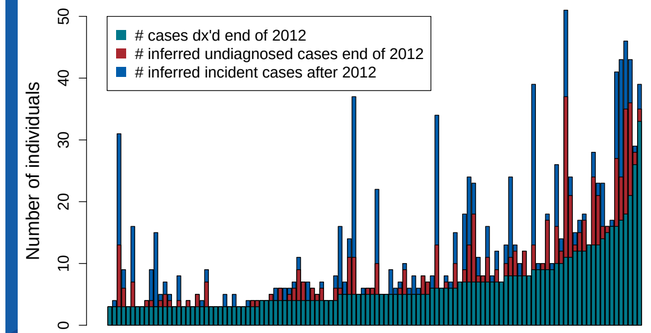


Figure 2. Priority clusters identified at end of 2012, sorted by cluster size in 2012. Number of diagnosed cases in cluster at time of prioritization shown in green. Number of cases inferred to be undiagnosed at time of prioritization shown in red. Number of cases inferred to be incident infections after prioritization shown in blue.

Table 1. Predictors of clusters with ≥1 incident infection between 2013–2017 in priority clusters in multivariate logistic regression model

Cluster attribute as of end of 2012	aOR	95% CI	*p*-value[1]
# diagnosed but unsuppressed	1.57	1.03–2.58	0.049
# undiagnosed	1.57	1.11–2.48	0.027
Cluster size	1.32	0.97–1.87	0.093
Time of most recent common ancestor	0.71	0.50–0.93	0.033
Median viral load	1.06	0.79–1.42	0.688
Majority[2] men who have sex with men	0.20	0.04–0.88	0.043
Majority[2] Hispanic/Latino	1.07	0.24–4.71	0.403
Majority[2] Black/African American	1.94	0.41–9.51	0.930
Majority[2] White	0.47	0.11–1.98	0.304

aOR, adjust odds ratio of ≥1 incident infection in cluster; CI, confidence interval
[1]Attributes significantly associated with subsequent incident case highlighted in red
[2]Representing more than 50% of individuals in the cluster

Conclusions

- New infections in priority clusters are equally associated with previously diagnosed, un-suppressed cases and undiagnosed infections
- Priority clusters with older TMRCAs (as of 2012) are less likely to give rise to incident infections
- Cluster size did not have a significant association with incident growth in priority clusters
- Priority clusters in which the majority of individuals were MSM were less likely to be associated with incident infection

Implications

- These results highlight the importance of promoting both retention in care and viral suppression as well as partner notification and other case-finding activities when investigating and intervening on priority molecular transmission clusters.

References

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