Using real-time phylogenetic analysis to assess and guide public health interventions in an HIV outbreak among people who inject drugs in Scotland

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background

- People who inject drugs (PWID) are at high risk for HIV acquisition if they share equipment or have unprotected sex.
- Harm reduction in the UK and the rest of Europe dramatically decreased incidence in this group in the 1980s.
- Recently a number of HIV outbreaks among PWID have been reported in Europe2, linked to the economic recession, funding cuts, homelessness and the injection of new psychoactive substances.
- In 2015 a rise of subtype C HIV diagnoses with two drug resistant mutations among PWID was noted in Scotland.
- All 104 sequences were closely linked (≤0.01 substitutions per site), had both mutations and mean transmission intervals were <6 months.
- The utility of phylogenetic analysis to detect clusters of HIV infections and subsequent public health response has been demonstrated4.
- Given the scale of the current outbreak, we want to use molecular epidemiology to help guide public health interventions during an ongoing outbreak3 with a particular focus on contact tracing investigations.

methods

2. Source Attribution

- We are displaying transmission events >70% probability of being direct.
- The timing of each transmission event can be estimated from the phylogeny.
- Source Attribution can be used to find individuals associated with the highest number of transmissions over time:
  - Here, 25% of individuals were responsible for >50% of onward transmissions.
- Individuals with recent onward transmissions can be contacted to ensure they are on suppressive treatment and their partners are on pre-exposure prophylaxis (PrEP) to interrupt further transmission.

3. HIV-TRACE

- We used HIV-TRACE to identify clusters with rapid (≤0.05 substitutions per site) transmissions, and calculated their recent (2017/2018) growth:
  - Growth = (\frac{s2 - s1}{\text{date of last negative test} - \text{CD4 count and avidity result}})

Figure 1: Source Attribution method

- Phylogenetic analysis of viral sequences provides an alternative and independent route to reconstructing transmission networks.
- The West of Scotland specialist virology centre sequences pol for all new HIV diagnoses.
- The National Health Service portal collects clinical data, including:
  - date of last negative test, CD4 count and avidity result
  - We time-resolved the phylogeny using BEAST5.
- Source attribution methods estimate the probability of a direct transmission event between two individuals based on the time-resolved phylogeny, estimated dates of infection, prevalence and incidence (Figure 1).
- HIV-TRACE can be used to rapidly find clusters based on a genetic distance threshold and is being used by CDC to detect transmission clusters as they arise6.

results

1. Time resolved phylogeny of the outbreak

- Single cluster of 145 sequences with both mutations, all from Scotland (Figure 2).
- Mean genetic distance <1%.
- 3 subclusters, all with recent transmissions.
- The coloured branches indicate clusters selected by HIV-TRACE.
- HIV-TRACE does not enforce monophyly.
- The circles and stars in the phylogeny indicate the most probable transmission pairs (donors and recipients) based on the Source Attribution method7.

Figure 2: BEAST phylogeny

- Clusters with recent growth are the most likely to keep growing.
- One large cluster had high growth in 2016 but not in 2017/2018.
- From a public health perspective, clusters with recent growth are termed “priority clusters.”
- As such, they serve as a focal point for contact tracing to collect information about partner contacts and social network contacts (to determine the larger risk network).
- This group can then be tested, treated if positive, or provided with appropriate post-exposure prophylaxis.

Figure 3: Recent & Rapid clusters

- Growth = \frac{\text{number of transmissions} - \text{date of last negative test}}{\text{CD4 count and avidity result}}

Figure 3: Recent & Rapid clusters

- Probability of a mixed intermediary (based on HIV prevalence, incidence and sampling proportion)
- Estimated time of transmission event
- Estimated duration of infection (based on CD4 at diagnosis)

conclusions

- 145 linked HIV cases among PWID in Scotland between 2005 and 2018, the biggest outbreak since the 1980s.
- Two different methods for identifying priority cases for public health interventions.
- There is some overlap between individuals prioritized by each method but they are calculating different things (probable direct transmissions versus recent cluster growth).
- LIMITATIONS
  - Neither method has been tested/evaluated in known transmission chains.
  - SA model relies on many parameters (incidence, prevalence, CD4 counts).
  - Both methods can be used to:
    - Select specific individuals for enhanced public health interventions (viral suppression, contact tracing, partner notification, partner testing, treatment/PrEP for partners).
    - Determine the risk factors for transmission and thus guide public health interventions towards subpopulations at highest risk of transmission/infection.
- ETHICS
  - The ethics and acceptability of these approaches still need to be ascertained among the HIV+ community.

references