Beyond Drug Resistance Testing: Using HIV-1 Sequence Data to Infer Transmission Networks and Inform Public Health Action

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Overview

- U.S. National HIV Surveillance System
- Molecular HIV Surveillance (MHS)
  - Collection of HIV nucleotide sequences
- Use of sequences to understand transmission patterns and identify clusters of concern
- Analytic platform to visualize transmission networks
- Application of analytic tools in an outbreak setting
U.S. National HIV Surveillance System

- Maintained by CDC to monitor HIV infection
- 50 states, the District of Columbia, and 6 U.S. dependent areas* collect data on persons with diagnosed HIV
- Surveillance data used to focus prevention efforts, plan services, allocate resources, develop policy, monitor trends
- In 2014, the estimated number of diagnoses of HIV infection was 44,784

*American Samoa, Guam, the Northern Mariana Islands, Puerto Rico, the Republic of Palau, and the U.S. Virgin Islands
Spectrum of reportable events in HIV surveillance

- HIV infection (incidence)
- HIV diagnosis
  - CD4 tests
  - Viral load tests
    - Drug resistance (genotypic) tests
  - CD4 test result <200 cells/μL or AIDS-defining condition
- Death

Entry to care Retention in care and viral suppression
Molecular HIV Surveillance (MHS): a component of the National HIV Surveillance System

- **Purpose:**
  - Describe HIV transmission patterns
  - Assess prevalence of drug resistant strains
  - Monitor genetic diversity of HIV

- **Data Source:**
  - HIV nucleotide sequence data generated from routine genotypic drug resistance testing
  - Other case information collected through HIV surveillance: demographics, HIV-related laboratory results, clinical information, risk

- Sequences have been reported for >130,000 people living with diagnosed HIV infection
Molecular HIV Surveillance data flow:
Collection of HIV nucleotide sequences

1. Provider orders HIV drug resistance (genotypic) testing
2. Specimen sent to laboratory
3. Laboratory performs genotypic testing (Sanger)
   - Specimen prepared
   - Viral RNA converted to DNA and amplified
   - Genetic sequence generated and compared with reference
   - Mutations identified and resistance interpreted
4. Resistance report sent to provider
5. HIV sequence reported electronically to health department
6. 27 MHS jurisdictions
MHS jurisdictions (n=27) reported 70% of new HIV diagnoses occurring in 2014.
Using HIV nucleotide sequence data to identify active transmission

- HIV nucleotide sequence data can provide information on transmission relationships and allow us to
  - Construct transmission networks that link persons infected with genetically similar HIV variants
  - Understand HIV transmission patterns between subgroups
  - Identify growing clusters that represent active transmission
  - Focus prevention interventions to interrupt transmission
Molecular epidemiology and HIV

- HIV mutates/evolves over time
- People living with HIV infection whose viral strains are genetically similar may be more closely related in transmission

**Analysis:** compares nucleotide sequences to determine relatedness

<table>
<thead>
<tr>
<th>ACCGGATAACGGTTATCCG</th>
<th>ACCGGATAACGGTTATCCG</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTGGATAACGGTTATCCG</td>
<td>ACCGAATCACGGAAATCCG</td>
</tr>
</tbody>
</table>
Identifying transmission networks

- Align all sequences (polymerase) to a single reference sequence
- Perform comparisons of all pairs of sequences to calculate genetic distance
- Identify pairs of sequences below a given genetic distance threshold

- Infer a transmission network
- Accomplished using HIV-TRACE (HIV TRAnsmission Cluster Engine)
  - Developed by University of California, San Diego

link drawn between 2 sequences with ≤1.5% distance

Potential transmission partners
What do potential transmission partners represent?

Multiple options:

- Person A infected person B
- Person A infected person C, who infected person B
- Person B infected person A
- Persons D infected persons A and B

So, we can infer a direct OR indirect epidemiologic link
We cannot infer directionality
Transmission category of potential transmission partners among persons with HIV diagnosed through 2012

<table>
<thead>
<tr>
<th>Transmission category</th>
<th>MSM (N=9839)</th>
<th>MSM who inject drugs (N=496)</th>
<th>Male PWID (N=309)</th>
<th>Female PWID (N=268)</th>
<th>Heterosexual men (N=583)</th>
<th>Heterosexual women (N=1409)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSM</td>
<td>88</td>
<td>76</td>
<td>25</td>
<td>33</td>
<td>49</td>
<td>35</td>
</tr>
<tr>
<td>MSM who inject drugs</td>
<td>6</td>
<td>9</td>
<td>6</td>
<td>13</td>
<td>7</td>
<td>21</td>
</tr>
<tr>
<td>Male PWID</td>
<td>49</td>
<td>10</td>
<td>14</td>
<td>7</td>
<td>34</td>
<td>21</td>
</tr>
<tr>
<td>Female PWID</td>
<td>6</td>
<td>9</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Heterosexual men</td>
<td>27</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterosexual women</td>
<td>34</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSM</td>
<td>29</td>
<td>6</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Most MSM were linked to other MSM

Other risk groups were also commonly linked to MSM

MSM: men who have sex with men; PWID: persons who inject drugs.
Identifying clusters of concern

- After constructing a transmission network, can identify growing clusters.

- Those clusters that grow over time likely represent ongoing transmission and would benefit from prevention interventions, such as:
  - Efforts to improve engagement in care and viral suppression
  - Elicitation and testing of partners, PrEP provision to those that are negative
### Cluster-level or population-level options for public health intervention

<table>
<thead>
<tr>
<th>Characteristic of cluster</th>
<th>Potential intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Associated with injection drug use</td>
<td>Ensure/expand appropriate provision of syringe exchange and substance use treatment</td>
</tr>
<tr>
<td>Associated with a particular venue</td>
<td>Targeted outreach for testing and PrEP</td>
</tr>
<tr>
<td>In a remote location</td>
<td>Educate providers on testing and treatment</td>
</tr>
<tr>
<td>In a jurisdiction with limited resources</td>
<td>Initiate state or CDC assistance</td>
</tr>
<tr>
<td>Spans multiple jurisdictions</td>
<td>Collaborate to intervene appropriately</td>
</tr>
</tbody>
</table>

- Communicate with population at risk about transmission risk
- Conduct cluster investigation to identify factors facilitating transmission
- Review existing surveillance, partner services, and other data to identify training needs and protocol gaps/changes
CDC’s Advanced Molecular Detection (AMD) initiative

- Fosters scientific innovation to transform public health and protect people from disease threats
- By applying AMD methods to data collected through surveillance, we
  - begin to tackle the challenge of interrupting HIV transmission
  - ensure application of public health principles and latest scientific approaches in our battle against HIV
Data integration, analysis, and visualization: Microbial Transmission Networks Analytics Platform (MTNAP)

- National and local integration of molecular and epidemiologic data
  - National Center for HIV/AIDS, Viral Hepatitis, STDs, and Tuberculosis Prevention (NCHHSTP)
  - Working group: lab scientists, epidemiologists and computational biologists
  - Integration, exploration, analysis, and visualization of national and local public health data
  - Advanced Molecular Detection funds received April 2014
    - CDC deployment (beta) – End of 2016
    - Local deployment (pilots) – Summer of 2017
Data integration, analysis, and visualization: Microbial Transmission Networks Analytics Platform (MTNAP)
Contact tracing information from partner services activities

High-Risk Contact Type

- Sex Partner
- IDU Partner
- Sex+IDU Partner

Contact Tracing Network
Scott County, Indiana
HIV-1 Outbreak, 2015

Visualization
Gaps in existing approaches

- Partner services data provide incomplete picture of HIV transmission
  - Many partners not named or outside of local jurisdiction
  - Named partners often do not represent transmission partners
  - Many jurisdictions do not offer partner services for all new diagnoses

- Case surveillance identifies trends in diagnoses, but, particularly in high burden areas, these data may obscure growing clusters of active transmission amid other trends
Genetic distance networks

What is gained from using molecular data?

- Infer transmission pairs without contact information from partner services
- Quantitative support of reported contacts (where partner services are available)
- Powerful quantitative tools that will enable:
  - Quantification of growth
  - Identification of factors that impact growth
  - Validate preventative measures that blunt growth

Molecular HIV Network

HIV-1 Outbreak, Indiana 2015
HIV-1 Outbreak, Indiana 2015
Minimum Spanning Tree (MST)

Discount: Close genetic linkage does not imply transmission
HIV-1 Outbreak, Indiana 2015
Minimum Spanning Tree (MST)

Earliest HIV Diagnosis (2006)
Reported no IDU behavior
Reported no high-risk contacts

1. Detect growth
2. Understand risk and transmission
3. Implement tailored intervention

Disclaimer: Close genetic linkage does not imply transmission
‘Big Picture’ requires integration of epi and lab

**Context is key:**
- Close genetic links may not be direct transmission partners
- Epi and molecular networks should be used in combination to provide qualitative and quantitative support for linkage
Challenges and opportunities

- Ethical and legal issues related to some potential uses or possible misinterpretation of transmission network data
- Identification of clusters most likely to represent active transmission
- Incorporation of transmission network analyses into routine surveillance processes and integration of findings into HIV prevention planning
  - Molecular analytical tools for use by health departments are being developed to help build local and state capacity to conduct transmission network analyses
Summary

- It is an exciting time for incorporating the use of molecular epidemiology data to guide HIV prevention efforts
- The opportunities to use molecular epidemiology data for prevention planning and public health intervention are great
- Addressing challenges is critical to achieving the potential afforded by widespread availability of sequence data and new analytical tools
Acknowledgements

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