Inference and Characterization of a Transmission Network in an Opioid-driven HIV-1 Outbreak

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HIV Outbreak – Scott County, Indiana [1]

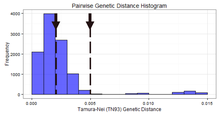
- 181 HIV+ cases
- 552 at-risk contacts
- 92% HCV co-infection rate
- 95% inject oxymorphone
- Frequent sharing of injection equipment
- Inject 4-15x daily
  - 1-6 partners per event

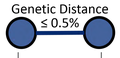
Transmission Network Inference

- Epidemiologic and viral sequence data can be used to infer transmission with quantifiable support
- Can be used to identify:
  - Unreported transmission pairs
  - Reported, but genetically distinct contacts
- Transmission inference offers high resolution of transmission
  - Directly comparable to contact tracing networks
  - Informs outbreak and community-specific intervention and prevention strategies

METHODS

- Patient interviews captured high-risk contacts, including those who shared injection equipment and sexual partners
- Risk behaviors and demographic traits were used to characterize the contact network
- Decision tree was built using HIV status as an outcome whose likelihood was based on high-risk contacts and demographics
- HIV *pol* gene used for phylogenetic reconstruction
- Genetic distance network represents only the closest genetic links between viral sequences
  - 1.5% genetic distance correlates to ~10 years of divergence [2]
  - Transmission inferred at ≤0.1% and ≤0.5% [3]

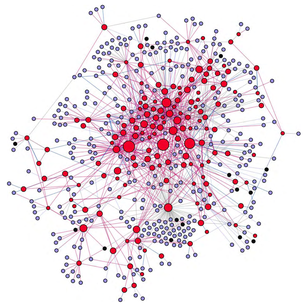




- Recency of infection established using BioRad Avidity Index
  - Longitudinal controls used to characterize duration of infection
  - Observed incidence curve inferred by stochastic simulation
  - Missing data handled by hot-deck imputation

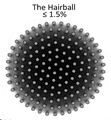
Contact Tracing Network

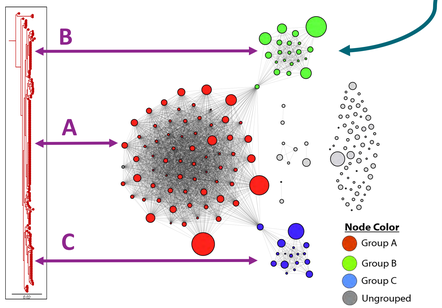
- 552 Named Contacts
  - 32.8% of contacts HIV-positive
  - 1,267 total reported contacts
- Over 75% of contacts were high-risk
  - 7.8% sexual contact only
  - 80% injection drug use (IDU) only
  - 12.2% IDU and sexual contact



Genetic Distance Network

- Three distinct clades of identical HIV-1 *pol* sequences shown in the phylogenetic tree
- Three corresponding communities in genetic network
  - Earliest infections remain disconnected at ≤0.1% threshold
  - 1.5% distance threshold too strict, shows explosive growth
- Community recency profiles differ
- Solitary bridge nodes separate these communities
  - Both female, one self-reported trading sex for drugs or money
  - May be potential points for future prevention or intervention efforts





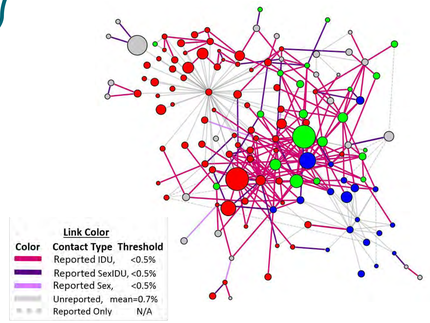
Inferred Transmission Network

Using epidemiologic data to contextualize genetic data

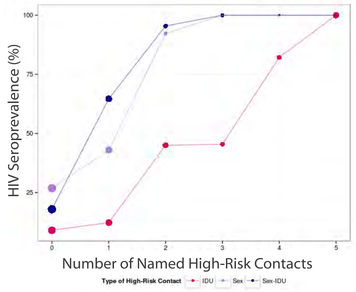
Inference Algorithm

1. Consider each reported high-risk contact
2. Save contacts supported by close linkage (≤0.5%)
3. Insert unreported transmission links
   - Only closest link(s) for those with no reported risk contacts

Genetic groups also apparent in the inferred transmission network
Assortativity Index (Pearson Correlation Coefficient) = 0.35



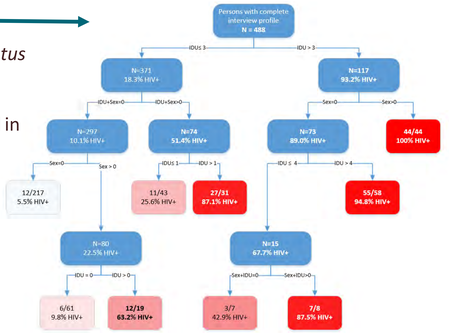
Role of High-Risk Behavior



Decision Tree Analysis

Goal: *Generate simple rules predictive of HIV status*

- Multiple IDU partners is primary risk factor
  - 3+ IDU partners is power predictor of HIV+ status
- Sex accounts for 20% of contacts but included in each rule generated by the decision tree



Risk Response Curves

What role did sex play in transmission?

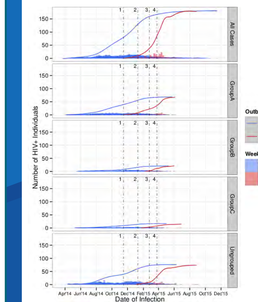
HIV seroprevalence for individuals reporting:

- Two sexual contacts – 92.3%
- Two IDU + sexual contacts – 95.5%
- 3+ sexual contacts – 100%
- 3+ IDU + sexual contacts – 100%

Incidence Curve Inference

Problem: *Outbreak investigations generate sampling bias when estimating true rates of disease incidence*

- Adjusting date of sample collection using experimentally validated mean duration of recent infection (MDRI)
- Transmission among Ungrouped and Group A likely occurred before Groups B and C



Avidity-based inference of incidence suggests that over:

1) 50% were infected prior to **initial HIV+ diagnosis**
1) 70% were infected prior to **cluster identification**
1) 85% were infected prior to **establishing incident command**
2) 90% were infected prior to declaration of **State of Emergency**

Summary

- An HIV-1 outbreak in rural Indiana originated from a single strain
- Explosive transmission during late 2014 and early 2015 resulted from frequent sharing of injection equipment and commercial sex work associated with injection drug use
- Contact tracing data contextualized transmission inference, especially when rapid transmission leads to low viral diversity
- Recency assays combined with transmission networks provide insight into potential points of prevention and intervention
- Machine learning can be applied to contact network data to assist in decision making during outbreak investigations
- Transmission network inference requires high-coverage of both epidemiologic data collection and pathogen sequencing

References

[1] Conrad et al. "Community Outbreak of HIV Infection Linked to Injection Drug Use of Oxymorphone — Indiana, 2015." MMWR. *Centers for Disease Control and Prevention*. Centers for Disease Control and Prevention, 01 May 2015.

[2] *Wertheim et al.* "The Global Transmission Network of HIV-1." *Journal of Infectious Diseases. 2013*

[3] HIVTrace, Viral Evolution Group, UC San Diego. https://github.com/veg/hivtrace

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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