

Use of molecular surveillance data to identify clusters of recent and rapid HIV transmission

Alexa Oster, MD

Acting Lead, Incidence and Molecular Epidemiology Team

Lead, Molecular HIV Surveillance

Division of HIV/AIDS Prevention

Centers for Disease Control and Prevention

March 24, 2017



Background

Identifying active HIV transmission is key to focusing prevention efforts

- Important to identify growing clusters of recent and rapid transmission in order to intervene to interrupt transmission
- How do we identify clusters of recent and rapid transmission?
 - HIV case surveillance data can identify trends in diagnoses, but, particularly in high burden areas, these data may obscure growing clusters of active transmission amid other trends
 - Partner services/contact tracing data provide information about transmission networks, however:
 - Not all index patients are interviewed
 - Many partners not named or located
 - Named partners may not represent transmission partners
 - Many jurisdictions do not offer partner services for all new diagnoses



HIV nucleotide sequence data are available and can identify active transmission

- In the United States, drug resistance testing is recommended for all HIV-infected persons
 - Generates HIV nucleotide sequence data
- Harnessing these nucleotide sequence data can provide information on transmission relationships and allows to
 - Construct transmission networks that link persons infected with genetically similar HIV variants
 - Identify growing clusters that represent active transmission
 - Focus prevention interventions



Monitoring and preventing HIV


- The National HIV Surveillance System (NHSS) is the primary source for monitoring HIV infection in the United States
 - Monitors and characterizes trends in HIV to guide public health action at the federal, state, and local levels



Molecular HIV surveillance (MHS): A component of the National HIV Surveillance System

HIV nucleotide sequences*
ATGGCATCAATGGCATCATTATCC

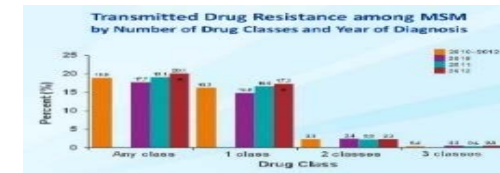
Antiretroviral use information



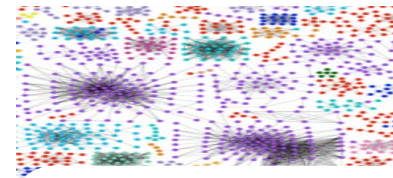
Demographics, risk, other case information
HIV Confidential Case Report Form

Purpose

Assess prevalence of drug resistant strains



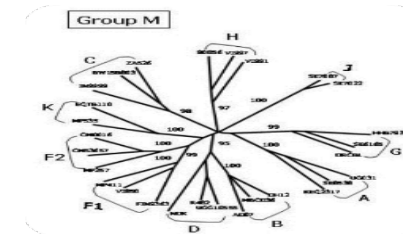
Describe HIV transmission patterns



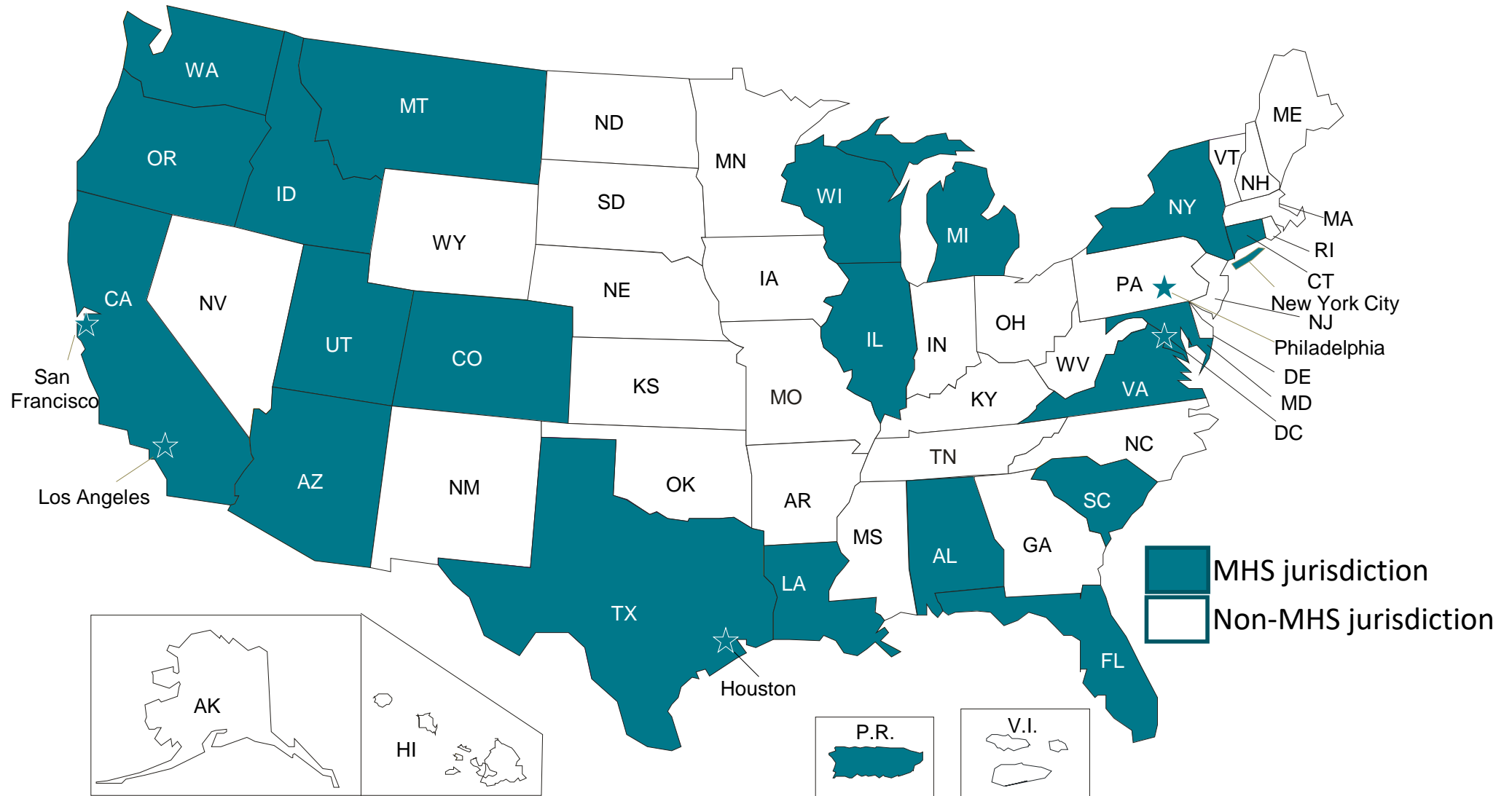
Identification of clusters and potential outbreaks

Cluster Growth

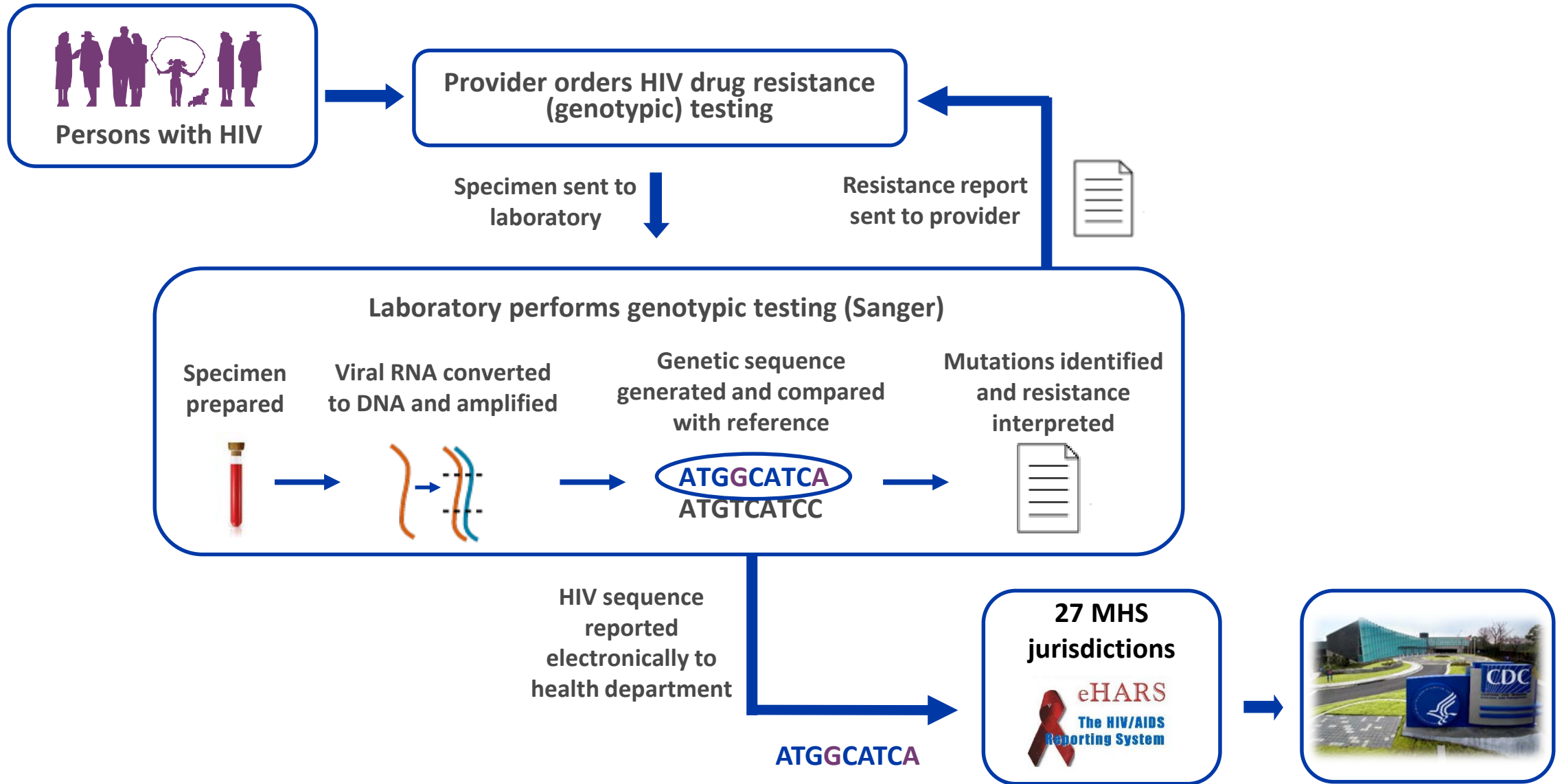
Monitor genetic diversity of HIV



MHS jurisdictions (N=27), which reported 70% of new HIV diagnoses occurring in 2014



Collection of nucleotide sequences



Using surveillance data to inform prevention

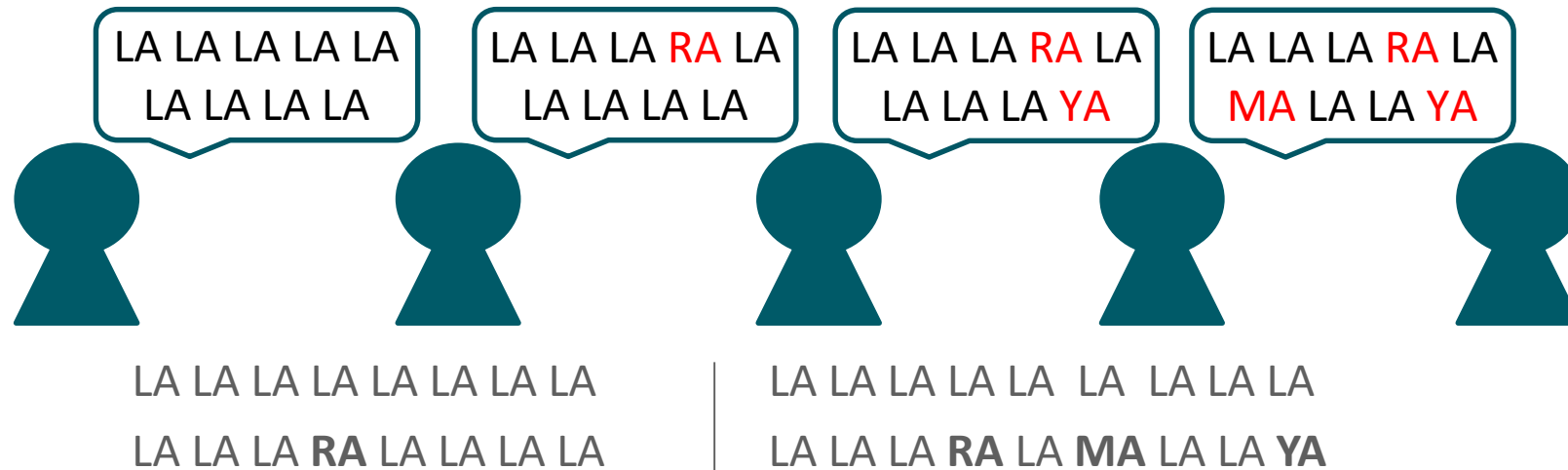
Ways to use molecular HIV data

- Monitor drug resistance (transmitted and acquired)
- Examine subtype diversity
- Understand transmission patterns
- Corroborate, refute, and understand suspected outbreaks (e.g., Indiana)
- Identify possible outbreaks and trigger investigation and intervention
- Monitor outbreaks over time
- Identify subgroups and networks with active transmission
- Prioritize prevention efforts



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

ACCGGATAACGGTTATCCG
ACTGGATAACGGTTATCCG

ACCGGATAACGGTTATCCG
ACCGAATCACGGAAATCCG

Identifying transmission clusters

- Compare all pairs of sequences to calculate genetic distance between them
- Identify pairs of sequences that are very closely related
- Connect all closely related pairs to identify clusters

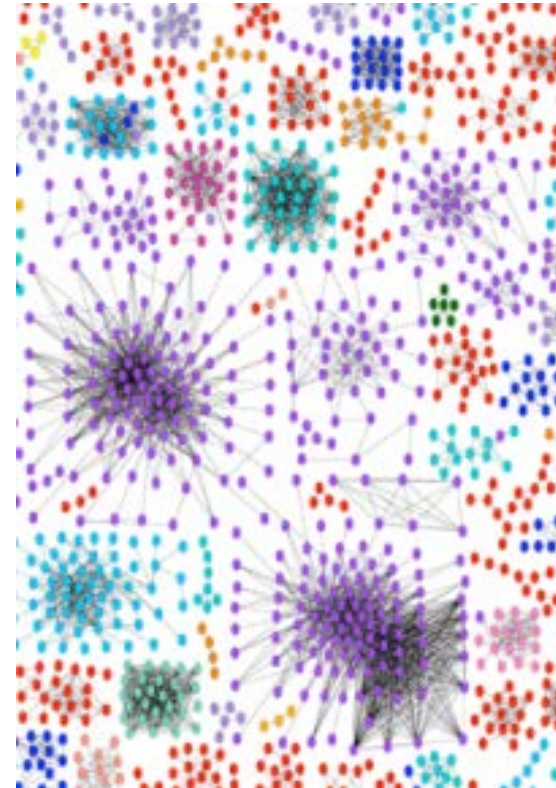
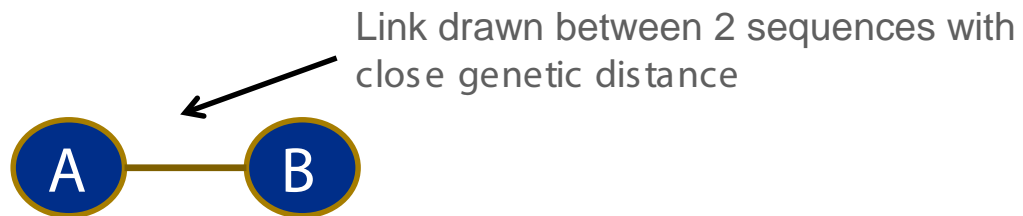
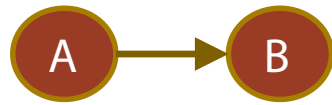


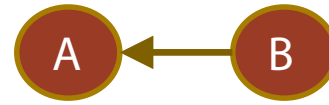
Image courtesy of Joel Wertheim

Molecular epidemiology and HIV

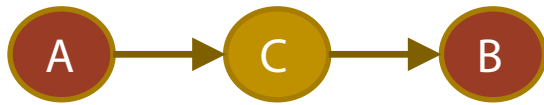
- Analysis: compares nucleotide sequences to determine relatedness



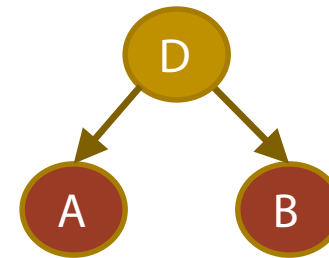
Person A infected person B



Person B infected person A



Person A infected person C, who
infected person B

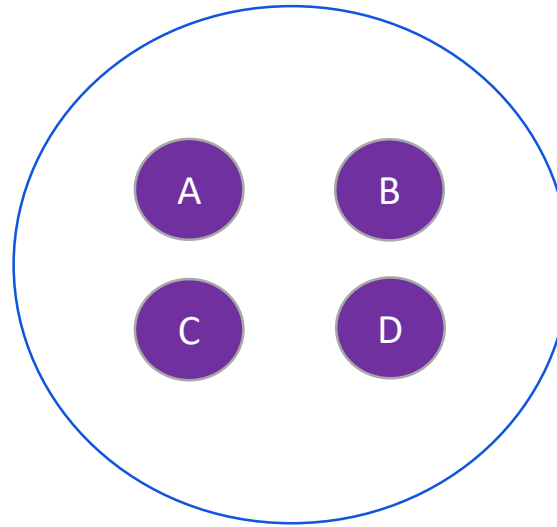


Persons D infected persons A and B

We can infer a direct OR indirect epidemiologic link; we cannot infer directionality



Hypothetical molecular cluster identified through sequence analysis



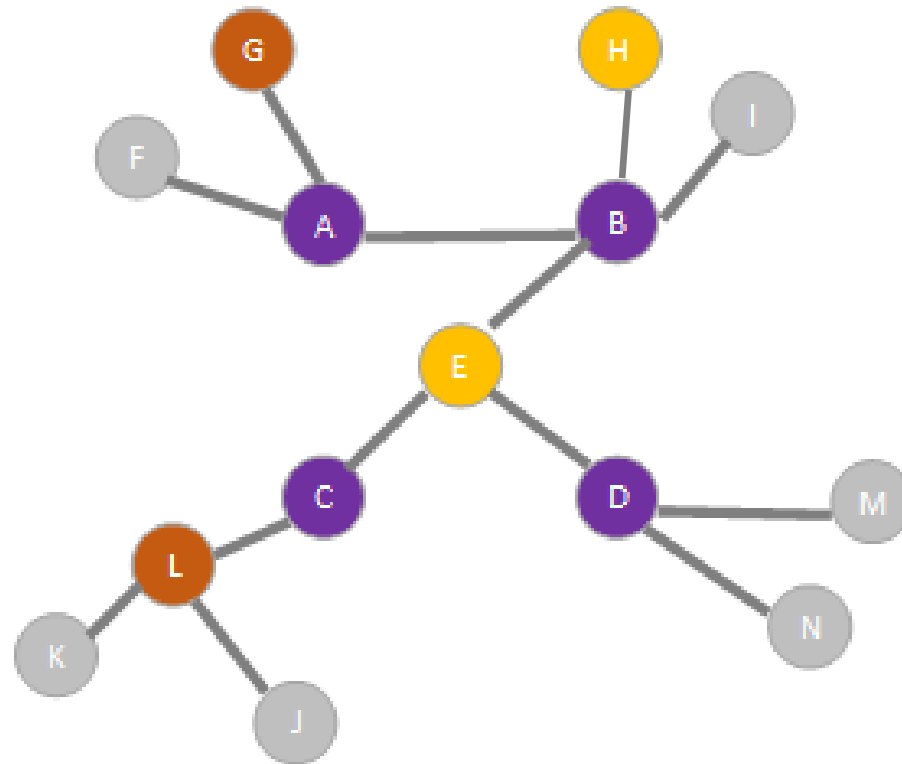
● HIV-infected, diagnosed, linked to care



Interpreting transmission cluster data

- A transmission cluster includes only those cases that have been diagnosed and have a sequence
- This represents a subset of the underlying transmission cluster and risk network, which can also include:
 - People who are diagnosed but do not have a sequence included in analysis
 - Diagnosed, but never linked to care
 - Linked to care, but haven't received a genetic resistance test
 - Sequence hasn't been reported to health department
 - People with undiagnosed infection
 - HIV-negative contacts who may be at risk of acquiring HIV

Hypothetical underlying sexual/risk network



- HIV-infected, diagnosed, linked to care
- HIV-infected, diagnosed but not linked to care
- HIV-infected, not diagnosed
- HIV-uninfected, at risk

Routine CDC analyses to identify active transmission clusters

- Each quarter, analyze data to identify growing clusters that represent recent, rapid transmission
 - Clusters are prioritized to identify the most concerning clusters nationally
 - Tightly related cases, suggesting rapid transmission
 - At least 5 cases in the cluster identified in most recent 12 month period
- Initial analysis of data collected through December 2015
 - 1,923 clusters identified, ranging in size from 2-22 cases
 - Of these, 13 met our criteria for rapid growth, with at least 5 cases in most recent 12-month period

Characteristics of 13 high priority clusters

Cluster ID	Total in cluster	Diagnosed in 2015	MSM	Drug resistance	Virally suppressed§	Primary census region*
A	16	8	94%	3 of 16	69%	Northeast
B	22	7	91%	17 of 17	68%	West
C	21	7	86%	20 of 20	57%	South
D	18	7	83%	0 of 17	67%	South
E	17	7	94%	15 of 15	94%	Northeast
F	15	7	93%	15 of 15	73%	South
G	16	6	100%	14 of 14	63%	West
H	6	6	100%	0 of 6	67%	West
I	18	5	94%	0 of 17	78%	South
J	17	5	94%	0 of 16	82%	Multiple, incl. Midwest
K	17	5	100%	0 of 16	77%	South
L	7	5	86%	0 of 6	43%	West
M	6	5	100%	0 of 6	17%	West

§Most recent viral load was suppressed and occurred in the past 12 months

*10 of 13 clusters included cases from more than one surveillance jurisdiction

What steps is CDC taking as we identify high priority clusters?

- Analyze national surveillance data for cluster and create cluster snapshot
- Discuss cluster findings with relevant state or local health departments
- Communicate and collaborate with health departments on
 - Investigation
 - Intervention
- Quarterly updates provide information on new cases added to previously identified clusters, as well as identifying new clusters meeting the priority criteria for the first time
 - Analysis of 5 quarterly data sets to date have identified approximately 60 total priority clusters
 - As of December 2016, sequences available for >250,000 cases nationally



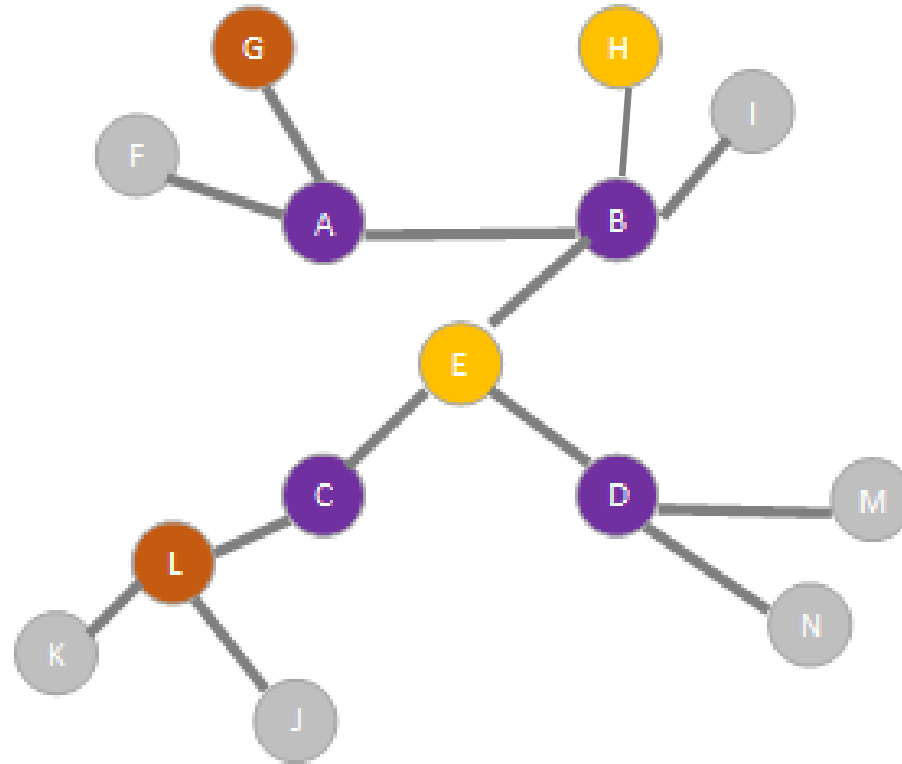
Cluster investigation is critical

- Necessary to determine the underlying transmission cluster and risk network
 - Identify persons with diagnosed HIV infection that did not have a sequence included in analysis but are likely cluster cases, and could be contributing to ongoing transmission
 - Identify partners in the network that have not received a diagnosis of HIV infection for
 - Testing or retesting
 - Prevention efforts

- Determine characteristics of the cluster that could be contributing to ongoing transmission

- Understanding the cluster allows public health officials to implement public health interventions tailored to the characteristics of the cluster (i.e., geographic, risk, and clinical)

Intervene in entire network as appropriate



- HIV-infected, diagnosed, linked to care
- HIV-infected, diagnosed but not linked to care
- HIV-infected, not diagnosed
- HIV-uninfected, at risk

Intervening in transmission clusters: Individual-level interventions

Characteristic	Potential action
Persons with diagnosed infection who are in care but unsuppressed	Promote viral suppression
Persons with diagnosed infection who are not in care	Promote engagement in care, viral suppression
Persons with undiagnosed infection	Identify (e.g., through partner services or social networks testing project) and link to care
HIV-negative persons at risk for acquiring HIV	Identify (e.g., through partner services or social networks testing project) and offer PrEP

Intervening in transmission clusters: Cluster-level interventions

Characteristic	Potential action
Cluster associated with a particular venue	Targeted outreach for testing and PrEP
Cluster in a remote location	Educate providers on testing and treatment
Cluster spans multiple jurisdictions	Collaborate to intervene appropriately
Cluster associated with injection drug use	Ensure/expand appropriate provision of syringe exchange and substance use treatment
Cluster affects a specific population	Communicate with population at risk about transmission risk

An example cluster

One cluster example

- NHSS data from December 2015
 - 13 clusters met criteria for rapid growth: at least 5 cases in most recent 12 month period
- One cluster in TX was particularly concerning
 - As of December 2015 data: 18 members
 - As of June 2016 data: 24 members
 - Primarily young Hispanic/Latino MSM in one metropolitan statistical area
- CDC and TX Department of State Health Services partnered to investigate
- Methods: abstraction of medical records and partner services records

Key investigation findings

- Used partner services data to identify people who might have been part of the transmission cluster but didn't have sequence data
 - Molecular cluster members: n=24
 - Other people who were sexual or needle sharing partners of molecular cluster cases and their partners: n=87
- Abstracted medical records to understand epidemiology of the cluster and identify factors that may have facilitated transmission
 - Despite high levels of risk behaviors and large numbers of partners (many of whom were anonymous partners), no patients had previously taken PrEP
 - Some patients had not been tested using the appropriate algorithm → missed opportunity to diagnosed acute infection

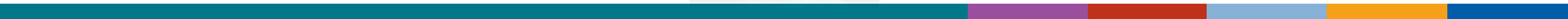
Actions taken to address community factors

- Drafted a Dear Colleague letter
 - Outlines the rapid growth clusters observed
 - Recommendations for following HIV testing algorithm
 - Recommendations to prescribe PrEP to patients at risk
- Drafted a health alert
 - Will go out to entire state, medical providers and stakeholders
 - Details the need to use diagnostic algorithm to identify acute HIV cases
 - Recommends HIV genotype testing to identify these clusters
- 70% increase in prevention funding to San Antonio from DSHS
 - Will fund more testing and additional PrEP clinics
- Expanding options for notification of 'anonymous' partners via apps and social media sites

A cluster example

Ongoing efforts

- Guidance for detecting, investigating, and responding to transmission clusters released this month
- Continuing to expand collection of nucleotide sequence data
- Developing bioinformatics tools to automate analysis and visualization of molecular data at national and state/local levels
- Building our knowledge base on optimal approaches to investigate and respond to clusters



Summary

- Molecular analysis provides an opportunity to identify bursts of recent and rapid transmission
 - The current level of HIV transmission in the United States is likely largely sustained by these types of bursts of transmission
- Using molecular surveillance data to identify, investigate and intervene recent HIV transmission events can support efforts to improve health outcomes and prevent transmission among these networks
 - May allow us to make progress in reducing new infections in populations that have not yet seen reductions in incidence
- Cluster data can be a powerful tool to help target the interventions we know are effective (engagement in care, HIV testing, PrEP)

Acknowledgments

Local & state HIV surveillance staff

Division of HIV/AIDS Prevention

- Ells Campbell
- Sharoda Dasgupta
- Irene Hall
- Angela Hernandez
- Anne Marie France
- Cheryl Ocfemia
- Nivedha Panneer
- Neeraja Saduvala
- Bill Switzer

University of California, San Diego:

- Joel Wertheim

TX Department of State Health Services:

- Analise Monterosso

