DETECTING AND RESPONDING TO
HIV Transmission Clusters

A GUIDE FOR HEALTH DEPARTMENTS

JUNE 2018

DRAFT Version 2.0

National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention

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Acknowledgements

Executive summary

A critical step toward bringing the nation closer to the goal of no new infections is identifying and responding to groups of HIV-infected persons who have an epidemiological connection related to HIV transmission (i.e., HIV transmission cluster of persons with diagnosed or undiagnosed HIV). Evidence shows that HIV surveillance can identify transmission clusters that would otherwise go unrecognized. Information about these transmission clusters and the associated risk networks can help us to focus proven HIV prevention tools where they are needed most. In this way, expanded use of HIV surveillance has the potential to significantly improve HIV prevention efforts.

This document describes the use of HIV surveillance data to detect transmission clusters through the identification of both clusters of HIV diagnoses clustered in time and space (i.e., time-space clusters) and clusters of HIV infections with closely related strains (i.e., molecular clusters). This document also describes the public health response to those clusters, including efforts to better understand the transmission cluster and risk network and prevention modalities to reduce transmission, as well as related evaluation measures stipulated under CDC's PS18-1802 cooperative agreement.

This document describes new activities for which jurisdictions will need to develop capacity and strategy for implementation. Identifying and engaging key partners, both within and outside of the health department and including the community, will be important to lay the groundwork for the successful implementation of these activities. Considerations related to integrating these activities in the surveillance and prevention program and the development of the capacity and communication regarding this work are discussed. The 'Cluster and Outbreak Detection and Response Plan Template' included as an appendix to this document presents a template for programs to address key elements that will be necessary to implement these activities. This document provides general guidance for cluster detection and response; for specific guidance focused on HIV outbreaks among persons who inject drugs, CDC has developed a documents entitled 'Managing HIV and hepatitis C outbreaks among people who inject drugs: A guide for state and local health departments.' This document is available at CDC's HIV cluster and outbreak detection and response webpage.

This is a living document: as our understanding of how to most effectively identify and respond to transmission clusters grows, this guidance will be updated.

Section 1. What is a transmission cluster?

- A **transmission cluster** is a group of HIV-infected persons (with diagnosed or undiagnosed HIV) who are connected by HIV transmission. Transmission clusters can represent recent and ongoing HIV transmission in a population, where prevention efforts could prevent new infections. Section 2, 'How can identifying transmission clusters help focus prevention efforts?' describes the importance of identifying transmission clusters for prevention efforts in more detail.
- A transmission cluster represents a subset of an underlying **risk network**. A risk network includes the group of persons among which HIV transmission has occurred and could be ongoing. This network includes persons who are not HIV-infected but may be at risk for infection, as well as the HIV-infected persons in the transmission cluster. Transmission clusters present opportunities for prevention in the larger underlying risk network.
- Transmission clusters can be identified through multiple mechanisms:

- **HIV case surveillance data.** An increase in diagnoses in a particular geographic area or population (i.e., a time-space cluster). In areas with low incidence of HIV (like many rural communities in the United States), transmission clusters can be more easily detected through HIV case surveillance. Improved timeliness of reporting may improve a jurisdiction's ability to detect a transmission cluster. It is important to note, however, that an increase in the number of diagnoses may not reflect an increase in transmission. Rather, an increase in diagnoses may reflect an increase in HIV testing that has diagnosed infections that may be longstanding. The use of HIV case surveillance data to identify transmission clusters is discussed in more detail in Section 3, 'Identifying growing transmission clusters using surveillance data'.
- **HIV partner services and contact investigations.** Partner services staff (referred to as disease intervention specialists [DIS] in many jurisdictions) routinely perform investigations for persons with newly diagnosed HIV infection, interviewing them to elicit information about their partners, who can then be confidentially notified of their possible exposure or potential risk. Partner services activities can also include prevention counseling, testing for HIV and STDs, and linkage or referral to medical care. As DIS work intensively in local communities, they are positioned to notice unexpected patterns or increases in HIV diagnoses.
- **Molecular HIV surveillance data.** Analysis of molecular HIV surveillance data can identify clusters of cases with closely related HIV strains (i.e., molecular clusters). This method may be particularly useful in identifying transmission clusters that are not detected through other mechanisms. Examples include transmission clusters occurring in an area with a high incidence of HIV infection, that cross jurisdictions, or in populations in which persons do not provide contact tracing information to DIS.
- **Astute health department staff, care providers, or community members.** HIV transmission clusters are sometimes first detected through astute observations from frontline staff at the health department or clinical providers. Observations of increases in HIV diagnoses call for further investigation to determine if and how these persons are connected and the extent of other connections they may have in a community.

What is a molecular cluster, and how does it relate to a transmission cluster?

- Identification of **molecular clusters** provides a tool to identify transmission clusters. A **molecular cluster** is a group of persons with diagnosed HIV infection who have genetically similar HIV strains. Because HIV is constantly evolving, persons whose viral strains are genetically similar may be closely related by transmission. For more information on HIV evolution, see Appendix B.
- A **molecular cluster** contains only those people for whom molecular data are available and can be analyzed, and contains a subset of what is likely a larger underlying transmission cluster**.
- Molecular clusters are identified through analysis of HIV molecular sequence data that are generated through HIV drug resistance testing. Drug resistance testing is conducted to identify mutations associated with resistance to HIV antiretroviral medications and helps the HIV care provider select an appropriate treatment regimen. This testing is recommended for all persons with diagnosed HIV infection, with the recommendation that testing be conducted at entry to HIV care.
- As a result, molecular clusters include persons with diagnosed HIV infection who have entered care and have had genetic resistance testing, and have had sequences transmitted to the health department for analysis.
- This represents a subset of the underlying transmission cluster, which can also include:
  - Persons with diagnosed HIV infection who do not have a sequence available for analysis, either because:
    - They did not enter care

- o They entered care, but have not had a genetic resistance test
- o They entered care and have had a genetic resistance test, but the sequence was not transmitted to the health department for analysis, or was of poor quality and could not be analyzed
- o Persons with <u>undiagnosed infection</u>
- In addition to the persons in the transmission cluster, the underlying <u>risk network</u> will include:
  - o HIV-negative persons <u>at risk for acquiring HIV</u>

Figure 1a. Molecular cluster and its underlying transmission cluster and risk network.

Molecular Cluster
Includes people with HIV in care, with related genetic sequences identified and sent to surveillance program.

Transmission Cluster
Includes people with HIV who share a direct or indirect transmission connection and are undiagnosed or diagnosed but without identified genetic sequences.

Risk Network
Includes people who share risk behaviors and contacts who may or may not have HIV.

- Molecular data cannot reveal which cases are directly related by transmission or determine the direction of transmission. This limitation is because two persons with genetically similar HIV strains are not necessarily directly linked by transmission: the relationship could be indirect, and there could be unidentified persons involved in transmission relationships.
- Use of molecular sequence data to identify molecular clusters is described in detail in Section 3, 'Identifying growing transmission clusters using surveillance data'.

- Once a molecular cluster is identified, the corresponding transmission cluster and risk networks can only be identified through investigation, which is described in detail later in this document.

Figure 1b. Hypothetical molecular cluster (a) and corresponding underlying transmission cluster (b) and risk network (c).

a. Hypothetical molecular cluster identified through sequence analysis	b. Hypothetical underlying transmission cluster	c. Hypothetical underlying risk network

Legend: Circles represent persons with HIV infection or persons at high risk of HIV infection; lines represent sexual or risk relationships between persons.

- HIV-infected, diagnosed, in care
- HIV-infected, diagnosed without a sequence
- HIV-infected, not diagnosed
- HIV-uninfected, at risk

What is a time-space cluster, and how does it relate to a transmission cluster?

Analysis of case surveillance data to find **time-space clusters** provides another tool to identify transmission clusters. A **time-space cluster** occurs when the number of diagnoses of HIV infection in a particular geographic area is elevated above levels expected given previous patterns. In some cases, time-space clusters may reflect one or more transmission clusters that have not yet been identified through molecular data or other approaches.

Why are time-space clusters important?

Surveillance systems should systematically use all data and methods (time-space and molecular sequence-based approaches) available to detect clusters and outbreaks. Reported diagnoses, which are timelier and more complete, can complement sequence-based techniques by detecting increases in diagnoses clustered in time and space. Routine use of this systematic method in near real time can automate detection of increases in HIV diagnoses that potentially merit further investigation and help state and local health departments prioritize and target HIV prevention efforts for maximal public health impact.

Time-space clusters may represent recent and ongoing HIV transmission. In some cases, time-space clusters may reflect transmission clusters that have not yet been identified through molecular data or other approaches. Time-space increases may indicate a single transmission cluster or multiple, smaller transmission clusters, both of which are important to investigate for prevention interventions. Increases in the number of diagnoses may also reflect an increase in HIV testing that has identified longstanding infections, which can also indicate a need for focused prevention efforts. Following the identification of time-space clusters, the review of additional data is important to determine whether investigations and interventions are needed.

For those time-space clusters that appear likely to represent recent and ongoing HIV transmission, steps should be taken to investigate and intervene, using many of the same principles as are outlined in the remainder of this document for molecular clusters.

Analysis of HIV surveillance data to identify time-space clusters can complement analysis of molecular data, because time-space clusters can be detected in areas where collection of HIV nucleotide sequences is incomplete or delayed. Time-space cluster detection methods may be particularly useful for subgroups of HIV transmission that might warrant different investigative and intervention approaches, as specific analyses can look at time-space clusters specficially among these groups. Notably, infections attributable to IDU constitute a small proportion of total diagnoses, so the ability to identify potential IDU transmission clusters by analyzing IDU-attributable infections separately is a strength of this method.

Section 2. How can identifying transmission clusters help focus prevention efforts?

- Transmission clusters can identify risk networks that are concerning because of ongoing transmission, poor outcomes, or other reasons, such as transmission in a particularly vulnerable or underserved population, or transmission of drug resistance. Networks of concern include:
    - *Networks in which HIV transmission occurred rapidly* (with multiple new infections occurring within months of one another), and within a recent time window (within ~1-2 years). Recent, rapid transmission suggests extremely high-risk transmission networks, and could represent an ongoing outbreak for which public health intervention could interrupt transmission and prevent future infections.
    - *Networks with charactaristics suggesting high potential for ongoing transmission,* such as identification of risk behaviors including IDU, or co-infection with STDs or hepatitis
    - *Networks characterized by poor outcomes*, such as late diagnosis, lack of viral suppression, or co-infection with STDs, hepatitis, or other comorbities; this could suggest poor access to care, and could indicate a network in which persons with HIV infection that has not yet been diagnosed could be contributing to ongoing transmission.
    - *Networks representing vulnerable or underserved populations*, such as pregnant women, adolescents, rural populations, persons who inject drugs (PWID), foreign-born persons, or other groups defined by local epidemiology and context.
    - *Networks in which drug-resistant strains of HIV are being transmitted*; particularly networks with resistance to pre-exposure prophylaxis (PrEP) regimens.
    - *Networks not reached by testing efforts*, as evidenced by large proportions of cases that were diagnosed through incidental testing, such as screening in plasma centers, emergency

departments, or correctional institutions; this could indicate other cases in the network that have not yet been diagnosed and could be contributing to ongoing transmission.

- Investigation of transmission clusters can identify key characteristics of the underlying risk network to guide intervention efforts to improve outcomes and prevent additional infections.
    o Investigation includes the examination of existing data, including partner services data, or collection of new data to identify factors associated with transmission. Investigation will be discussed in detail in Section 4, 'Assessing, prioritizing, and responding to clusters'.
- Intervening in risk networks can improve outcomes and interrupt transmission through activities that include:
    o Identifying persons with diagnosed HIV infection in the transmission cluster who are out of care, and ensuring that these persons are linked to or re-engaged in care
    o Identifying persons with undiagnosed infection who are part of the transmission cluster, and linking these persons to care
    o Identifying HIV-negative persons in the risk network who are at risk for acquiring HIV and offering effective prevention interventions, such as PrEP
    o Interventions at the transmission cluster or population-level to address social-structural or programmatic factors that contributed to transmission
    o Other transmission cluster and risk network-specific interventions
- By expanding our knowledge of transmission dynamics, transmission cluster data can be a powerful tool to help target the interventions we know are effective (engagement in care, HIV testing, PrEP).

Using transmission cluster data to target prevention efforts requires identifying, interpreting, prioritizing, investigating, and intervening in growing transmission clusters. Each of these activities will be described in more detail.

Section 3. Identifying growing transmission clusters using surveillance data

Routine analyses of surveillance data can identify growing transmission clusters that would otherwise not be identified. Transmission clusters can be identified both through molecular and time-space clusters, and surveillance systems should systematically use all data and methods (time-space and molecular sequence-based approaches) available to detect clusters and outbreaks.

How are molecular clusters identified?

HIV is constantly evolving

- The molecular sequence (also called nucleotide sequence) of HIV accumulates changes over time. Immediately following transmission of HIV between two people, the molecular sequence of the HIV strain in the recipient will be nearly identical to strains found in the transmitting person. As time passes, however, the strains infecting each person will change independently of one another and will look more and more different. In each new person infected, the virus will continue to change independently, so the HIV strains will look less and less similar over the course of a transmission chain. This relationship between the extent of the difference and the relatedness of strains is sometimes referred to as a 'molecular clock'. For more detail about the evolution of HIV, including the rate of change, please see Appendices B and C.
- Analysis of the molecular sequence of viral strains can determine how genetically similar the strains are.

- People whose viral strains are genetically similar may be closely related (directly or indirectly) via transmission.

Analysis of sequence data
- There are many approaches to analyzing HIV sequence data. The current approach used by CDC and that should also be used by state and local health departments is transmission network analysis. In this analysis, each HIV molecular sequence is compared to every other HIV molecular sequence to identify pairs of sequences that are extremely similar (i.e., sequences that have a very small genetic distance, or difference). The level of genetic similarity used to identify closely related pairs is referred to as the **genetic distance threshold**.
  - o The genetic distance threshold applied can vary based on the goal of the analysis. For example, to identify cases related by recent and rapid transmission, a very close genetic distance threshold can be used—for example, 0.5% (which, for a sequence that is 1000 nucleotides long, corresponds approximately to 5 different nucleotides). A genetic threshold of 0.5% corresponds to approximately a maximum of approximately 2-3 years of viral evolution separating these strains (which may correspond to time since a common transmission event). By contrast, if the goal is to identify all possible cases that could be related to a given case, a larger genetic distance threshold can be used—for example, 1.5%. A 1.5% threshold corresponds to a maximum of approximately 7-8 years of viral evolution separating these strains.
- Pairs of cases with similar sequences are then connected with one another to construct transmission networks and identify clusters of very closely related cases.
  - o Lines are drawn between each pair of sequences that is closely related. This creates clusters that may have as few as two connected sequences, but can contain many more sequences that are connected.
  - o Although data on potential transmission linkages between persons (i.e., which pairs of people have genetically linked sequences) are useful in constructing molecular clusters, these data may be subject to misinterpretation by those not familiar with this type of analysis. As a result, CDC recommends minimizing use of these data and instead focusing on cluster-level data (i.e., considering all people in a cluster for intervention rather than focusing on people based on their position in the cluster). CDC does not recommend disseminating genetic network diagrams beyond the group of staff involved in the analysis of sequence data.

> **Limitations of and considerations for visualizing networks based on genetic data**
> Importantly, although some tools, such as Secure HIV-TRACE and MicrobeTrace, generate network diagrams of clusters based on genetic distance data, there are important limitations to drawing inferences from these data at an individual level. Although two persons infected with highly similar HIV strains could be directly linked through transmission, other transmission relationships could be consistent with this sequence similarity: both could have been infected from a third source, or they could be connected indirectly through a transmission chain including 1 or more intermediaries. Because of this scientific uncertainty, the potential for the misuse and misinterpretation of these data presents a concern. Moreover, presence of or patterns of linkages can be affected by timing of diagnoses and drug resistance testing. Although analysis of molecular data to identify growing transmission clusters can identify important opportunities for individual- and cluster-level public health interventions, inferences about specific transmission linkages or indirect inferences about sexual or other risk behaviors should not be used to guide services or follow-up at the individual level. Because of the potential for misinterpretation of these diagrams, **it is not recommend to disseminate genetic network diagrams beyond the group of staff involved in the analysis of sequence data.**

- The time period of data included in the analysis may vary depending upon the goals. CDC recommends that analyses focused on identifying clusters that represent recent HIV transmission include only sequences from cases diagnosed in recent years (e.g., the 3 most recent years).
  - Using a shorter time period, such as 3 years, can identify bursts of recently infected cases that indicate recent and potentially ongoing transmission. Although persons with diagnoses outside of the time window who are out of care could be sources of ongoing transmission, limiting the time window allows the analysis to flag clusters with substantial recent growth. A secondary analysis can then be conducted to identify additional potentially related persons with HIV who might be considered in the investigation.
  - Analysis conducted for other purposes, such as understanding a larger transmission network, might include cases diagnosed over a much longer time period.
- For details about HIV sequence data analysis, including the selection of the genetic distance threshold to define a cluster, a description of the regions of the HIV genome included in the analysis, and other technical details, please see Appendices B and C.

How are molecular sequence data generated and collected?

Generation of molecular sequences

- Molecular sequences are generated through drug resistance testing.
- Drug resistance testing is conducted to identify mutations associated with viral resistance to antiretroviral medications and helps the HIV care provider select an appropriate treatment regimen. This testing is recommended for all persons with diagnosed HIV infection, with the recommendation that testing be conducted at entry to HIV care.
- Drug resistance testing is typically ordered by providers at entry to HIV care, but can also be ordered at later time points (for example, if a patient is on treatment but does not have a suppressed viral load).
- The final output of drug resistance testing is a report identifying known mutations that confer drug resistance, which is sent to the care provider. The HIV molecular sequence is generated as a part of the testing process, and laboratories can retrieve this information for surveillance reporting purposes. Current testing methods generate sequences using a sequencing method called Sanger sequencing.

Collection of molecular sequence data

- Laboratories report HIV molecular sequence data to HIV surveillance jurisdictions; these data are an integrated component of the National HIV Surveillance System in all jurisdictions.
- Health departments report all HIV case information collected by HIV surveillance to CDC (demographics, transmission category, CD4 results, viral load results, HIV molecular sequence) without identifying information (name, street address). See Figure 3a.
- Collection of HIV sequence data is monitored as part of the National HIV Surveillance System, with the target of sequence reporting of ≥60% of persons with diagnosed HIV infection.

> **PS18-1802 Measure 1.2.11:** *≥60% of cases for a diagnosis year have an analyzable molecular sequence, assessed at 12 months after the diagnosis year.*
>
> Jurisdictions are expected to achieve molecular HIV sequence reporting of ≥60% of persons with diagnosed HIV infection each year. Achieving high sequence reporting completeness is essential in order to detect clusters and to capture the greatest extent of molecularly linked cases in a cluster.

Figure 3a. Collection of HIV molecular sequence data
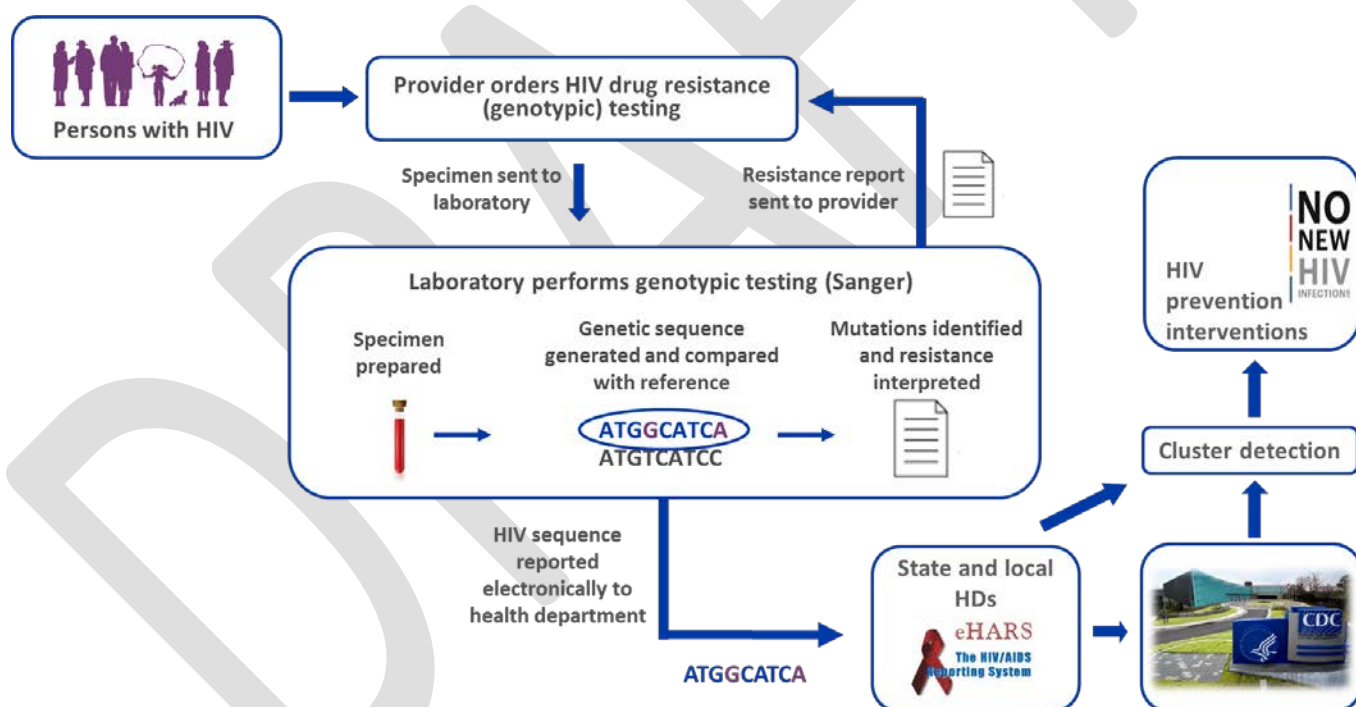
Limitations in molecular sequence data

- Although drug resistance testing is recommended for all persons with diagnosed HIV infection, in practice, not all persons receive a drug resistance test.
- In some instances, even if a drug resistance test is completed, reporting challenges prevent a health department from receiving a molecular sequence for a person.
  - For example, in some jurisdictions, sequences may not be reported for persons receiving medical care in federal systems (e.g., Veterans Affairs or federal prisons) or those in blinded clinical trials.

- o In some cases, the identifying and locating information provided by the laboratory could be so incomplete that the sequence cannot be linked to a person in the surveillance data.

How can jurisdictions identify molecular clusters?

- Analysis of molecular HIV surveillance data by state and local HIV surveillance programs can allow for identification of clusters in closer to real time and for monitoring of clusters that have been previously identified. It is important to address barriers to reporting and processing of HIV sequences to allow prompt identification of growing clusters.
- Secure HIV-TRACE (supported by CDC, University of California, San Diego, and Temple University) is a bioinformatics tool that allows HIV surveillance programs to detect, analyze, and visualize clusters. This tool is available to jurisdictions to conduct analyses locally.
  - o HIV surveillance programs are expected to analyze their data using Secure HIV-TRACE at least monthly.
    - HIV surveillance programs can obtain additional information and technical assistance related to Secure HIV-TRACE by emailing hivtrace@ucsd.edu.
  - o Separately funded city/county HIV surveillance programs should collaborate with their respective state health department to develop standard analysis protocols (i.e., to determine if and when data will be analyzed separately or jointly).
  - o An enhancement to facilitate the identification of multijurisdictional clusters in Secure HIV-Trace is currently in development. CDC will routinely analyze national data to identify clusters that involve cases from multiple jurisdictions. Discussion of multijurisdictional clusters can be found in Section 7, 'Approaching multijurisdictional clusters'.

> **PS18-1802 Measure 3.1.1:** *Analyze surveillance data using CDC-recommended approaches at least monthly to identify HIV transmission clusters and outbreaks.*
>
> Under PS18-1802, all jurisdictions are expected to collect HIV sequence data and run local analysis at least monthly using Secure HIV-TRACE. Additionally, jurisdictions should analyze HIV case surveillance data monthly to identify time-space clusters.

- When partnering with external collaborators (e.g., academic institutions) to analyze sequence data to identify clusters, ensure the jurisdiction's protocols consider key factors, including data sharing and security and confidentiality of HIV-related information. Such collaborations should have a legitimate public health purpose and support the jurisdiction's HIV prevention efforts, use de-identified data if data are shared, and involve the minimum amount of information necessary. It is recommended that the parameters of such collaborations be outlined in a written project plan or agreement (e.g., a data use agreement [DUA], Memoranda of Agreement [MOA], Memoranda of Understanding [MOU] or business contract if applicable). Agreements should include a description of the project and goals, methods, data elements, access, and storage requirements, roles and responsibilities, confidentiality and security provisions, disposition of the data, and a description of the dissemination plan or products. Some collaborations determined to be non-research or exempt from Institutional Review Board (IRB) review should still be approved by the jurisdiction's Overall Responsible Party (ORP) and may benefit from an additional review and vetting by a standing data analysis review group or public health advisory group (e.g., community planning group or advisory board) or ad hoc review group. Determining whether proposed data sharing with an academic institution supports public health and a jurisdiction's HIV prevention efforts often involves ethical and legal questions. Consulting with an autonomous body of persons experienced in public health ethics may provide insight and feedback on proposed activities.

- Any use of sequence data for research purposes must be carefully considered and must be approved by the jurisdiction's ORP and be subject to IRB approval as appropriate. Any use of identifiable surveillance data as part of any research is contingent on a clearly stated public health purpose, a demonstrated need for identifiable data, IRB and ORP approval, and the signing of a confidentiality agreement regarding rules of access and final disposition of the data and plans for dissemination or publication of results. Depending on the amount and type of data requested, the use of nonidentifiable data for research is generally permissible but because of the sensitive nature of cluster analyses, IRB approval is recommended and may be required. For more information, see the [Data Security and Confidentiality Guidelines for HIV, Viral Hepatitis, Sexually Transmitted Diseases, and Tuberculosis Programs](#).

How can decisions in the analysis to identify molecular clusters impact the cluster assessment, prioritiziation, and response process?

Key decisions in the analyses to identify clusters can have a large impact on the number and composition of clusters identified. For example, analysis using a larger genetic distance threshold (e.g., 1.5%) can identify clusters where some or all transmissions occurred in the more distant past, and where transmission connections between cases are more likely to be indirect; these clusters would likely include more persons and be more intensive to investigate. Additionally, analysis conducted using datasets that include cases diagnosed over many years may result in the identification of large, complex clusters comprised of many independent transmission chains, where investigation and intervention could be challenging. In general, to focus on recent transmission, we recommend identifying clusters using a smaller genetic distance threshold (0.5%) which would identify clusters of persons more closely temporally linked, and limiting analyses to cases diagnosed in the most recent 3-year period. CDC's criteria to identify priority clusters includes a 0.5% genetic distance threshold and the most recent 3-year period of data.

How does CDC identify molecular clusters?

- CDC conducts routine analyses to identify clusters that are concerning for recent and rapid transmission of HIV. CDC analyses will not be as timely as local analyses, because of the timeline for submission of data to CDC and data processing prior to the data becoming available for analysis. However, CDC analyses can help ensure the identification of clusters meeting national priority cluster criteria, particularly those that cross jurisdictions.
- These analyses are conducted using national data that are available each quarter (based on data transmitted by HIV surveillance jurisdictions to CDC in March, June, September, and December).
- Prior to analysis, all HIV sequences in the national dataset are evaluated to determine the quality of the data and remove potential contaminants. Only sequences that include protease or reverse transcriptase regions of the HIV genome and are of sufficient length are included in the analysis.
- CDC analyzes data using a secure local installation of HIV-TRACE (HIV TRAnsmission Cluster Engine), a software tool developed by University of California, San Diego and Temple University.
- With the goal of identifying clusters consistent with recent and rapid HIV transmission, these analyses include only cases diagnosed in the most recent 3-year period, and use a genetic distance threshold of 0.5%.
- National priority clusters are defined based on the burden of HIV in the jurisdiction. For lower burden jurisdictions (defined by membership in CDC's low-burden jurisdiction workgroup), priority clusters are defined as clusters with at least 3 cases diagnosed within the most recent 12-month period. For all other jurisdictions, priority clusters are defined as those with at least 5 cases diagnosed within the most recent 12-month period. Many clusters cross jurisdictional boundaries; in

these cases, the priority cluster determination is made based on the number of cases diagnosed in the cluster overall, regardless of jurisdiction.

- When a cluster of concern is identified, the primary jurisdiction (the jurisdiction with the majority of cases in a cluster) is notified and a cluster snapshot describing the cluster is transmitted securely via SAMS. This cluster snapshot will include case count information for all cases in the cluster, regardless of jurisdiction, but will only include line-listed information for persons in the primary jurisdiction, unless a specific data sharing agreement between the jurisdictions involved and CDC allows this information to be shared. A cluster snapshot companion document, showing the elements included in a cluster snapshot, can be found in Appendix D. Jurisdictions that have persons involved in a cluster but are not the primary jurisdiction will have access to the statenos of their cases in the cluster through CDC, however the mechanism for routinely sharing this information is still being determined.
- CDC's prioritization criteria may be modified and expanded in the future, as capacity allows.

Assessing and responding to molecular clusters will be discussed in detail in Section 4, 'Assessing, prioritizing, and responding to clusters'.

Figure 3b. Examples of clusters that would not (a) and would (b) meet national priority criteria.

a)   b)

🔴 Diagnosis in most recent 12-month period

⚪ Earlier diagnosis

— Genetic similarity at or below genetic distance threshold
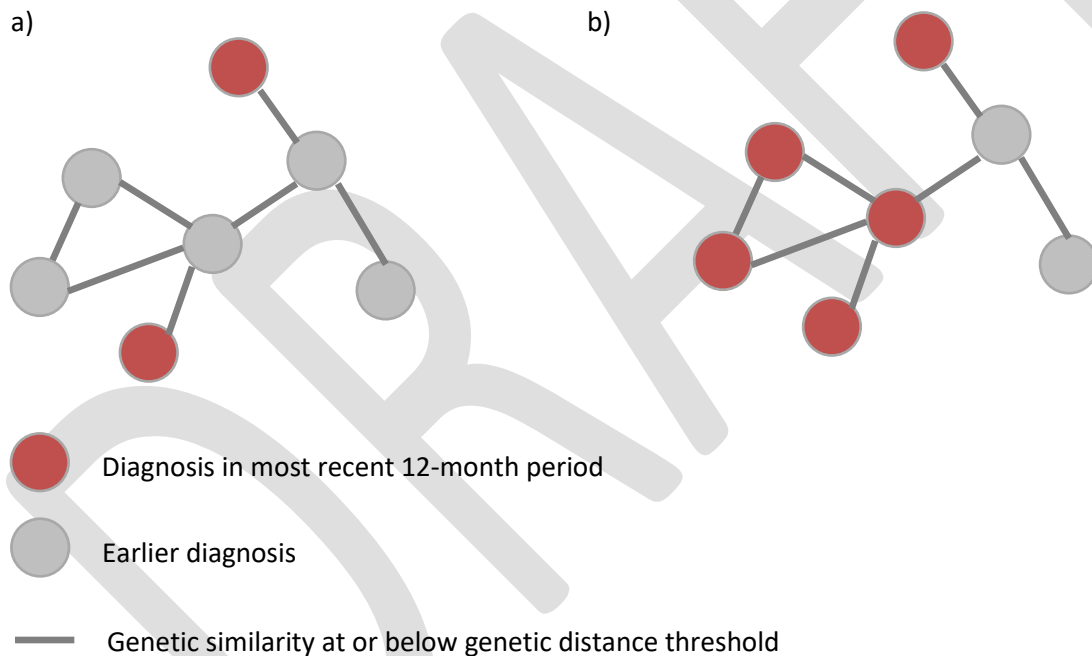
How are time-space clusters identified?

- CDC, with input from some jurisdictions who conduct this type of routine analysis, has developed methods for analysis of surveillance data to detect unusual increases or changes in normal HIV diagnosis and reporting patterns.
- Jurisdictions should routinely conduct time-space analysis locally. CDC provides a SAS program that jurisdictions can use to conduct time-space analysis at the local level. The program implements the current approach:
  - Define the time period of interest for analysis as the most recent 12 months of HIV diagnosis (e.g. Jan 2017-Dec 2017).
  - Define the comparison group as the previous 36 months (e.g. Jan 2014-Dec 2016).

- Define the geographic area of interest. At a minimum, this should include the state and each county within the state. Other geographic areas of interest may include metropolitan statistical areas, cross-jurisdictional counties, etc.
  - Calculate the HIV case counts for each county (or other relevant geographic area) for the most recent 12 months (or other time period of interest). Jurisdictions must also calculate the average HIV case counts per year for the same areas for the previous 36 months.
- Performing time-space analysis requires the following steps:
  - Calculate the standard deviation for the mean number of cases during the 36-month comparison group.
  - Construct an interval of $\pm$ 2 standard deviations around the mean.
  - Compare the results to the most recent 12 months of data. The CDC-provided SAS code creates an "alert" for case counts that fall more than two standard deviations above the mean. Jurisdictions may add additional, more stringent criteria in defining geographic and time period windows to suit their needs.
- Although the primary responsibility for time-space analysis is with jurisdictions, CDC will also routinely conduct these analyses to identify clusters crossing jurisdictions

Figure 3c. Example of analysis to identify time-space clusters, comparing number of diagnoses in the most recent 12 month period to 36-month baseline
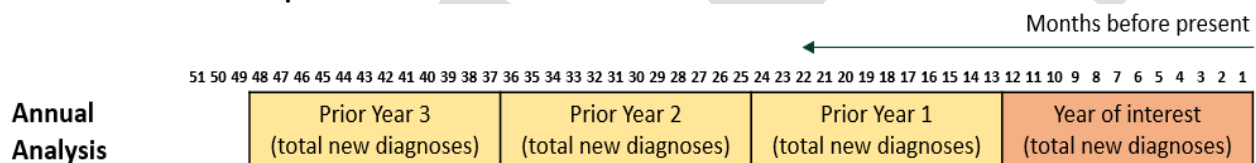
Prioritizing time-space clusters for investigation and intervention

Once time-space clusters have been detected, several factors should be considered in prioritizing the clusters for investigation and intervention activities. Jurisdictions must examine the data to determine whether there is evidence that a cluster represents recent and ongoing transmission, or if there are alternative explanations for the increase in diagnoses. Key sources of information for making the determination to investigate a time-space cluster includes the magnitude of increase, information about testing levels (especially recent changes in testing) in the area, demographic information, risk information, presence of early HIV infection, facility of diagnosis, and review of molecular data, when available.

Level of concern
- What is the magnitude of increase (absolute and relative)?
- What population(s) is/are involved in the time-space cluster(s)? Do any of these reflect populations of particular vulnerability, such as PWID? Have there been recent changes in the population of the area?

Evaluating time-space clusters to assess if increased case counts reflect recent increases in infections
- Is there evidence that recent diagnoses reflect recent HIV infection? To address this question, consider:
  - How many Stage 0 infections are there?

- How many diagnoses are acute?
- How many cases have a self-reported history of a recent negative HIV test?
- Are there coinfections with other STIs?
- How many had a high initial viral load (e.g. >500,000)?
- Is molecular data available on any of the cases? If so, does molecular analysis indicate the presence of a single transmission cluster? If not, does it show multiple smaller transmission clusters?

Alternative explanations for time-space clusters
- Have there been documented increases of HIV diagnoses in this area? If so, consider the following possible alternative explanations:
  - Have there been testing events, population changes, policy changes, or other reasons for increased diagnosis? For example, were a large number identified at testing sites that are new or have dramatically expanded testing? Discussions with HIV prevention staff (e.g. DIS, field staff, partner services staff) may reveal testing or other prevention initiatives that could have resulted in an increase in diagnoses.
  - Are there any data quality issues that may account for these increases, such as duplicate cases? (Performing a soundex check is recommended.)
  - Were any of the cases previously diagnosed?

Investigating and responding to time-space clusters
An investigation should be conducted for all time-space clusters determined to be a priority after reviewing the data described above. HIV surveillance and prevention staff, at a minimum, should be involved in reviewing and discussing the data.

Investigation efforts for time-space clusters should begin with reviewing available data (HIV and STD surveillance, partner services, etc.) for the cases that were diagnosed in that county during the previous 12 months. A line list with key variables (transmission mode, gender, race/ethnicity, age, geographic area, care status, initial viral load, most recent viral load to-date, stage 0 at diagnosis, acute diagnosis, and date of last negative HIV test) can be helpful to understand commonalities and potential interventions. As linkages between cases are identified, or as molecular cluster data becomes available, staff may choose to narrow the investigation to focus on the underlying transmission cluster(s) or broaden it to include other cases that may not have been identified through time-space analysis but have been identified as part of a molecular cluster. However, individuals without HIV sequences may still be a part of the transmission cluster. Defining the transmission cluster and larger risk network, along with common facilities of diagnosis and possible exposure, can provide guidance into which types of interventions would be most useful to interrupt transmission. For more guidance on investigating and intervening in transmission clusters, see Section 4 of this document.

Jurisdictions will report the results of time-space cluster analysis and response quarterly through the cluster investigation worksheet (see Appendix E) for all identified clusters of concern that jurisdictions deemed warranted an investigation. In some instances, more frequent reporting should take place, when the cluster(s) identified demonstrate the potential for heightened concern or enhanced response efforts. See Section 4 for guidance on criteria for enhanced cluster response efforts.

Section 4. Assessing, prioritizing, and responding to clusters

Analysis of HIV surveillance data can lead to the identification of large numbers of molecular and time-space clusters in a jurisdiction, and not all clusters will be equally concerning from a public health perspective. The level of public health response needed for each cluster will vary across a spectrum; for some clusters, routine public health actions such as partner services and linkage to care activities might be sufficient, while for other clusters, enhanced response activities might be needed (for additional information on implementing an enhanced response, see 'Managing HIV and Hepatitis C Outbreaks Among People Who Inject Drugs'). Assessing and prioritizing molecular clusters to determine the level of response needed is important to effectively focus public health resources on clusters where enhanced response activities are likely to have the greatest impact on increasing case detection and interrupting disease transmission.

National priority clusters

As described in Section 3, 'Identifying growing transmission clusters using surveillance data', CDC's current molecular cluster identification approach focuses on identifying a small subset of clusters nationally that are most concerning for recent, rapid transmission that could represent an outbreak. Jurisdictions should ensure that their routine analyses of HIV sequence data will identify clusters that meet national priority cluster criteria in which priority clusters are selected based on clustering at a low genetic threshold (0.5%) that is consistent with recent transmission (choosing a low threshold identifies pairs of sequences that are very closely related, i.e., there has not been time for the virus to evolve much between transmissions).

Priority Clusters. CDC considers priority HIV clusters as those defined at 0.5% genetic distance threshold in the most recent 3-years of data, where at least 5 cases in the cluster were diagnosed in the most recent 12 month period. For lower burden jurisdictions (as defined by membership in CDC's low-burden jurisdiction workgroup), priority clusters are those with at least 3 cases in the most recent 12 month period.

Jurisdictions might also have jurisdiction-specific criteria to identify additional local priority clusters, dependent on local epidemiology and resources.

Jurisdictions may develop criteria to identify additional local priority clusters, based on local epidemiology and resources.

National priority clusters are all suggestive of recent, rapid transmission; transmission rates in these clusters have been found, on average, to be 11 times the estimated national transmission rate[1]. Not all priority clusters are of equal concern, however; some priority clusters might be more likely to contribute disproportionately to new infections and poor outcomes than other clusters. While some clusters might be contained with a focused response, others might require enhanced or escalated public health response. The specific nature of the response needed to effectively interrupt transmission in a cluster may vary from one cluster to the next, and the level of response activity needed will also vary. Thoughtful consideration of each cluster, including its potential for growth, poor outcomes, and potential approaches to intervene to interrupt transmission, is essential.

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[1]France AM, Panneer N, Ocfemia MCB, Saduvala N, Campbell E, Switzer WM, Wertheim JO, Oster AM. Rapidly growing HIV transmission clusters in the United States, 2013–2016. Conference on Retroviruses and Opportunistic Infections, 5 March 2018.

Figure 4a, 'Roadmap to investigating and intervening in transmission clusters', introduces key steps of the cluster assessment and response process, which are described in more detail in the corresponding sections below.

When clusters of concern are identified, programs are to share pertinent information about the cluster, including analysis, investigation, and intervention results, with CDC. Communication with CDC about clusters should take place quarterly; however, for highly concerning clusters that require an urgent response, initial notification to CDC is required to the joint monitoring team within 72 hours.

The 'Cluster investigation worksheet and companion document' (Appendix E), should used by programs to organize information about cluster investigations and facilitate communication with CDC.

PS18-1802 Measure 3.1.2: *For each cluster of concern identified through analysis of surveillance and other data, submit analysis, investigation, and intervention results to CDC quarterly after identification of cluster until investigation and intervention activities are closed.*

Each quarter, jurisdictions must report analysis, investigation, and intervention results for all clusters meeting national priority cluster criteria that have been identified in the jurisdiction, and for which response activities have not yet been closed. The 'Cluster investigation worksheet' (see Appendix E) is a tool to facilitate this communication.

Figure 4a. Roadmap to molecular cluster assessment and response

This figure outlines the cluster assessment and response process, described in detail in this section. For all clusters meeting national priority cluster criteria, Steps 1,2a, 2b, and 4 should be completed; the enhanced response activities described in Step 3 should be considered for concerning clusters, as appropriate.

Step 1	**Identify known transmission cluster and risk network**
	 • Determine how transmission cluster and risk network will be defined (Figure 4b)
	 • Systematically review HIV and STD data (including partner services investigations) for all persons in the molecular cluster to identify known members of the transmission cluster and risk network, and assess completeness and outcomes of partner services investigations
	     o For HIV-positive persons in the transmission cluster, use surveillance and other data sources to obtain updated viral suppression information and early infection status
	     o For HIV-negative persons in the risk network, determine time since most recent HIV test and whether the person was referred for PrEP

Step 2a	**Assess level of concern and need for enhanced investigation and response**
	 • Review data collected in Step 1 for the transmission cluster and risk network to assess:
	     o How effectively the transmission cluster and risk network have been identified
	     o Potential for ongoing transmission, poor outcomes, and other concerning factors
	     o Reach and coverage of HIV testing and PrEP within the cluster
	 • Determine whether enhanced investigation and/or investigation activities are needed

Step 2b	**Initiate critical initial interventions (for all priority clusters)** • **Initiate strategies to promote viral suppression for all HIV-positive persons** who do not have evidence of viral suppression, particularly those with early infection • **Initiate testing and re-testing activities, including PrEP referral**, for persons in the risk network who are not known to be HIV infected • Initiate partner services for all persons in the transmission cluster for whom partner services was not already initiated
Step 3	**Conduct enhanced investigation and intervention activities, as appropriate** • Consider strategies to *identify undetected infections* including targeted testing, social network interviewing, and other prevention interventions • Consider strategies to *better understand factors associated with delays in diagnosis or interruptions in care*, or other factors contributing to transmission in the cluster; strategies can include medical record review or qualitative interviews • Consider *additional interventions depending on the characteristics of the cluster*, which could include but are not limited to targeted outreach at venues, HIP interventions, communication campaigns through media or apps, health alerts, and scale-up of PrEP or testing services
Step 4	**Monitor progress and determine when a cluster response should be closed** • Continue to monitor cluster growth over time to determine whether transmission has been interrupted or is still ongoing • Assess the impact of the investigation and subsequent interventions • Identify lessons learned for future cluster response activities • Determine when a cluster response should be closed *New increases in diagnoses in a cluster for which response activities had ceased should be re-evaluated and re-initiation of response activities should be considered

Cluster assessment

Once a priority cluster (e.g., based on guidance criteria or local-priority) is identified, the next step is to assess the cluster. Cluster assessment includes evaluating available data to gauge the extent of transmission in the cluster, the level of concern for ongoing transmission and poor outcomes, and the likelihood that transmission has stopped. Because the molecular cluster identified through analysis will include only a subset of the full transmission cluster, reviewing available data to determine what has already been identified of the full transmission cluster and risk network is a critical first component of the assessment process.

Step 1. Identify known transmission cluster and risk network

Data from both STD and HIV partner services investigations, in addition to surveillance data, are essential for identifying what is known of the transmission cluster. As described in Section 1, 'What is a transmission cluster?', the transmission cluster will include, in addition to those persons identified through molecular analysis: 1) persons with diagnosed HIV infection who do not have a sequence available for analysis (either because they did not enter care, they entered care, but have not had a genetic resistance test, or they entered care and have had a genetic resistance test, but the sequence was not transmitted to the health department for analysis, or was of poor quality and could not be analyzed), and 2) persons with undiagnosed infection.

In reviewing available data to identify what is known of the transmission cluster, a definition of criteria to include persons in the transmission cluster is needed. At a minimum, this transmission cluster definition should include HIV-infected sex or needle-sharing partners of persons in the molecular cluster. Additional considerations could expand who is considered to be a part of the transmission cluster. This expansion can improve the understanding of the full transmission network, and the potential effectiveness of interventions (Figure 4b). Keep in mind that HIV-infected persons who are truly a part of the transmission cluster but were not identified as linked to a molecular cluster member through partner services, or in whom HIV infection has not yet been diagnosed, will not be identified through this data review. Therefore, this review of existing data will capture those persons who are known to be part of the transmission cluster, but it is unlikely to capture everyone in the transmission cluster.

A risk network will include, at a minimum, all sex or needle-sharing partners of persons in the molecular cluster who are known to be HIV uninfected, or for whom HIV status is unknown. As with the transmission cluster, additional considerations could expand who is considered to be a part of the risk network; such expansion could improve the effectiveness of interventions.

Figure 4b. Suggested definitions for molecular clusters, transmission clusters, and risk networks, with considerations for expansion.

Risk Network	• All persons in the transmission cluster, **plus a**ll HIV-uninfected or HIV-unknown sexual or needle-sharing partners of persons in the identified molecular cluster or their immediate HIV-infected partners^* • Expansion considerations: Partners from greater than a one-year timeframe of HIV diagnosis, social contacts of index cases (e.g., response to the question, 'Who else do you know who could benefit from HIV testing or PrEP)?'**, and partners of partners
Transmission Cluster	• All persons in the molecular cluster plus all HIV-infected sexual or needle-sharing partners of persons in the identified molecular cluster or their immediate HIV-infected partners* • Expansion considerations: HIV-infected partners from greater than a one-year timeframe of HIV diagnosis, HIV-infected social contacts of index cases (e.g., response to the question, 'Who else do you know who could benefit from HIV testing or PrEP)?'**,
Molecular Cluster	• All persons in the molecular cluster as defined at 0.5% within a 3 year period • Expansion considerations: all persons in the molecular cluster defined at 0.5% across all years of data; all persons connected directly to a person in the 0.5% cluster at the 1.5% genetic distance threshold

*Identified as partners within a 1-year timeframe of HIV diagnosis, or anytime following HIV diagnosis during which the index case was not virally suppressed.

** Note that in some cases, HIV infected partners identified through partner services might have discordant molecular sequences. For purposes of public health response, these persons should still be included in the transmission cluster.

^*Note that the risk network will include all claimed partners, even if these persons were not named, did not have sufficient information to initiate contact, or cannot be located.

Named partners with sequences that are not closely related

In some situations, molecular sequence data will not be available for HIV-infected partners of molecular cluster members. In other situations, however, these data will be available, and may show that the sequences are not closely related (i.e., >1.5% genetic distance threshold). By virtue of being named as a partner, these persons are part of a related network. Because they are part of the same network where recent, rapid HIV transmission has been identified, CDC does not recommend excluding persons from a transmission cluster and risk network based on infection with HIV strains that are not closely related, for the purposes of public health action. The presence of multiple distinct strains suggests that persons in the associated risk network could be at even higher risk for HIV infection, as it suggests the potential for multiple overlapping risk networks, or multiple introductions of HIV into a network. For these reasons, critical intervention activities are particularly warranted in these situations.

Conducting an initial review of partner services data to assess the transmission cluster and risk network

Information from Partner Services (PS), including both HIV and STD PS, is a critical element to understanding what is known of the transmission cluster and risk network, and assessing what investigation and intervention activities are needed for the cluster. After determining how the transmission cluster and risk network will be defined (Figure 4b), the next step is to systematically review STD and HIV PS data for all persons in the molecular cluster to identify what is known of the transmission cluster and risk network. Data systematically collected from PS interviews and notes from PS interviews are important sources of information, and can add important context to a cluster review. Information from the cluster review, may reveal common behaviors, venues, or methods of partner recruitment that can be important for intervention in a cluster.

Persons in a cluster might have had multiple PS interviews over many years, particularly if there were multiple STD diagnoses prior to HIV diagnosis. Including partners elicited within a 1 year timeframe before HIV diagnosis (or anytime afterward, during which the person was not virally suppressed), can help focus on the likely network most relevant to current HIV transmission.

Key considerations when conducting an initial review of these data to assess the transmission cluster and risk network include:
- How many HIV-infected persons in the molecular cluster had PS interviews prior to cluster detection? How long ago were they interviewed?
- What is the total number of claimed partners (the total number of partners identified, whether named, anonymous, or marginal), in addition to those named? Claimed partners, including anonymous and 'marginal' partners (those for which some information is provided, but it is insufficient to locate the person) should be included in the consideration of the underlying risk network and potential transmission cluster size, even if the persons cannot be identified or located.
- How many persons in the molecular cluster were connected to other persons in the molecular cluster through named sexual partner/needle-sharing contacts?
- What were the results of HIV testing conducted through PS for named partners of persons in the molecular cluster?
  - For partners who tested HIV negative, how many were referred for PrEP?
- How much time has passed since the data were collected? How have risk behaviors, risk networks, and other factors changed over that time period?
- In some cases, screen names, handles on internet sites, or apps might be available (perhaps in interview notes). If so, consider including this information as it could provide a mechanism to make connections between cases and identify additional partners. Additionally, some programs are able to use this information to reach out to contacts or more broadly to others in the network.
- Is additional information available in PS data or interview notes that can help identify factors associated with transmission in the cluster, and potential intervention points? For example, were sex partner recruitment venues named (e.g., sex club, bar, etc.) that may help inform cluster interviews? The same may be true for needle-sharing (e.g., a location with lots of IDU). Were specific risks such as drug use (e.g, meth, opioids, etc.), gang affiliation, or incarceration history mentioned that may help define the risk network?

Summarizing the results of this initial review of PS data will allow for an overall assessment of the implications of the PS results for the transmission cluster and risk network size, and of the extent to which the full transmission cluster and risk network is likely to have been identified by PS work that has already been conducted. These are critical elements of the assessment of the level of concern of the

cluster for ongoing transmission, and of prioritization for enhanced or escalated response activities. Example summary tables for this data include Table 4a, 'Example summary of outcomes of initial partner services investigation', and Table 4b, 'Example table of initial partner services testing results')

Table 4a. Example summary of outcomes of initial partner services investigation

Molecular cluster size	Number interviewed	Total number of partners claimed	Number of named partners	Number of marginal partners	Number of anonymous partners	Number of persons in the molecular cluster linked to at least one other person in the molecular cluster through PS data

Table 4b. Example table of initial partner services testing results

Tested: # = Click or tap here to enter text.		Not Tested: # = Click or tap here to enter text.	
New Positive[1]:	# = Click or tap here to enter text.	Previous Positive:	# = Click or tap here to enter text.
Acute:	(subset: # = Click or tap here to enter text.)	Refused:	# = Click or tap here to enter text.
Negative:	# = Click or tap here to enter text.	Not Located:	# = Click or tap here to enter text.
Referred for PrEP:	(subset: # = Click or tap here to enter text.)	Outside Jurisdiction:	# = Click or tap here to enter text.
Unknown:	# = Click or tap here to enter text.	Deceased:	# = Click or tap here to enter text.
		Other:	# = Click or tap here to enter text.

Review surveillance, partner services and other available data for the full transmission cluster and risk network.

Review of PS data will result in the identification of additional persons in the transmission cluster that were not in the molecular cluster (e.g., named partners of persons in the molecular cluster). To create a full line list for the known transmission cluster and risk network, create a line list of all persons in the molecular cluster, and add all partners identified in the review of PS. Following the creation of this full line list, the next step of the cluster assessment process is to review surveillance data, PS and other readily available data for all persons in the transmission cluster and risk network.

In addition to HIV surveillance data, data sources to consider reviewing include STD surveillance data, viral hepatitis surveillance data, Ryan White HIV/AIDS program data (including ADAP), primary care

services, ED visits, STD clinic data, substance abuse and mental health service databases, homeless outreach and services databases, jail and detention data bases. Data from persons in the cluster who reside in other jurisdictions should also be included (see Section 7, "Approaching multijurisdictional clusters'). Key data elements to include in this line list are illustrated in Table 4c, 'Suggested data elements to include in line list of the transmission and risk network'. More discussion of suggested variables can be found in Appendix F, 'Suggested variables to capture during a cluster investigation'.

> **Cases outside of your jurisdiction.** Transmission clusters and risk networks often cross jurisdictional borders, and investigations should not stop at these borders. Additionally, some persons may reside in one jurisdiction, have partners in or seek care in a different jurisdiction. Cluster assessment and response should include all persons linked to a cluster, regardless of jurisdiction. For details on coordinating investigations across jurisdictions, see Section 7, 'Approaching multijurisdictional clusters'.

The goals of this review are to assess the potential for ongoing transmission and poor outcomes in the identified transmission cluster, identify persons for whom public health action is needed to ensure linkage to care and viral suppression, and identify any factors that could potentially be facilitating transmission in the cluster that are apparent from this readily available data. For HIV-negative persons in the risk network, available data should be reviewed to determine time since most recent HIV test and if a referral for PrEP was provided.

Table 4c. Suggested data elements to include in the line list of the transmission cluster and risk network

Data source	Variables
eHARS	Stateno, date of HIV diagnosis, facility at HIV diagnosis, residence at HIV diagnosis, current residence, transmission category, sex, age, race/ethnicity, date of last HIV negative, acute/stage 0 status, AIDS at diagnosis, most recent VL value, most recent VL date, whether drug resistance detected, specific drug resistance mutation
Partner services	Number of partners claimed, number of partners named, number of partners tested, number of new positive partners identified, number of previous positive partners, number of partners testing HIV negative, risk behaviors
STD surveillance databases	Syphilis diagnoses and dates, other STD diagnoses and dates
Hepatitis surveillance databases	Hepatitis A,B,C infection status
Other data sources/variables to consider: Ryan White HIV/AIDS program data (including ADAP), primary care services, ED visits, STD clinic data (e.g., visits to municipal STD clinics and dates), substance abuse and mental health service databases (e.g., ever use of mental health or substance abuse services and dates), homeless outreach and services databases, jail and detention data bases (e.g., incarceration history).	

> **Organizing and managing data generated in a cluster investigation**
> A cluster investigation will generate a large amount of information. The development of a database to input, organize, and maintain this information will be critical to effectively assessing the data. A simple excel spreadsheet may be sufficient for many investigations, though a more complex relational database could also be useful, particularly when managing data on connections between patients. Considerations for developing a database for cluster investigation, including key variables to consider collecting, are described in Appendix H, 'Additional resources for cluster investigation'.

Synthesize data

Once data have been systematically gathered for all persons in the transmission cluster and risk network, the next step is to systematically review these data to address the questions outlined in Step 2a, 'Assess priority level for enhanced investigation and response', below.

The purpose of this data synthesis is to facilitate a review of the data for all persons in the transmission cluster to characterize what is known about the transmission network, identify any commonalities between cases, address the key questions outlined in the above sections, and other key questions determined to be important to the investigation. This review could include both quantitative and qualitative reviews of the data, such as simple descriptive statistics for systematically collected variables, and a qualitative assessment of themes identified in PS notes. Simple quantitative analysis could be conducted in MS Excel, or data could be imported to SAS or other analysis tools for analysis.

Narratives

Often, narrative descriptions of information gathered about a cluster, or an individual person in a transmission cluster or risk network, resonates in a way that quantitative data cannot. Generating patient or cluster narratives can be helpful to identifying key themes and factors that could be contributing to high levels of transmission in a cluster. Additionally, cluster-level narratives can be helpful for communicating about clusters internally and with key stakeholders.

Patient narrative

Patient narratives can contain key demographic, social, and risk information related to the patient, as well as present the clinical story from any initial symptoms or presentation to testing, to the diagnostic course and care/treatment history. Such narratives can help identify recurring issues and themes across the transmission network and may help identify potential intervention points. Additionally, such narratives can be compelling to tell the 'story' of the transmission network, and may help communicate key issues to leadership and stakeholders. While narratives could be initiated from review of available surveillance and PS data, in many cases, these narratives could be further developed by adding information from medical chart reviews and patient interviews or re-interviews, if conducted.

Cluster narrative

A narrative that describes a cluster can summarize key findings, which may be particularly useful in reviewing cluster investigations or if a cluster begins to grow again at a later time. A cluster narrative can include a description of the population and geographic area involved, timing of HIV diagnoses in the cluster, findings related to the likely scope of the transmission cluster and risk network, and any key commonalities or factors pertinent to ongoing transmission in a cluster.

Example cluster narrative
- Molecular cluster including 12 HIV diagnoses among predominantly young black MSM in a rural part of State X within the 18 month period ending December 2017; all 7/12 with testing history data have evidence of infection within 12 months of diagnosis. All sequences have K103N mutation. 6 of 12 have no evidence of viral suppression.
- Partner services conducted for 8 of 12 molecular cluster members identified 3 named partners, 1 new positive, 1 prior positive, and 1 uninfected. Cluster members identified large numbers of anonymous or marginal partners, with multiple cluster members identifying GRINDR as the primary way they meet partners.
- Likely scope of transmission cluster and risk network much larger than identified through molecular analysis and available partner services information.

Data visualization

Diagrams to visualize connections between patients identified through partner services can be helpful to synthesize and illustrate what is known about potential transmission relationships between persons in the cluster. Multiple network visualization tools exist, including MicrobeTrace, a CDC-developed software tool that enables rapid visualization of networks and associated data.

Limitations of and considerations for visualizing networks based on genetic data
Importantly, although some tools, such as Secure HIV-TRACE and MicrobeTrace, generate network diagrams of clusters based on genetic distance data, there are important limitations to drawing inferences from these data at an individual level. Although two persons infected with highly similar HIV strains could be directly linked through transmission, other transmission relationships could be consistent with this sequence similarity: both could have been infected from a third source, or they could be connected indirectly through a transmission chain including 1 or more intermediaries. Because of this scientific uncertainty, the potential for the misuse and misinterpretation of these data presents a concern.Moreover, presence of or patterns of linkages can be affected by timing of diagnoses and drug resistance testing. Although analysis of molecular data to identify growing transmission clusters can identify important opportunities for individual- and cluster-level public health interventions, inferences about specific transmission linkages or indirect inferences about sexual or other risk behaviors should not be used to guide services or follow-up at the individual level. Because of the potential for misinterpretation of these diagrams, **it is not recommend to disseminate genetic network diagrams beyond the group of staff involved in the analysis of sequence data.**

Step 2a. Assess level of concern and need for enhanced investigation and response

For all clusters meeting national priority cluster criteria, critical interventions, including linkage to care for all newly and previously diagnosed persons in the transmission cluster, HIV testing or re-testing, and PrEP referral for all high-risk HIV-negative persons in the risk network, should be initiated. These interventions are described in more detail in Step 2b, 'Initiate critical interventions'. At the same time that these interventions are being initiated, it is critical to review the available data from the cluster to determine whether additional investigation and response activities are needed in addition to these critical interventions.

Key questions to consider are: 1) How effectively have the transmission cluster and risk network been identified through partner services?, 2) What is the likelihood of or potential for ongoing transmission in the cluster?, 3) What are the opportunities that need to be leveraged?, and 4) Does transmission in the cluster appear have been interrupted with activities already conducted? Other considerations specific to local epidemiology and resource availability should also be considered.

Assessing the level of concern about a cluster is a dynamic process, and factors used for assessing concern could change as new information becomes available or new cases are added to a cluster. Particularly in settings where there are multiple clusters meeting national priority cluster criteria, it can be helpful to systematically assign a level of concern to each cluster, with these levels corresponding to activities. These levels of concern can be easily tracked and can be revised as more information becomes available or the situation changes. Example concern levels are illustrated in Table 4d.

Table 4d. Example cluster concern levels. For a detailed discussion of factors to consider in prioritizing cluster for response, see section below, 'Factors to consider in prioritizing clusters for additional action'

Concern level	Example of characteristics of clusters that could be consistent with this level of concern	Corresponding action
High	High levels of concern for continued ongoing transmission, impact on population groups known to be	**Additional response is needed (refer to Step 3, 'Conduct enhanced investigation**

Concern level	Example of characteristics of clusters that could be consistent with this level of concern	Corresponding action
	underserved or with high potential for poor outcomes.	**and intervention activities, as appropriate').**
Medium	Transmission cluster with concerning characteristics but uncertain potential for ongoing transmission or uncertainty about whether current public health activities have successfully interrupted transmission. For example, a cluster with some recent activity, but where few or no persons in the cluster were interviewed by PS so the likely extent of the transmission cluster and risk network is unknown.	**Additional information about the cluster is needed to determine whether additional action is needed.** **In addition to initiating critical interventions for persons in the transmission cluster and risk network, conduct key investigation activities to gather additional information.** **(refer to Step 3, 'Conduct enhanced investigation and intervention activities, as appropriate')**
Low	Transmission cluster with little recent activity, and no evidence of ongoing transmission (e.g., in the past 6 months).	**Initiate critical interventions for persons in transmission cluster and risk network.** **Continue to monitor, no additional investigation or intervention efforts at this time.**

Factors to consider in prioritizing clusters for additional action

How effectively have the transmission cluster and risk network been identified?

- Partner services is a key public health intervention, and provides information that can be a first step to identifying a transmission cluster and risk network. When partner services investigations are unable to effectively identify a full transmission cluster and risk network surrounding a molecular cluster, transmission could be ongoing with opportunities to intervene unrecognized. While it is not possible to know with certainty whether partner services effectively identified the transmission cluster and risk network, key data points can increase or decrease concern that the transmission cluster and risk network are not well captured.
- Are there cases in the molecular cluster for which partner services was not initiated, or where persons could not be located or refused interview? If partner services interviews were not conducted for cases in the molecular cluster, or if interviews were conducted but no partners were identified, this should raise concern as the extent of the underlying risk network is unknown.
- Did persons in the cluster claim partners that were not named? The presence of large numbers of anonymous or marginal partners suggests a much larger underlying transmission cluster and risk network. This could suggest a high potential for persons with undiagnosed infection contributing to ongoing transmission in the cluster. This can be particularly challenging in clusters where many persons use Apps, such as GRINDR, to find partners.
- Were cluster cases named as partners to other cluster cases? If so, this could be reassuring that the network has been captured well through partner services. If not, however, this suggests that the network has not been captured through partner services investigation, and raises concern that the underlying transmission/risk network could include additional HIV-infected partners that have not been diagnosed, or HIV-uninfected partners at high risk of HIV infection.

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What is the potential for ongoing transmission?

Are there factors that raise concern for potential ongoing transmission in the cluster? Such factors include:

- **Extent of recent cluster growth**
  - How many cases in the transmission cluster have been diagnosed recently, particularly within the most recent 6–12 month period? Multiple recently diagnosed cases could indicate ongoing transmission, particularly if evidence suggests that these cases were infected recently.
- **Evidence of early infection**
  - Was the timing of infection likely recent or distant? Recent infection suggests that transmission was recent and may be ongoing and indicates a potential to intervene to prevent new infections. To address this question, consider:
    - Stage of infection at diagnosis – determine whether cases had acute/stage 0 infection, or late diagnosis.
    - Dates of diagnosis. Even if many cases were diagnosed with acute infection, if the cases were diagnosed in the distant past, this is not necessarily evidence of current ongoing transmission. However, delays in reporting of both case and sequence data should be considered in this assessment.
    - Recency testing, if available.

Stage of infection at diagnosis
Stage of infection might be adequately captured by surveillance data, particularly if reporting of the full diagnostic algorithm is good and if data on last negative HIV test is captured. Alternatively, additional data sources could provide information to establish likely timing of infection. This could include alternative sources of data on last negative HIV test (e.g., data from STD programs or HIV testing programs), or medical chart review. Data indicative of diagnosis during acute infection or symptoms consistent with acute infection could also be identified from medical chart review.

Is there evidence of ongoing risk behavior that could facilitate HIV transmission?

Do persons in the transmission cluster have STD co-infection, or evidence of multiple STD diagnoses? If the cluster involves persons who inject drugs, has hepatitis co-infection been identified in the population at risk? Do partner services interviews note large numbers of sexual partners? These factors could indicate potential for ongoing transmission in the cluster.

- To address this question, consider:
  - STD diagnoses suggesting ongoing risk behavior. From a review of STD data, have cases of STD been diagnosed since HIV diagnosis?
  - Evidence of sexual risk behavior captured in HIV and other STD partner services interview records and notes. Risk behavior to consider could include:
    - Evidence of injection or other drug use. This could be captured in partner services interview data or medical record data. Alternatively, linkages with viral hepatitis data could identify hepatitis C virus coinfection suggesting injection drug use.
    - Anonymous partners
    - Multiple partners
    - No or little condom use
    - Public sex environments, such as bathhouses and bookstores
    - Sex parties

- ▪ Transactional sex
- ▪ Human trafficking or other forms of victimization
- ▪ Social media use to identify sex partners (apps, facebook, websites)
- ▪ Partners not on PrEP

Is there evidence of cases with unsuppressed viral loads or not in care?
- • How many cases in the cluster do not have evidence of a suppressed viral load or evidence that they are in medical care for HIV? Persons not in medical care or not virally suppressed could contribute to ongoing transmission in the cluster. Importantly, persons in the underlying transmission cluster and risk network who are not in the identified molecular cluster could contribute to ongoing transmission, so high levels of viral suppression in the molecular cluster may be falsely reassuring and the potential for such unrecognized cases should be considered.
  - o Sources of data on care and viral load data include:
    - ▪ Surveillance data (reported CD4 and viral load tests)
    - ▪ Ryan White HIV/AIDS Program data
    - ▪ ADAP
    - ▪ Medcaid data
    - ▪ Medical chart review

Factors to consider in prioritizing clusters for additional action
1. Has the transmission cluster and risk network been well described through partner services data?
2. Potential for ongoing transmission
3. Potential for poor outcomes
4. Local epidemiology
5. Assess whether key questions can be adequately addressed with the readily available data that were collected, or if there is a need to gather additional data
6. Opportunities to intervene

Are there factors that raise concern for the potential of poor outcomes among persons in the cluster?
Such factors could include:
- • **Presence of drug resistance**
  - o Have the same drug resistance mutations been detected among multiple cases in the molecular cluster, suggesting transmission of a drug-resistant strain?
- • **Vulnerable and underserved populations**
  - o Is the population affected by the cluster particularly vulnerable or underserved? Populations of concern could include the very young (e.g., persons aged <20 years), pregnant women, persons experiencing homelessness, mental health or substance abuse issues, language barriers, populations with limited access to health care, or rural or other populations with limited access to testing or treatment facilities.
- • **Late diagnoses**
  - o Were many cases in the cluster diagnosed late (e.g., diagnosed with HIV and AIDS concurrently, or diagnosed with AIDS within 6 months of HIV diagnosis)? This could indicate limited testing opportunities, or poor access to care among the underlying risk network represented by the cluster. Evidence that patients aren't being captured rapidly through testing raises concern that multiple HIV-positive persons in the cluster might remain undiagnosed.
- • **Incidental diagnoses**

- Were many cases in the cluster diagnosed through incidental testing, such as screening in plasma centers, emergency departments, or correctional institutions? This could indicate other cases in the network that have not yet been diagnosed and could be contributing to ongoing transmission

What is the local epidemiology?
- Local epidemiology is important to consider in cluster prioritization. For example, does the molecular cluster involve a population of concern based on local epidemiology?
- Is there evidence of non-traditional demographic or risk profiles among cases in a certain geographic area? A marked increase in a particular transmission risk category or demographic group may indicate transmission into a novel population. For instance, an increase in cases occurring in young women in an area in which diagnoses typically occur among men who have sex with men likely warrants further exploration.

Assess whether key questions can be adequately addressed with the readily available data that were collected, or if there is a need to gather additional data.
- Is there sufficient information to assess and update the level of concern for ongoing transmission and potential for undiagnosed cases? If so, this information can be used to determine whether additional investigation and intervention is needed. If there is not sufficient information to address this question, more information should be gathered.
    - If partner services was not conducted for many persons in the cluster, initiation of partner services is a critical initial intervention to consider. If partner services was initiated but no interview was conducted, re-initiation of partner services for these persons could be helpful.
- If key questions remain about how or why persons were seeking testing, frequency of testing, likely timing of exposure, or treatment and viral load history, review of medical charts could be warranted.
- Medical chart review can be an important source of information on symptoms of acute HIV infection and missed opportunities for diagnosis of HIV, which could be useful to understand community and systems issues contributing to ongoing transmission.
- If key questions remain about partner history (for example, if persons did not receive partner services, or if there were periods during which persons were not virally suppressed for which partners were not elicited), risk behaviors, and meeting venues, patient interview or re-interview, where possible, should be considered. Enhanced interviews can include more specific or in-depth questions that can be useful in understanding a cluster. Open-ended, qualitative interviews might also be considered. Interviews with front-line DIS staff, if not already completed, could also be helpful to address these questions. Broader questions may be developed based on cluster analysis to identify additional members of the at-risk social network. These questions may seek to identify other users of a particular social media platform, non-injecting drug partners, or other individuals who frequented priority venues.
- In addition to medical chart review and patient interview or re-interview, additional sources of information to consider include:
    - Discussions with patient's HIV care provider
    - Discussions with Ryan White medical case manager
    - Discussions with frontline DIS

Assess opportunities to intervene
- Data available at this initial review and assessment phase might reveal factors potentially associated with transmission that could present opportunities for intervention.

- o From partner services data, have common venues been named? Are apps/internet sites frequently mentioned, or is there geographic similarity in venues/hook up sites? Are sex parties or other gatherings noted? Do patients report behaviors associated with anonymous sex or injection or other drug use? Is there a lack of access to PrEP, or factors that would make access to preventative services more difficult? Reviewing notes from partner services interviews will likely be needed to answer these questions.
  - o Arrests, drug treatment, or use of syringe exchange services may identify venues where services may reach others at risk.
  - o From surveillance or other data sources on location, analyze data at finer geographic levels and assess prevention and care services in this location. Determine locations of diagnosis and care to determine whether collaborations with certain providers would be useful.
- If transmission in a cluster occurred in the distant past, opportunities to intervene might be limited. For this reason, timely identification of transmission clusters is critical.
  - o The addition of new cases to a molecular cluster could indicate new transmission and potential opportunities to intervene; therefore, continued monitoring of molecular clusters is important.

Cluster assessment is an iterative process, and new information might change the level of concern for a cluster. This process will ideally be dynamic and ongoing, incorporating new information on a cluster as it becomes available.

Step 2b. Initiate critical initial interventions

Initiate key actions for persons in the identified transmission cluster and risk network.

A core component of cluster response is to identify infected and uninfected persons in the risk network and intervene to reduce transmission to or from these persons by providing critical prevention interventions that are known to be effective. Such interventions include ensuring that HIV infections are diagnosed, that persons with HIV are engaged in medical care and virally suppressed, and that HIV-uninfected persons are evaluated and referred for PrEP and other prevention services. These activities should be conducted for all persons in transmission clusters that meet the national priority cluster criteria, and considered for clusters that meet local priority cluster criteria. Each of these activities correspond to evaluation measures included in the 18-1802 Evaluation and Performance Measurement Plan (EPMP), which are described in more detail in Section 10, 'Description of PS18-1802 evaluation measures'. Tracking the outcomes of these activities can be helpful in assessing ongoing concern related to a cluster.

Initiating partner services for all persons in the transmission cluster

Partner services interviews are the critical first step to identifying the full transmission cluster and risk network. In some cases, partner services will not have been initiated for all persons identified in a transmission cluster. In these situations, a critical initial intervention is to initiate partner services for all persons in the cluster, particularly for those persons with recently diagnosed HIV (in the past 6-12 months), and regardless of whether the person was diagnosed with HIV in a public or private setting. For persons who were sought for partner services but could not be located, or who were not interviewed for other reasons, re-initiation of partner services might be considered as part of Step 3, 'Conduct enhanced investigation and intervention activities', described later in this section.

Ensuring viral suppression for all persons in the transmission cluster

One outcome of a cluster investigation is the identification of persons with diagnosed HIV in the transmission cluster — not merely for those persons who were initially identified as part of the cluster

based on molecular sequences or other means — who are out of medical care, or in medical care but not virally suppressed. Interventions can be directed to these persons to promote re-engagement in care, ART adherence, and viral suppression. These types of interventions for HIV-infected persons are often part of the jurisdiction's data-to-care activities.

- As part of cluster interventions, these data-to-care activities might be enhanced as follows:
    - o HIV-infected persons in transmission clusters prioritized for data-to-care activities.
    - o Additional resources used to promote linkage to care, ART adherence, and viral suppression, such as navigators, case managers, adherence or other support services.
    - o Identifying and working with stakeholders such as behavioral health providers, housing providers, school health, and corrections in developing a comprehensive system of care to ensure access.
- Monitoring the outcomes of re-engagement in care activities for persons in the transmission cluster is important in order to track the impact of the cluster response, identify additional work needed, and refine the priority assessment of the cluster.

PS18-1802 Measure 3.2.1: Of all HIV-positive persons in transmission clusters who were not known to be virally suppressed at the time of identification as part of the cluster, percentage that achieved viral suppression within 6 months of identification as part of the cluster.

Jurisdictions should use existing data sources (and additional investigation techniques if needed) to identify which HIV-positive persons in the transmission cluster are out of care or lack viral suppression, then implement interventions to link them to care and promote viral suppression. The effectiveness of these efforts will be measured by assessing how many HIV-positive persons who were not virally suppressed at the time of identification as part of the cluster (or had unknown viral suppression status) have achieved viral suppression six months later.

Table 4e. Example summary of outcomes of linkage to care efforts for transmission cluster members

	Of those persons in the transmission cluster without evidence of viral suppression at the time of identification of part of the cluster:				
Number of persons in the transmission cluster without evidence of viral suppression at the time of identification as part of the cluster	**Number found to be virally suppressed (e.g., in another jurisdiction or unreported result)**	**Number initiated for engagement or re-engagement in care**	**Number successfully linked or re-engaged to care**	**Number achieved viral suppression within 6 months of identification of part of the cluster**	**Number achieved viral suppression to date**

Testing or re-testing all persons in the risk network who were not known to be HIV positive at the time of cluster identification

Persons identified in the risk network of a growing cluster who are not known to be HIV-infected are likely at high risk of HIV infection. In some locations, a high yield for identification of new diagnoses has been found when testing and re-testing of persons in the risk network was implemented. Individual-level interventions to improve HIV diagnosis and reduce the likelihood of HIV acquisition should be promoted for HIV-infected persons in the risk network, including:

- Persons in a risk network who previously tested HIV-negative should be re-tested within 6 months of identification as part of the risk network. **HIV-negative partners who were recently tested (within three months of identification as part of the risk network) may be excluded from re-testing activities.**
- Persons in a risk network with previously unknown HIV status should be tested within 6 months of identification as part of risk network.
- HIV-negative persons in risk networks should be evaluated and referred for PrEP and other prevention services.
  - o Establish a referral procedure for PrEP services.
  - o Additional resources, such as patient navigators, to promote linkage to PrEP and other prevention services or to promote adherence with PrEP might be considered.
  - o Resources are available through the AIDS Education and Training Centers (AETCs) Clinical Consultation Center to assist in linking persons to PrEP, as well as expanding the capacity to deliver PrEP.
    - ▪ PrEP Provider Locator Services provides links to National PrEP provider directories.
  - o Many state and local jurisdictions have PrEP resources available that include directories and education opportunities to expand PrEP services.
  - o In some situations, existing PrEP services might be insufficient to provide PrEP for persons identified in a growing transmission network. In these situations, consider what resources are available to increase availability of PrEP services.
    - ▪ Resources are available through the AIDS Education and Training Centers (AETCs) Clinical Consultation Center to expand the capacity to deliver PrEP.
      - PrEPline provides clinical consultation for PrEP.
      - Local AETCs provide PrEP education for providers and other PrEP resources. Regional directories and links to the local AETCs can be found here.

Monitoring results of testing, re-testing, and PrEP referral activities can provide key information to assess the impact of cluster response work, refine the priority assessment of the cluster, and identify key actions needed.

PS18-1802 Measure 3.2.2: *Of all partners of transmission cluster members who were not known to be HIV positive at the time of cluster identification, percentage tested or re-tested within 6 months of identification as part of the risk network.*

All partners of transmission cluster members who had unknown HIV status at identification as part of the risk network should be tested within 6 months. Similarly, all partners who were HIV-negative at identification as part of the risk network should be re-tested within 6 months. While this work serves to define the transmission cluster and risk network, it also serves as an intervention for those who do not know their HIV status and serves as an entry point for connecting individuals to high impact prevention services, such as PrEP.

> *PS18-1802 Measure 3.2.3:* *Of all partners of transmission cluster members who were determined to be HIV-negative and not on PrEP, percentage referred for PrEP within 6 months of identification as part of the risk network.*
>
> Any HIV-negative partners who are screened and determined to be eligible for PrEP should be referred within 6 months of identification as part of the risk network. This may include HIV-negative partners who were previously identified as named partners before the cluster was identified but were not referred to PrEP or did not accept a PrEP referral at that time, as well as HIV-negative partners newly identified through the course of cluster investigation and response activities. This measure captures the effectiveness of efforts to refer eligible HIV-negative risk network members for PrEP.

Table 4f. Example table of results of testing and re-testing for persons in the risk network who previously tested HIV negative or had unknown HIV status

Tested: # = Click or tap here to enter text.		Not Tested: # = Click or tap here to enter text.	
New Positive:	# = Click or tap here to enter text.	Refused:	# = Click or tap here to enter text.
Acute:	(subset: # = Click or tap to enter text.)	Not Located:	# = Click or tap here to enter text.
Negative:	# = Click or tap here to enter text.	Outside Jurisdiction:	# = Click or tap here to enter text.
Referred for PrEP:	(subset: # = Click or tap here to enter text.)	Deceased:	# = Click or tap here to enter text.
Unknown:	# = Click or tap here to enter text.	Other:	# = Click or tap here to enter text.

Table 4g. Example summary of outcomes of PrEP referral for members of the risk network

Number of HIV uninfected persons in the risk network identified as not on PrEP	Number screened for PrEP eligibility	Number determined to be eligible for PrEP	Number referred for PrEP

Based upon identified needs, active referrals for or direct provision of **other interventions or services** as appropriate should be prioritized **for HIV-positive and HIV-negative persons in the transmission cluster and risk network**, including but not limited to:
- Testing for sexually transmitted infections and hepatitis B and C
- Vaccination for hepatitis A, hepatitis B, and/or human papillomavirus
- Referral to syringe services programs or treatment programs for substance use disorder
- Referral for mental health services
- Referral for ADAP, Medicaid, or other health insurance and medication assistance programs

- Referral for other healthcare and prevention services, including sexual health and family planning, as appropriate
- Referral for social services, including housing, food assistance, and transportation, as appropriate
- Navigation and adherence support for such interventions might be considered

Step 3. Conduct enhanced investigation and intervention activities, as appropriate

High Impact Prevention strategies are proven, cost-effective approaches to reduce the risk of HIV infection that can be applied to HIV transmission clusters. These interventions include ensuring all persons in the transmission cluster are linked to care and receiving antiretroviral therapy, and conducting HIV testing and PrEP referral for persons in the risk network. A critical challenge for implementing these interventions in the context of a transmission cluster is ensuring that the persons involved in the HIV transmission cluster and risk network are identified so that these effective HIV prevention interventions can be provided to those in need. Key goals of enhanced investigation strategies include effectively identifying persons in the transmission cluster and risk network and identifying cluster or community-level factors that impact the prompt diagnosis and effective treatment of persons in the cluster. Additionally, enhanced investigation strategies aim to identify factors contributing to ongoing transmission and identify opportunities to intervene to interrupt transmission. Enhanced investigation activities could include:

Strategies to identify previously unrecognized partners for testing and provision of prevention interventions or treatment, as appropriate

- Re-initiate partner services and re-interview for cases with periods for which they were out of care or not virally suppressed. If initial partner services interviews were not fruitful, consider alternative strategies, such as an interview by a trusted case manager.
- Initiate/re-initiate interviews of partners and social contacts of transmission cluster members. Resources for patient interviews and re-interviews can be found on the HICSB SharePoint Site.
  - Risk behaviors and circumstances that might increase HIV acquisition should be assessed.
  - Case managers, providers, or others who have an established, trusted relationship with the HIV-infected persons might re-interview them to obtain additional information about their risk behaviors or other needs that might then be addressed. (Note that re-interviews by those with established, trusted relationships might also be conducted to elicit additional names of partners who might not have been named previously, either because the infected person did not disclose their names or because they are new partners since the time of the original interview.)
- Discuss cluster members with cases managers and DIS staff, who might have insight into relationships and commonalities between persons in a cluster that aren't captured in partner services data or interview notes.
- Conduct social network interviewing and testing or second generation interviews. These can be used to increase uptake of HIV testing (including using incentives), increase uptake of PrEP or other prevention services, and to conduct interviews to better characterize the cluster and associated risk network. A key component of social network interviewing is that recruitment does not stop when a person who is HIV uninfected is reached, allowing for fuller elaboration of the risk network. For more information about social network strategies, see Appendix G, 'Additional resources'.
- For clusters associated with a particular physical venue, conduct targeted outreach at identified venues for testing, PrEP evaluation and referral, and promotion of other prevention

interventions; consider partnering or coordinating with community-based organizations that might already be actively involved in working with these venues.

- For clusters in which many partners are anonymous and members frequently mention particular internet sites or apps:
    - Have partner services staff explore reaching partners through apps and work with clients during partner services interviews to identify screen names or handles for partners whose name they do not know; also consider strategies to determine whether these persons came in for testing.
    - Consider general messaging campaigns through apps or internet sites to encourage testing and prevention strategies, while keeping in mind that these sites are large, and more nuanced targeting (e.g., based on geography) might be needed to more effectively reach the specific network involved.
    - Consider partnering with community-based organizations that have experience working through apps and internet sites.

As new persons with HIV in the transmission cluster are identified, include these persons in cluster investigation and assess factors that prevented earlier recognition, as these factors could help in the identification of other unrecognized cases or at-risk partners.

Considerations for conducting additional interviews or re-interviews

Although partner services data often offers a rich source of information on potential partners and routes of transmission, not everyone is interviewed and not everyone who is interviewed names notifiable partners. Thus, partner services initial interviews may not always yield useful information, and in certain circumstances, it may be beneficial to consider a re-interview, or an interview with a different approach, such as an interview by a trusted case manager.

When would additional interviews or re-interviews be most useful to an investigation?
1) If persons in the cluster were not interviewed initially, more information could be gained by interviewing these persons.
2) If the cluster continues to grow and existing links identified from initial interviews have been exhausted.
3) If 'cluster interviewing,' or elicitation of social contacts, was not incorporated into original interviews.
4) If persons in the cluster are not virally suppressed, additional partners may be at risk who were not elicited in initial interviews.
    a. If an individual is out of care and will be receiving a reengagement visit/encounter, it may be helpful to incorporate re-interview questions at the time of this visit.
5) To better understand the context of risk behaviors and prevention needs (e.g., enhanced interviews among cluster members who use drugs could provide nuanced information about drug use behaviors).
6) Consider involving trusted persons, such as case managers, in re-interviews. Some jurisdictions have found interviews to be more informative when such a trusted persons conducts the interview.
7) New partner services interviews based on STD diagnosis among HIV infected and not infected cluster group members (e.g. recent gonorrhea diagnosis where PS was not offered).

Examples of re-interview tools used by jurisdictions in cluster investigations
Documents on the HICSB SharePoint site provide sample scripts and protocols for
- Re-interviewing HIV-positive and/or negative persons part of an HIV cluster
- Approaching providers when discussing viremic, HIV-positive persons part of an HIV cluster

Since the type of questions to include in a re-interview will strongly depend on the characteristics of the persons in the cluster, the questions in the provided examples may not always be appropriate for a given cluster investigation but should be viewed as a starting point. See also Appendix H, 'Additional resources for cluster investigation'.

Strategies to better understand timing of infection, factors contributing to delayed diagnosis, or interruptions in care
- Medical record review
    o Systematic review of medical records for persons in a transmission cluster can be helpful to understand the context leading up to diagnosis of HIV infection and factors associated with linkage to care and treatment adherence. Key information that can be identified through medical record review includes:
        ▪ Reasons for HIV testing: Did persons involved in the cluster seek HIV testing routinely on their own, or did HIV diagnoses occur because of screening in emergency departments, jails, plasma centers, or because of symptoms? This

information can be helpful to understand what testing strategies might be most effective at reaching the risk network.

- Symptoms of acute HIV infection, or testing information that supports the identification of acute infection.
- Potential opportunities for earlier diagnosis, e.g.:
    - Missed opportunities for testing, such as clinical encounters where HIV testing was not offered.
    - Missed HIV diagnoses, such as testing that was offered but did not follow the recommended testing algorithm.
- Challenges associated with linkage to care, or adherence to ART, including features of the care system that might present barriers to consistent engagement.
- Identification of time periods where persons in the cluster were out of care.
- Interviews can also be particularly useful to understand factors contributing to delayed diagnosis or interrupions in care; please see the section below for additional information.

Strategies to better understand the context of transmission, including facilitating practices and conditions

Qualitative data gathered through individual interviews or focus groups with members of the transmission cluster/risk network or the broader community (i.e., persons who inject drugs, men who have sex with men, or others), service providers, or other relevant groups can be immensely helpful for understanding the context. Qualitative data can be collected for multiple reasons, including:

- As part of a rapid needs assessment
- To help inform the content and wording of questions to include in enhanced interviews or on a quantitative survey
- To provide an explanation for findings from quantitative data
- To describe particular practices or risks that may facilitate transmission, including any recent changes
    - In particular, qualitative data can help public health officials to understand the steps of injection drug use practices in a given community, which is critical for helping inform harm reduction strategies.
- To identify priorities and concerns of the affected community
- To understand beliefs, attitudes, barriers to prevention services, and acceptability of potential interventions
- To understand challenges faced by service providers as well as successful approaches for overcoming those challenges

Small incentives to compensate members of the affected community for their time and effort in participation in the interviews are commonly used, often in the form of gift cards. Incentives are typically not necessary when talking with service providers.

For more guidance on enhanced response activities specifically in the context of an outbreak involving PWID, see 'Managing HIV and Hepatitis C Outbreaks Among People Who Inject Drugs').

Continue to synthesize information and refine intervention strategies as new information becomes available

As new data is gathered and synthesized, understanding of factors driving transmission and determination of effective strategies for intervention can be refined. Consider re-assessing clusters each quarter, or as new information becomes available or new cases are added to the transmission cluster.

Population-level interventions

A cluster investigation may reveal social-structural or programmatic factors that contributed to transmission, which could be addressed through broader population-level interventions in addition to those targeted at the individual or at venues or other cluster-level factors. While population-level interventions might overlap with general prevention interventions already being undertaken in a jurisdiction, information from cluster investigations can provide more focused understanding of the gaps of current prevention programs, specific populations that are not being effectively reached by these activities, and reasons for poor access to or utilization of services. Additionally, growing transmission clusters could provide justification for the expansion of population-based interventions, or implementation of interventions which had been considered but are not yet implemented.

- Population-based interventions will vary based on the specific factors and circumstances identified through cluster investigation. Table 4h provides examples of population-based interventions and scenarios in which they might be warranted. Many other population-based interventions might be appropriate depending on the circumstances of a particular jurisdiction and transmission network.

Table 4h. Examples of population-based transmission network interventions, and situations in which they might be warranted.

Situation	Population-based intervention
Affected community is not accessing available resources	-Conduct media campaigns to affected community -Conduct program evaluation, needs assessment, or other qualitative assessment to evaluate reasons and to inform media campaigns
Cluster associated with injection drug use	-Ensure/expand appropriate provision of syringe service programs and substance use treatment; ensure these services consistently offer HIV testing and PrEP
Transmission network includes many persons at risk of HIV infection who were not on PrEP	-Expand PrEP resources available to affected population -Identify opportunities for PrEP evaluation and referral that reach affected network, such as standard referrals at STD clinics -Conduct media campaigns to increase PrEP awareness -Conduct targeted outreach to providers in areas where clusters have occurred to educate about PrEP
Persons in transmission cluster presented for care during likely acute HIV infection, but were not diagnosed	-Provide provider education on the HIV diagnostic testing algorithm -Disseminate health alerts to providers alerting them to rapid HIV transmission in the area and the need for HIV testing, increased recognition of acute HIV symptoms, and completion of HIV diagnostic testing algorithm
Cluster in a remote location with few providers trained in treatment	-Provide provider education on HIV treatment. -The AETCs provide training opportunities for clinicians on HIV care and treatment, including an HIV curriculum and preceptorships to expand treatment for those with HIV. -Also consider telehealth or ongoing learning collaboratives such as Project ECHO™. The Project ECHO model™ links specialists at academic hubs with primary care clinicians in local communities as mentors and colleagues. Through teleconferencing technology, primary care clinicians present cases to the specialist teams and then discuss appropriate approaches and treatments. Project ECHO creates ongoing learning communities so that primary care clinicians in local communities can provide comprehensive care for complex conditions based on current best practices.
Area with insufficient HIV testing resources and capacity	-Consider training on HIV testing -Consider short-term and long-term strategies to increase access to HIV testing -Consider provision of home testing kits
Infrequent HIV testing in affected risk network	-Increase testing resources -Incentivize testing -Conduct media campaign or other messaging to affected community about risk of HIV transmission and importance of HIV testing

	-Depending on factors associated with the risk network, consider expanding screening in jails, emergency rooms, or syringe-service programs
Partner services not initiated for large portion of cases in the HIV transmission networks	-Consider protocol or policy changes to increase partner services and/or prioritize partner services for populations involved in rapidly growing transmission clusters -Assess effectiveness and reach of partner services for a large portion of cases -Identify opportunities to deploy DIS and rapid testing materials to facilitate PS on the same day as HIV diagnosis
High percentage of cases not located or refused interview, or few partners named in interviews or re-interviews, leading to few or no members of cluster being identified or linked	-Consider additional training for DIS, based on identified factors leading to unsuccessful attempts to interview, to improve outcomes -Retrain DIS to improve partner elicitation skill; review policies, procedures, and access to essential PS tools with managers: consider cultural competency issues; investigate other issues leading to poor elucidation of sociosexual networks
Apps and internet hookup sites important in transmission networks, with insufficient information provided to DIS staff in partner services interviews to identify partners	-Address barriers to DIS staff accessing apps and internet sites in order to use these sites for locating partners and messaging to persons in high-risk networks
Insufficient public health response capacity, including DIS staff in an area	-Consider approaches to bring additional public health and DIS staff to the affected area (see Section 8, subsection 'Creating program capacity for cluster detection and response')
Limited or no access to health care services (lack of access to health insurance or health services)	Partnering with community providers or NGO's

Partnerships for intervention to prevent new HIV infections

- Partnerships within the state and local health departments between the health department and other agencies or organizations (i.e., CBOs, FQHCs, etc.) will be a critical component of intervention strategies, as they present an opportunity to leverage expertise and resources of other groups to effectively direct intervention. A strong partnership between HIV surveillance and prevention programs, and STD prevention and partner service programs, should be at the core of all cluster response work. STD programs will typically be involved early in the cluster investigation process, given the importance of STD program information to understand the transmission networks. Organizations to consider for partnerships should include:
  - **State and local health departments**
  - **STD clinics**
    - STD clinics could be an important component of intervention strategies, as a key point to access at-risk populations.
  - **Community-based organizations (CBOs)**
    - CBOs may have experience working with populations affected by a growing transmission cluster, and may be conducting effective targeted strategies to reach these populations. Additionally, CBOs might also have experience implementing strategies for intervention, such as the use of social media outlets (i.e., apps or internet sites) to reach partners, and/or the use of social networking testing strategies.
  - **HIV care providers**
    - HIV care providers could be an important component of intervention strategies, helping to access persons in the cluster who entered medical care but have not remained engaged in medical care, or who are engaged in medical care but not virally suppressed.
    - Providers with established, trusted relationships with individual cluster members may be an avenue for obtaining additional information (including partner elicitation) and promotion of services.
  - **Jails and other correctional institutions**
    - In some situations, jails and other correctional institutions might be important partners for both investigation and intervention. Situations where correctional institutions might be particularly important partners include transmission networks involving injection drug use, other substance abuse, or sex work. Broadly understanding the arrest history of cluster group members can inform the need for jail screening at intake.
  - **Other organizations, as appropriate.**
- When considering partnerships, it will often be most effective to create the foundation for strong partnerships before any transmission cluster is identified. For more information on planning ahead to develop partnerships, see Section 8, subsection 'Creating program capacity for cluster detection and response' and 'Managing HIV and Hepatitis C Outbreaks Among People Who Inject Drugs'. MOUs/MOAs should be developed when developing partnerships for conducting cluster activities.

Requesting CDC assistance
CDC may be available to provide remote or on-site technical assistance with cluster investigation and intervention.

If you are interested in exploring this option, please contact the CDC HIV Incidence and Case Surveillance Branch, either through your HIV Surveillance and/or PPB Project Officer, or through the HICSB email address (HIVSurveillance@cdc.gov)

Communication as an intervention strategy

Communication with affected populations, providers, and the general public is an important component of any intervention strategy. Providing prevention messages to the general public or affected populations through broad social marketing campaigns is an option as is more direct prevention communication interventions for targeted at-risk populations. For example, targeted advertising buys on a dating apps frequently used by the affected population may be a good use of prevention resources and geo-targeting functionality will allow for tailored messaging to those most at-risk. Developing a communication strategy should ideally start before any cluster is identified. For considerations in developing a communication plan, see Section 8, 'Operationalizing cluster and outbreak detection and response'. CDC's Act Against AIDS social marketing campaign provides many resources that are free to use. Campaign resources are available in a variety of formats including posters, web banners, palm cards, videos, and PSAs, and are geared toward a number of audiences, including gay and bisexual men, transgender people, people of color, infectious disease providers, and perinatal care providers. Additional HIV prevention resources can be found on the CDC HIV website.

Protecting patient confidentiality

Intervention approaches can raise concerns for patient privacy and confidentiality. Please see Section 6, 'Facilitating collaboration while protecting cluster data', for considerations regarding patient privacy and confidentiality in interventions.

Step 4. Monitor progress and determine when a cluster response should be closed

Monitoring the progress of interventions in transmission networks is important to 1) understand whether transmission has been successfully interrupted or whether more work is needed, 2) to assess the impact of the investigation and interventions, 3) identify lessons learned for future cluster response activities, and 4) determine when a cluster response should be closed. As we gain more experience with this new activity, this type of information will provide information about the tangible outcomes of these investigations and interventions, help to guide priorities in future investigations, and provide lessons learned.

1. Has transmission been interrupted, or is it ongoing?

- Monitoring transmission clusters over time to identify new cases added to the cluster is the key strategy to understanding if transmission has been successfully interrupted. Sequence data should be analyzed at least monthly to identify any new cases in a cluster.
    - o Keep in mind that the detection of new cases in a molecular cluster will be very sensitive to the completeness of sequence data. To address this, it is important to understand what patient populations are not represented in sequence data, and identify areas where there are opportunities to work with providers to ensure that they are conducting resistance testing, and to work with labs to ensure that they are submitting sequences.
    - o When new cases are identified, include them in the transmission cluster investigation to determine if there is new information that increases understanding of factors facilitating transmission or provides a refined understanding of opportunities for intervention.
- Additional cases in a transmission cluster might not reflect continued transmission, as case finding activities resulting from the investigation could result in newly diagnosed cases that had already acquired HIV before the time of the investigation. Continued monitoring over time can reveal unexpected new diagnoses after case finding activities have ceased, which could suggest that transmission has not been interrupted.
    - o Consider how new HIV-positive persons in the network are being identified. Are newly identified HIV-positive persons in the network being detected as a result of active case

finding activities, or through passive means, such as presentation for symptoms or through screening such as for plasma donation? If persons in the cluster are identified in the acute phase of infection or have evidence of recent infection, however, this suggests that transmission has been ongoing.

- Consider the potential for future growth, based on characteristics of persons identified in the transmission/risk network. Do HIV-infected persons in the network remain virally unsuppressed, or have previously suppressed persons become unsuppressed? Are there other factors that raise concern for ongoing growth, such as ongoing risk behaviors, or evidence that a network was not adequately captured through investigation and intervention? Have there been increases in hepatitis C infection, or changes in drug-use patterns? If any of these situations is the case, consider the potential for ongoing intervention activities.

2. What was the impact of the cluster response activities?

To assess the impact of the investigation, systematically gather information on what was learned from the investigation, and what actions took place as a consequence of the cluster investigation. Data collected should include:

- Had the molecular cluster been identified through other means (e.g., partner services), prior to detection through sequence analysis?
- What was the full size of the underlying transmission/risk network identified through cluster investigation?
  o Number identified as part of the molecular cluster
  o Number of HIV-positive persons without sequence data, or with discordant sequence data, linked to the transmission cluster
  o Number of HIV-negative persons in risk network at risk of infection
- Was social network interviewing conducted? What was the impact on the identification of the underlying transmission cluster and risk network?
- What individual-level interventions were implemented for persons in the transmission network? Data collected should include:
  o HIV-infected persons identified as out of care who were linked to care
    ▪ Number achieving viral suppression
  o Partner services interviews initiated
    ▪ Previously unidentified partners named as a result of interview or re-interview. Of these:
      a. Number tested
        i. New HIV-positive partners
        ii. Previous HIV-positive partners
        iii. HIV-negative partners
      b. Not tested
        i. Out of jurisdiction
        ii. Not located
        iii. Located but not tested
  o HIV-negative persons in the risk/transmission network referred for PrEP
- Did venue-based testing or other case-finding activities take place? If so, collect information on:
  o Number of persons tested
    ▪ Number of newly diagnosed HIV-positive persons identified
    ▪ Number of previously diagnosed HIV-positive persons identified
    ▪ Number testing HIV-negative
      a. Of these, number evaluated and referred for PrEP

- Did changes in policy or protocol result from the investigation, such as changes to the process for partner services interviews? If so, collect information on what actions were taken.
- Were changes to services made, such as expansion of PrEP or testing services, or were trainings related to these services conducted?
- Did education or communication efforts take place as a result of the investigation? This could include provider or community outreach, media campaigns, or heath alert notifications. If so, collect information on what actions were taken.

3. What are lessons learned for future cluster response activities?

Following cluster investigation and intervention activities, consider conducting assessment of what activities worked well and what activities were less effective. This can help inform strategies for future cluster investigations and interventions, and help ensure that resources are utilized as effectively as possible. Questions to consider include:

- Which components of the cluster investigation yielded the most useful information?
- Which data sources were most useful?
- What were the staffing/resource needs for the investigation and intervention activities?
- Which partnerships were most effective, and which could benefit from additional development?
- What were the costs associated with cluster investigation? With intervention?

4. Determine when a cluster response should be closed

Cluster investigation and response activities will be focused, time-limited and, in many cases, resource-intensive. For each cluster for which response activities are initiated, a decision will need to be made about when to wind-down or cease those activities. While multiple factors must be considered in making this decision, the key factor will be whether transmission in the cluster has been successfully interrupted. Monitoring cluster growth and routinely reviewing cluster outcome data are key to making this assessment. Considerations include:

- **Has transmission in the cluster been interrupted?**
    - o Are there no or few recent diagnoses (past 6-9 months)?
    - o While there is no hard and fast criteria for the threshold of cluster growth that could be considered 'under control', 12 consecutive months in which the cluster did not meet national priority cluster criteria could be used to as a starting point to make this assessment.
- **Have persons in the transmission cluster without initial evidence of viral suppression been successfully linked to care?**
- **Have persons in the risk network been tested or re-tested and referred for PrEP?**
- **Are new diagnoses in the cluster identified through active investigation and intervention activities, such as partner services and testing?**
    - o Identifying new diagnoses through cluster response activities suggests these activities are successful. Additional diagnoses that are not identified through investigation activities could suggest that the investigation has not successfully identified contributors to ongoing transmission or the full risk network.
    - o Were cluster cases named as partners to other cluster cases? If so, this could be reassuring that the network has been captured well through partner services.
- **Does the rate of new diagnoses identified through cluster-focused testing activities suggest that more testing is warranted to identify undiagnosed HIV-infected persons in the network?**
    - o A high rate of new diagnoses from cluster-focused testing activities activities suggests that these activities should continue.

o While a low rate of new diagnoses from cluster-focused testing activities could suggest that HIV-infected persons in the network have already been identified, it could also indicate that the persons identified for testing do not represent the true risk network, or the highest risk part of the risk network. Testing results should be evaluated in the context of cluster growth; if cluster growth continues despite a low rate of positivity in testing activities, consider that more work is needed to identify and understand the risk network.

Section 5. Communicating about HIV transmission clusters

Responding to HIV transmission clusters requires collaboration and communication with internal and external partners and stakeholders. Having a communication plan in place before cluster detection and response activities begin can help facilitate the cluster response process. However, clusters are sometimes detected prior to the development of communications plans and materials, or new cluster characteristics may emerge, requiring existing tools and products to be updated. More information on developing a communication plan is provided below. Additionally, developing a community engagement plan and engaging key stakeholders prior to cluster detection can help prepare the groundwork. Informing partners, allowing them time to understand and ask questions about cluster detection and response activities, clarifying roles ahead of time, and continued engagement may result in more efficient collaborations in a response situation when time is crucial. More information on community engagement can be found in Section 8, 'Operationalizing cluster and outbreak detection and response'.

Resources for Developing a Communication Plan

For more specific information on developing a communication plan, see these resources:

HIV program guidance for clusters and outbreaks

CDC Crisis and Emergency Risk Communication (CERC)

National Public Health Information Coalition: Outbreak Communications Guide

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Developing a cluster communication plan
- Identify key partners and stakeholders who may need to be informed of a cluster investigation.
- Develop a schedule to maintain regular communication with key stakeholders throughout an investigation and response activities. Such a schedule could include routine (e.g., weekly) updates.
- **Internal** stakeholders may include:
  - Health department leadership and staff, including those responsible for leadership, management, and oversight of outbreak activities
  - Surveillance and prevention program leadership and staff
  - STI/Hepatitis/TB units at the health department
  - Health department media/communication contacts
  - Health department legal counsel
  - DIS and front-line staff
- **External** stakeholders may include:
  - Local health department staff and leadership
  - Community-based organizations

- o Community planning group
- o Ryan White HIV/AIDS Program grant recipients, including service providers' care facilities leadership or leadership from other key care facilities
- o Affected individuals or the larger at-risk community
- o Providers and provider organizations
    - i. Health alerts may be helpful to communicate with providers. STD and partner services staff often have experience developing these alerts.
- o Media
    - i. In some cases, the media may become aware of the existence of a cluster. In order to be prepared, consider developing press release templates to be prepared for multiple media requests.
    - ii. Identify the health department press officer who would be the media contact. Consider early education opportunities for this individual to make them aware of cluster detection and investigation activities.
- o Other groups as appropriate, depending on cluster characteristics.
    - i. For example, correctional or military facilities, tribal organizations, or behavioral providers.
- ▪ Consider the potential that messaging could stigmatize affected populations; craft messages carefully to avoid creating or contributing to stigma.
- • Cluster and outbreak detection and response communication tools for various partners are available at CDC's HIV cluster and outbreak detection and response webpage. These resources currently include a fact sheet on HIV cluster detection and response and a fact sheet on drug resistance testing; other items currently in development include a sample press release, dear colleague letter, health alert, Q&A, and powerpoint for use when discussing MHS with community and stakeholders.
- • Social marketing campaigns for general HIV awareness, testing, and prevention, as well as targeted campaigns for at-risk populations are available here.

Tips for Effective Communication

DO build trust and credibility by:
- Being the first source of information
- Expressing empathy and compassion
- Demonstrating competence and expertise
- Being honest and transparent
- Addressing rumors or myths in real-time
- Showing commitment and dedication
- Developing and using consistent messages
- Knowing your organization's policies
- Promoting action (what can people do?)

Avoid:
- Public power struggles and confusion
- Mixed messages from multiple departments or spokespeople
- Paternalistic language or approaches towards the impacted communities
- Delaying the release of information

Consider the following in message development:
- Be clear about the scale of the issue and the geographic areas of concern
- Be sensitive to existing stigma for at-risk populations and the impact of further scrutiny
- Audience:
  - Relationship to the cluster
  - Demographics
- Purpose of the message:
  - Prevent new infections
  - Routine update
  - Satisfy media requests
  - Collaborate with public health partners
- Language:
  - Be concise
  - Be relevant
  - Speak in voice of the intended audience
  - Choose words and phrases carefully
  - Avoid sensationalist language, acronyms, and public health jargon
  - Provide positive action steps
- Delivery:
  - Print
  - Web
  - Social Media
  - Dating or Hook-Up Apps and Websites
  - Agency Spokesperson
  - Media (Radio, Television, Print)
  - Other

Section 6. Facilitating collaboration while protecting cluster data

Data regarding clusters of concern is inherently sensitive, and, as with all HIV surveillance data, protecting data security and confidentiality is essential. At the same time, collaboration, both within and across programs and jurisdictions, is essential to responding to HIV transmission clusters to guide public health action and prevent new infections, and effective collaboration will require sharing of data. Striking a balance between sharing data with those who have a need to know, while maintaining data protections, is important. Assessing where this balance lies should be made with a consideration of the potential public health benefit of an effective cluster response.

Key collaborators for cluster response outside the HIV surveillance program include, but are not limited to, HIV prevention and DIS staff, staff from STD programs, local and regional health departments, and other states and jurisdictions involved in the cluster. Sharing key data on members of an HIV transmission cluster with these collaborators will be key to respond. Developing data sharing protocols can facilitate collaboration while protecting sensitive data.

Data should be shared in accordance with state/local public health law and procedures outlined in the NCHHSTP Data Security and Confidentiality Guidelines, including, but not limited to, the following:
1. All data should be stored securely whether in electronic or paper form.
2. Access to identifiable information should be limited to authorized persons.
3. Any electronic output that could breach confidentiality (e.g., line listings, STATENOs) should be stored on a secure server. Hard copies should only be produced when necessary; when produced, they should be locked up and not taken out of the office. Paper copies should be shredded when no longer in use.
4. All confidential data (including line lists and any documents including STATENOs) should be marked as confidential and encrypted for transfer or when not in use.
5. Any information taken into the field as part of field investigation or service provision should include only the minimum amount of information necessary and be maintained securely at all times. Areas should develop specific procedures for securing information during field investigations.
6. Data should only be shared with staff who have a need to know the information.

Additionally, ensure data on clusters of concern are handled consistently with any state or local public health law and privacy and confidentiality guidelines relevant to this activity.

Because cluster data can represent potential transmission linkages between persons, there are additional sensitivities in using this data beyond those inherent to HIV surveillance data. Particular considerations include:

7. Data on potential transmission linkages between persons (i.e., which pairs of people have genetically linked sequences) may be subject to misinterpretation by those not familiar with this type of analysis. Consider minimizing use of these data and instead focusing on cluster-level data (i.e., considering all people in a cluster for intervention rather than focusing on people based on their position in the cluster).

> **Limitations of and considerations for visualizing networks based on genetic data**
>
> Importantly, although some tools, such as Secure HIV-TRACE and MicrobeTrace, generate network diagrams of clusters based on genetic distance data, there are important limitations to drawing inferences from these data at an individual level. Although two persons infected with highly similar HIV strains could be directly linked through transmission, other transmission relationships could be consistent with this sequence similarity: both could have been infected from a third source, or they could be connected indirectly through a transmission chain including 1 or more intermediaries. Because of this scientific uncertainty, the potential for the misuse and misinterpretation of these data presents a concern.Moreover, presence of or patterns of linkages can be affected by timing of diagnoses and drug resistance testing. Although analysis of molecular data to identify growing transmission clusters can identify important opportunities for individual- and cluster-level public health interventions, inferences about specific transmission linkages or indirect inferences about sexual or other risk behaviors should not be used to guide services or follow-up at the individual level. Because of the potential for misinterpretation of these diagrams, **we do not recommend disseminating genetic network diagrams beyond the group of staff involved in the analysis of sequence data.**

8. Communication about transmission clusters should be considered carefully to ensure that the privacy and confidentiality of members of a cluster is protected. Particular consideration should be made when communicating about a cluster with:
   a. Frontline staff (e.g., DIS who might re-interview cluster patients)
   b. Healthcare providers
   c. Persons involved in the risk network (e.g., when interviewing or re-interviewing persons in the risk network)
   d. Community-based organizations and other potential referral resources
   e. The general public (e.g., press releases or other messaging about a transmission cluster)
9. For each of these audiences, consider that minimal amount of information about the cluster needs to be shared in order to communicate effectively, while not sharing more than is needed. Ensure that in all settings where data will be accessed, physical, legal ,and electronic data protections are in place and monitored.

Section 7. Approaching multijurisdictional clusters

Considerations in approaching multijurisdictional clusters

- HIV transmission does not respect jurisdictional boundaries. Molecular cluster detection conducted at the national level has led to the recognition that many molecular HIV clusters cross state boundaries, and many more will cross within-state jurisdictional boundaries.
- A multijurisdictional cluster is any cluster that includes persons in more than one state, or persons in the same state that are in different jurisdictions across which public health investigation and response efforts must be coordinated. In many multijurisdictional clusters, the majority of persons in the cluster reside in one single jurisdiction (referred to as the 'primary jurisdiction'), with other jurisdictions having fewer persons involved (referred to as 'non-primary jurisdictions'). In other multijurisdictional clusters, however, there is no single 'primary jurisdiction'.
- Some considerations for multijurisdictional clusters might also be relevant for clusters involving institutions such as correctional or military facilities, or tribal organizations,where coordination and data sharing across systems would be required.

- Some time-space clusters may affect an area that crosses jurisdictional boundaries, and the principles outlined below often apply to these situations as well.

Importance of including out-of-jurisdiction (OOJ) persons in a cluster investigation

- To capture the full transmission cluster and associated risk network, including all persons, including those in other jurisdicitons, is essential. This is important because persons who reside outside of the jurisdiction might be contributing to ongoing transmission in the cluster. This could include persons who are not detected by the molecular analysis, but who would be identified through an investigation that involved OOJ persons. Additionally, persons who reside outside the primary jurisdiction might be part of the risk network and at risk of HIV infection. Identifying the full risk network is key to ensuring that prevention interventions, including HIV testing, referrals to PrEP, and linkage to care, are made available to all persons in the risk network.
- Understanding connections between persons in a cluster is a key step to understanding how well the transmission network has been identified through partner services, and how effective prevention interventions which have already been conducted have reached the full network. Determining whether an OOJ cluster member has been linked through partner services is therefore helpful in prioritizing investigation and response efforts, both in the primary and secondary jurisdictions.
- Understanding factors that might be facilitating transmission that span jurisdictions, such as:
  - Risk behaviors
  - Venues visited (e.g., travel to gatherings, etc.)

Goals of sharing information on cluster members across jurisdictions

For persons associated with a transmission cluster:

- Determine care status and update viral suppression information
- Understand what has been learned from partner services investigations for these persons. Key questions to discuss include:
  - Were any partners identified?
  - Were any partners tested? What were the testing results?
  - Were partners identified in the primary jurisdiction, in the second jurisdiction, or in additional jurisdictions?
  - Were key locations, venues, or gatherings noted?
  - Are there commonalities across the cluster?
- Determine if persons in the molecular cluster across jurisdictions have been linked to other persons in the molecular cluster by partner services. Identifying these linkages can be reassuring, as it indicates that public health intervention efforts conducted already have been successful in identifying the connection. If the linkage has not been identified, this could be worrisome, as it suggests that partner services efforts have not identified the full transmission network. This could suggest that it is more likely that additional, yet unrecognized persons in the network are yet to be diagnosed.

Which jurisdiction leads an an investigation involving multiple jurisdictions?

- Generally, the jurisdiction with the majority of cases in a cluster, referred to by CDC as the 'primary jurisdiction', will take the lead on a cluster investigation. In situations where multiple jurisdictions are involved and no single jurisdiction has a majority of cases, CDC may take the lead, organizing data collection, investigation, and intervention efforts.
- The lead jurisdiction has the responsibility for coordinating and leading the investigation and keeping all involved jurisdictions informed of investigation progress and findings.

- All involved jurisdictions should participate in synthesizing investigation findings across multiple jurisdictions, and making decisions about next steps and interventions that will have implications for the jurisdictions involved.
- Secure data sharing methods, such as a secure FTP site, are essential for data sharing across jurisdictions.

Communicating with other jurisdictions about persons in a cluster

- The most effective approach to communicate with another jurisdiction about a cluster is to reach out directly to the surveillance coordinator for that jurisdiction; this ensures both that appropriate personnel are involved in data exchange, and that these key staff are aware of their jurisdiction's involvement in a cluster. For multijurisdictional clusters identified by CDC, CDC will facilitate sharing of information for persons in non-primary jursidictions on request by the primary jurisdiction in the cluster.
- As the investigation progresses, continued communication and coordination could be needed.

Considerations in sharing names and identifying information across jurisdictions

- While it might not always be necessary to share names and other identifying information across jurisdictions, certain key questions can be assessed only with names:
  - Is a cluster member in another jurisdiction a partner of a case in the primary jurisdiction who could not be found or who was lost to follow up?
  - Is a single person listed multiple times in the transmission cluster or risk network across different jurisdictions?
  - Gathering updated care status and viral suppression information for a person that has been treated in multiple jurisdictions

Who has responsibility for outcomes of persons in clusters that are not in the primary jurisdiction?

- Each jurisdiction has responsibility for the outcomes related to transmission cluster and risk network members currently residing in that jurisdiction. These outcomes include:
  - Identification of partners to determine what is known of the full transmission cluster and risk network
  - Ensuring viral suppression for persons in the transmission cluster
  - Testing or re-testing of persons in the risk network not known to be HIV positive
  - PrEP referral for HIV uninfected persons in the risk network
- Additionally, it is important that all jurisdictions with persons involved in the cluster participate in interventions to interrupt transmission.

What to do when you are contacted by another jurisdiction about a cluster

- When contacted by another jurisdiction for information on a case involved in a cluster, please prioritize sharing information to the extent allowed by your state and local data sharing policies. Even if few or just one case in your jurisdiction is identified by sequence data as belonging to a transmission cluster, the true extent of the transmission cluster or risk network in your jurisdiction could be much larger, and investigation and intervention efforts could present prevention opportunities that could reduce transmission in your jurisdiction as well as the primary jurisdiction.

Special considerations for communication and coordination across jurisdictions

- Jurisdictions may differ in the relative priority given to a particular cluster investigation, and relative resources available. Consider if higher level leadership discussions might be needed, to determine joint priorities and available resources.
- Jurisdictions might also differ on legal restrictions in data sharing. Developing plans for data sharing early, developing data sharing agreements if needed, and identifying secure means of data transfer, can help facilitate communication and coordination.
- Effective communication and coordination could require the development of new collaborations/relationships between jurisdictions, or the strengthening of already existing relationships. Such relationships will provide a strong foundation for future cluster investigations.
- For jurisdictions within a state, existing contracts (such as those from a state funding county programs) could have implications for the scope of work a given jurisdiction can take on in the context of a cluster investigation.

The needs for communication and coordination across jurisdictions could evolve as an investigation expands.

CDC's role in multijurisdictional clusters

- CDC will routinely analyze national data to identify multijurisdictional clusters. In clusters for which no single jurisdiction has more than 50% of the cases in the cluster, CDC will take the lead role, or will ask one of the jurisdictions involved in the cluster to take the lead role, as appropriate.

For guidance on the relationship of 18-1802 evaluation measures related to transmission cluster and risk network members in non-primary jurisdictions, see Section 10, 'Description of PS18-1802 Strategy 3 evaluation measures'.

Section 8. Operationalizing cluster and outbreak detection and response

Creating program capacity for cluster detection and response

Jurisdictions must develop and maintain a plan and capacity for cluster and outbreak detection and response (PS18-1802 Measure 3.3.1). Health departments should ensure they have capacity to identify, review, prioritize, investigate, and intervene in clusters and outbreaks, ideally before any have been detected. Building capacity consists of two main components: 1. identifying key staff and partners, establishing roles, and providing training; and 2. identifying potential local resources that could be mobilized for investigation/response if needed.

PS18-1802 Measure 3.3.1: *Develop and maintain a plan and capacity for cluster and outbreak detection and response.*

Under PS18-1802, local jurisdictions must prepare a written plan for establishing and maintaining local capacity for cluster and outbreak detection and response. This includes recruiting necessary staff, ensuring training (including security and confidentiality training), identifying relevant experience, and procuring software (i.e. secure HIV-TRACE), equipment, and other resources.

Identify key staff and partners, establish roles, and provide training

- Identify the person(s) responsible for cluster analyses and detection and ensure adequate training is provided to conduct these analyses. At a minimum, training should cover the following topics:
    - Data security and confidentiality
    - Introduction to HIV evolution (this training serves as an important primer for staff using Secure HIV-TRACE)
    - Operating Secure HIV-TRACE (CDC has developed several resources such as user guides, power points, and webinars that are offered periodically to support the use of Secure HIV-TRACE)
- Identify key personnel and communication processes for cluster review, assessment, prioritization, decision making, and related resource-allocation. This group should review information for clusters identified by CDC and those identified locally. Key staff include:
    - Surveillance staff with experience reviewing, synthesizing, and interpreting data
    - Prevention staff with knowledge about partner services data and protocols and prevention interventions
    - Involving staff from both surveillance and prevention will be important; because prevention staff will typically be the ones to implement interventions, their participation in these processes is critical. Partner services staff, who will typically be an important contributor to these discussions, may fall under STD or HIV prevention programs. This review should be conducted by staff with expertise in epidemiology, data management, and/or with populations at greater risk for HIV infection.
- Select staff who represent the range of skills needed to conduct these activities (e.g., data management and analysis, knowledge of partner services, familiarity with medical chart review, and patient interview).
- Cluster and outbreak investigations may require a larger number of staff for short periods of time. Consider staffing resources that might be available from other health department divisions when surge capacity is needed, such as outbreak response staff outside of the HIV program. Other programs within a jurisdiction's health department, such as TB and STD, will often have experience with cluster or outbreak detection and response, and could be an important resource for HIV staff to learn from. Consider having HIV staff join presentations or other discussions of TB or STD cluster and outbreak investigations to learn from their experience, or even shadow these staff in the field if possible.
- Consider cross-training needs for staff involved from multiple divisions within the health department. For example, HIV surveillance and prevention staff involved in an outbreak may need training on the Incident Command System and crisis and emergency risk communication, whereas health department outbreak response staff may benefit from training on the sensitivity and security of HIV data, the risk of increased stigma among affected populations, and implementation of HIV-specific prevention interventions such as HIV testing, partner services (including contact tracing), community education (including condom distribution), risk-reduction services (including syringe service programs), HIV treatment, and HIV preexposure prophylaxis and HIV postexposure prophylaxis.
- Identify key stakeholders and partners who may need to be informed or involved in a cluster or outbreak investigation or response, depending on the situation. Consider at which point(s) before and during the cluster detection, investigation, and response process each stakeholders should be involved or informed. For more information about key stakeholders and partners who may need to be informed or involved in a cluster response, see Section 5, 'Communicating about HIV transmission clusters'.

Identify potential local resources that could be mobilized for investigation/response if needed

- Identify local resources and organizations that could be mobilized as partners for a potential intervention if needed. Such resources could include:
    a. Testing and vaccination sites
    b. Community-based organizations that routinely work with particular populations

c. Laboratory partners including local and state public health labs that may support increased testing during an outbreak, as well as the Laboratory Branch in the CDC's Division of HIV/AIDS Prevention which may provide additional laboratory assistance during an outbreak

d. Referral sources for mental health and substance use treatment services, particularly for clusters and outbreaks involving PWID (See 'Additional Resources' below for link to the CDC guidance document for managing HIV and HCV outbreaks among PWID.)

- Consider how these resources could be mobilized if needed. Preparation could include setting up a multidisciplinary workgroup to broker resources and developing policies/procedures to facilitate coordination.
- Consider the importance of using existing mechanisms/structures and interventions where available, rather than developing a new mechanism or structure.
- Develop relationships with community-based organizations and other partners for potential intervention activities.
  o Create memoranda of understanding that might be needed in advance of any collaboration, to facilitate rapid action when timely response is needed.

Developing a cluster and outbreak response plan

Having clear processes in place for cluster detection, prioritization, and response will help to facilitate action when clusters and outbreaks are identified. Jurisdictions should use the Cluster and Outbreak Detection and Response Plan Template (Appendix I) as a guide for developing this process. This template corresponds directly to this guidance document, and ensures that jurisdictions have incorporated the necessary components into their day-to-day cluster detection work while also developing capacity and processes for an escalated response.

PS18-1802 Measure 3.3.1: *Develop and maintain a plan and capacity for cluster and outbreak detection and response.*

Under PS18-1802, local jurisdictions must prepare a written plan for establishing and maintaining local capacity for cluster and outbreak detection and response. This includes recruiting necessary staff, ensuring training (including security and confidentiality training), identifying relevant experience, and procuring software (i.e. secure HIV-TRACE), equipment, and other resources.

After completing the Cluster and Outbreak Response Plan Template, programs should update the document at least annually, or more frequently as staffing or program changes require.

The Cluster and Outbreak Detection and Response Plan Template includes the main components of each section of the guidance document that jurisdictions should operationalize at the local level. For each activity, there is space provided for jurisdictions to specify their plan for conducting the activity and to indicate who is responsible for doing so. A summary of key components of the guidance document to address in the cluster and outbreak detection and response plan is included in Appendix J, 'Summary of key components to address in the Cluster and Outbreak Detection and Response Plan'.

The plan can be included as an addendum to any existing, general outbreak or public health response plan, if such a plan already exists at the health department.

After the HIV cluster and outbreak response plan has been developed, jurisdictions can test its effectiveness and make revisions to the plan accordingly.

Section 9. Initiating an escalated response

All clusters meeting national priority cluster criteria warrant public health attention – the transmission rate in these clusters has been consistently found to far exceed the estimated national transmission rate[2]. Additionally, clusters identified through other means, such as time-space clusters, can also reflect increases in transmission warranting public health attention. However, the type of public health response needed will vary from cluster to cluster; in some cases, routine public health actions such as partner services and linkage to care activities might be sufficient, while in other cases an escalated response might be needed. This could include incorporating surge staff in response efforts and accessing additional local resources, or seeking additional resources from the state or federal government if necessary. The level of response to a cluster can occur across a spectrum ranging from limited to emergency-level response.

When does a cluster represent an outbreak?

The term outbreak can be used in different ways. While a textbook definition of an outbreak is 'an increase, often sudden, above what is normally expected in that population or area'[1], the term is often used to describe situations in which an urgent or emergency-level public health response is needed. Determining whether an increase in HIV diagnoses or the identification of a transmission cluster warrants an escalated response is an iterative process, and multiple factors, including those outlined in this section, should be considered.

[1] Source: https://www.cdc.gov/ophss/csels/dsepd/ss1978/lesson1/section11.html

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In determining whether an escalated response for a cluster is warranted, the same factors that were considered in the initial assessment of the cluster (described in more detail in Section 4), will be important. The availability of resources for an investigation will also be an important consideration. These factors include (but are not limited to):
- Size of the transmission cluster, or magnitude of increase in cases
- Potential for ongoing transmission (i.e., extent of recent cluster growth, evidence of early infection [e.g., clusters with multiple acute infections], evidence of ongoing risk behavior, evidence of cases with unsuppressed viral loads or not in care, involvement of PWID, etc.)
- Potential for poor outcomes (i.e., presence of drug resistance, vulnerable and underserved populations, late diagnoses, incidental diagnoses, clusters involving pregnant women and/or perinatal HIV exposure, etc.)
- Local epidemiology
- Resources available

Each of these considerations must also be assessed in the context of alternative explanations. For example, could an increase in cases be explained by other factors such as changes in testing, data errors (i.e. duplicate cases), changes in the area's population, etc.?

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[2] France AM, Panneer N, Ocfemia MCB, Saduvala N, Campbell E, Switzer WM, Wertheim JO, Oster AM. Rapidly growing HIV transmission clusters in the United States, 2013–2016. Conference on Retroviruses and Opportunistic Infections, 5 March 2018.

Figure 9a: Process for determining what level of response is needed
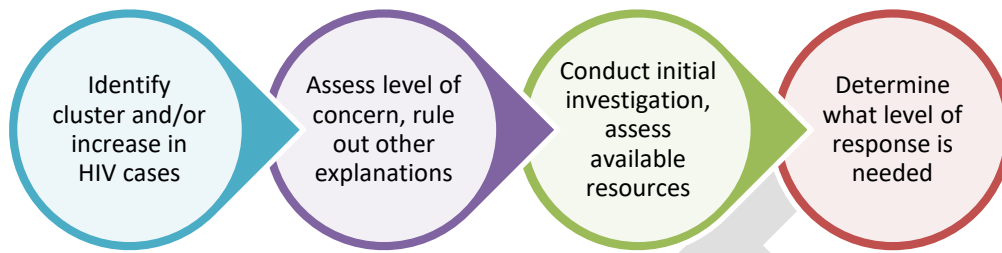
Actions to consider in an escalated response

A core component of an enhanced response is the initiation of enhanced investigation and intervention activities, as appropriate to the cluster. Potential enhanced investigation and intervention activities, and factors to consider in assessing the appropriate enhanced activities for a particular cluster, are described in detail in Section 4, Step 3 of this document.

In addition to enhanced investigation and intervention activities, the identification of additional resources, such as surge staff or state or federal support, and initiation of a communication plan, will be important. These topics are described in detail in Section 4, 'Assessing, prioritizing, and responding to clusters', and Section 5, 'Communicating about HIV transmission clusters', respectively. Additionally, leveraging resources through emergency operations structures might be considered. Consider whether use of the Incident Command System (ICS) might be needed in an escalated response. If so, it is recommended that HIV surveillance and prevention staff are included in key roles or are otherwise integrated into the ICS structure and response. See 'Additional resources' below for more information about the ICS.

Communicating with CDC in an escalated response

Communicating with CDC when an escalated response is initiated is important for the coordination of efforts and communications, even if CDC is not directly involved in the response activities. Please notify CDC HICSB and PPB staff within 72 hours of determination that an escalated response is needed. The notification should include how many cases have been identified thus far, what the primary mode of transmission is, which populations are most at risk, the determining factors that have prompted an escalated response, the immediate next steps that the jurisdiction plans to take, and whether they anticipate assistance may be needed from CDC in the form of laboratory resources, technical assistance, or an Epi Aid.

Assess local policies that might impact cluster investigation and potential intervention

- Programs might have policies in place that present potential obstacles to cluster investigation or potential intervention, such as policies limiting re-interview of persons by partner services. Review and assess these policies to identify any potential obstacles, and consider if there are alternative approaches, or opportunities to revise policies to accommodate cluster investigation and intervention activities.

- Consider incorporating these policies into existing outbreak response plans or other response plans already developed by the health department that could provide guidance for available resources and strategies in the context of a potential HIV cluster investigation and response.
- Also consider the importance of protecting patient privacy and confidentiality during a cluster investigation. Please see Section 6, 'Facilitating collaboration while protecting cluster data', for considerations regarding patient privacy and confidentiality in cluster investigations.

Scaling back and ending the cluster response activities

- Cluster response activities can be resource-intensive, and will be time-limited. Monitoring the progress of response activities is important to assess whether escalated response activities need to continue, or if they can be scaled back or ended. Considerations in monitoring progress, and depending when a response can be scaled back and closed, are described in detail in Section 4, 'Assessing, prioritizing, and responding to clusters', and Step 4, 'Monitor progress and determine when a cluster response should be closed'.

Additional resources

- Managing HIV and hepatitis C outbreaks among people who inject drugs: A guide for state and local health departments. Available at CDC's HIV cluster and outbreak detection and response webpage.
- FEMA Emergency Management Institute's ICS Resource Center.

Section 10. Description of PS18-1802 Strategy 3 evaluation measures

Measure 3.1.1: Analyze surveillance and other data using CDC-recommended approaches at least monthly to identify HIV transmission clusters and outbreaks.

Description: Local jurisdictions must use secure HIV-TRACE or other CDC-recommended approaches to conduct molecular analysis of HIV sequence data at least monthly, provided new data are available on a monthly basis. (For jurisdictions that have not collected HIV sequence data prior to PS18-1802, analysis of sequence data must occur once sequence data begin to be collected.) It is also required that jurisdictions analyze HIV case surveillance data monthly to identify time-space clusters in HIV diagnoses. This is an activity that can begin in all jurisdictions, including those that do not yet have molecular sequence data available. Analysis results of both molecular and time-space clusters will be used to identify new transmission clusters and to monitor the growth of existing clusters.

City-level jurisdictions may defer to the state to run this analysis monthly, as long as an agreement is in place between both parties. City-level jurisdictions must work with the state to ensure timely reporting of identified clusters and to develop plans for investigation.

Target: N/A

Data to be reported:
- Timing of analyses (when analyses were conducted)
- Type of analysis conducted (molecular and/or time-space)

Methods of Reporting Data: Jurisdictions will use the SER to report whether the analyses were conducted. Secure HIV-TRACE reports will be used to confirm the information provided in the SER.

Data Sources: APR, SER

Frequency of Reporting: annual

Measure 3.1.2: For each cluster of concern identified through analysis of surveillance and other data, submit analysis, investigation, and intervention results to CDC quarterly after identification of cluster until investigation and intervention activities are closed.

Description: CDC defines molecular national priority clusters (or clusters of concern) as those with five or more HIV cases at a genetic distance of ≤ 0.5 diagnosed within the previous 12 months for most jurisdictions. For jurisdictions with a lower burden of HIV (as defined by membership in the low morbidity workgroup), national priority clusters are those with three or more cases diagnosed in the previous 12 months. CDC encourages programs to develop criteria to identify additional clusters of concern in their jurisdictions based on local epidemiology; however, these clusters will not be included for evaluation purposes.

Jurisdictions must report analysis, investigation, and intervention results for all clusters of concern quarterly using the cluster investigation worksheet. See Section 4 of the technical guidance for details regarding cluster investigation and intervention activities in which jurisdictions should engage. At a minimum, jurisdictions must conduct a thorough review of surveillance and partner services data for all clusters identified. Jurisdictions also must ensure that all cluster information has been reported in eHARS prior to worksheet submission each quarter. Guidance on entering cluster information into eHARS will be forthcoming.

Jurisdictions must continue to report on all clusters for which an active investigation and/or intervention is underway on a quarterly basis. Refer to Section 4, Step 4, for information on how and when to stop cluster investigation and intervention activities.

Target: N/A

Data to be reported:
- Total number, size, and Cluster IDs of new clusters that meet CDC or local priority criteria and were newly identified during the reporting period
- Total number and growth of old clusters that jurisdictions continue to monitor and growth of these clusters
- Number, percent, and cluster IDs of clusters identified for which an investigation was conducted (*Numerator: Number of clusters in which an investigation was conducted / Denominator: Total number of clusters of concern identified in that quarter*)
- Outcomes of investigations and interventions (quantitative and qualitative)

Methods of Reporting Data: Jurisdictions will report their analysis, investigation, and intervention findings using the cluster investigation worksheet and securely transmit that data to CDC using SAMS.

Data Source: APR, SER, cluster investigation worksheet

Frequency of Reporting: quarterly

Measure 3.2.1: Of all HIV-positive persons in transmission clusters who were not known to be virally suppressed at the time of identification as part of the cluster, percentage that achieved viral suppression within 6 months of identification as part of the cluster.

Definition: For priority clusters identified as part of CDC or local analysis efforts, jurisdictions will gather data and/or conduct an investigation to determine how many HIV-positive persons are in the transmission cluster. Once the larger transmission cluster is identified, jurisdictions should use existing data sources (and additional investigation techniques if needed) to identify which HIV-positive persons are out of care or lack viral suppression, then implement interventions to link them to care. The effectiveness of these efforts will be measured by assessing how many HIV-positive persons who were not virally suppressed at the time of identification as part of the cluster (or had unknown viral suppression status) have achieved viral suppression six months later.

Target: 60%

Data to be Gathered:
- Numerator: Number of HIV-positive persons in transmission cluster who have achieved viral suppression within six months who were not virally suppressed or had unknown viral suppression at identification as part of the cluster
- Denominator: Number of HIV-positive persons in transmission cluster without viral suppression or with unknown viral suppression at identification as part of the cluster

Methods of Reporting Data: Using eHARS, jurisdictions can calculate the status of viral suppression for all HIV-positive persons who are members of transmission clusters provided they are assigned a Cluster ID. Additional viral suppression values at six-month follow-up can be calculated using eHARS as well. As of May 2018, CDC is developing a SAS program that will allow sites to run monthly analysis to determine viral suppression for all cluster members that reached six months of identification as part of the cluster and did not have evidence of viral suppression as of that date. The timeframe for inclusion in this measure will be based on the length of time since identification as a part of the cluster and the amount of time needed for lab data to be uploaded into eHARS. This measure will only be calculated for cluster members who are still alive at six months from identification as part of the cluster and will be reported annually through the SER. Cluster-based viral suppression totals will also be reported quarterly via the cluster investigation worksheet.

Any HIV-positive persons newly-identified through Measure 3.2.2 testing and re-testing activities (see below) or through other cluster investigation activities should also be included in the reporting for this measure. See Figure 10a.

Note: Jurisdictions are responsible for reporting this outcome for any cluster members that are residing within their jurisdiction at the time of six month follow up, regardless of whether they are the primary jurisdiction assigned to the cluster.

Data Source: NHSS, SER, cluster investigation worksheet

Frequency of Reporting: annual (jurisdiction-wide), quarterly (cluster-level)

Measure 3.2.2: Of all partners of transmission cluster members who were not known to be HIV positive at the time of cluster identification, percentage tested or re-tested within 6 months of identification as part of the risk network.

Definition: All partners of transmission cluster members who had unknown HIV status at identification as part of the risk network should be tested within 6 months. Similarly, all partners who were HIV negative at identification as part of the risk network should be re-tested within 6 months. This measure captures the effectiveness of efforts to identify and confirm HIV status among those who initially tested as negative when the cluster was first identified or had unknown HIV status.

For the purposes of this measure, 'partners' refers to named contacts of transmission cluster members, as well as marginal partners that have enough information provided for an attempt to be made by DIS to locate for testing. HIV-negative partners who were recently tested (within three months of identification as part of the risk network) may be excluded from re-testing activities.

Target: TBD

Data to be Gathered:
- Numerator: Number of partners who have been tested (for those with unknown HIV status) or re-tested (for those with HIV-negative status) within six months of identification as part of the risk network
- Denominator: Total number of partners of transmission cluster members with HIV-negative status or unknown HIV status at identification as part of the risk network

Methods of Reporting Data: Data reporting mechanisms for this measure are still in development. For all partners associated with a cluster with HIV-negative or unknown status at identification, jurisdictions should track the partner's initial status, date of testing/re-testing during the six month follow up period, and test results.

Any partners who are newly-identified as positive for HIV through testing/re-testing efforts should be entered in eHARS using the appropriate cluster ID and reported to CDC on an aggregate level quarterly using the cluster investigation worksheet. Jurisdictions should then conduct partner services interviews and test any newly-identified partners as part of this measure. See Figure 10a.

Note: Jurisdictions are responsible for reporting this outcome for any transmission cluster and risk network members that are residing within their jurisdiction at the time of six month follow up, regardless of whether they are the primary jurisdiction assigned to the cluster.

Data Source: data collection template for partners, APR, SER

Frequency of Reporting: annual

Measure 3.2.3: Of all partners of transmission cluster members who were determined to be HIV-negative and not on PrEP, percentage referred for PrEP within 6 months of identification as part of the risk network.

Definition: As local jurisdictions identify HIV-negative members of the risk network, these individuals should also be screened for PrEP eligibility. Any HIV-negative partners who are screened and determined to be eligible should be referred for PrEP within 6 months of identification as part of the risk network. This may include HIV-negative partners who were previously identified as named partners before the cluster was identified but were not referred to PrEP or did not accept a PrEP referral at that time, as well as HIV-negative partners newly identified through the course of cluster investigation and response activities. In the case of the former, the

date of cluster identification serves as the date the individual was identified as part of the risk network; in the case of the latter, the date the individual was named as a partner of a transmission cluster member serves as the date of identification as part of the risk network. This measure captures the effectiveness of efforts to refer eligible HIV-negative risk network members for PrEP.

For the purposes of this measure, referral to PrEP providers refers to a process involving the provision of information on who the providers are, what documents referred person should take with them, how to get to the providers' agency, and what to expect from the referral process. It is important that the agency that provides PrEP screening services tracks the referral and provides the necessary follow-up to verify the person attended the first appointment with the PrEP provider. A person can be referred to a PrEP provider internally (to another unit or person within the same agency) or externally (e.g. a CBO may screen and identify eligible persons, and then refer them to a healthcare provider that offers PrEP services).

Target: TBD

Data to be Gathered:
- Numerator: Number of HIV-negative partners who were not already on PrEP at identification as part of the risk network referred for PrEP within six months
- Denominator: Number of HIV-negative partners of transmission cluster members not already on PrEP at the time of identification as part of the risk network (excluding partners deemed to be ineligible for PrEP through screening efforts)

Methods of Reporting Data: Data reporting mechanisms for this measure are still in development. Jurisdicions should track partners with HIV-negative or unknown HIV status at identification, date screened for PrEP, screening outcomes, and date referred for PrEP.

Note: Jurisdictions are responsible for reporting this outcome for any cluster members that are residing within their jurisdiction at the time of six month follow up, regardless of whether they are the primary jurisdiction assigned to the cluster.

Data Source: data collection template for partners, APR, SER

Frequency of Reporting: annual

Measure 3.3.1: Develop and maintain a plan and capacity for cluster and outbreak detection and response.

Definition: Local jurisdictions must prepare a written plan for establishing and maintaining local capacity for cluster and outbreak detection and response. This includes recruiting necessary staff, ensuring training (including security and confidentiality training), identifying relevant experience, and procuring software (i.e. secure HIV-TRACE), equipment, and other resources. This plan should be entered into the CDC 'Cluster and Outbreak Detection and Response Plan Template', found in Appendix I.

Target: N/A

Data to be Gathered:
- document review (jurisdiction's cluster and outbreak detection and response plan)
- qualitative responses from jurisdictions indicating sufficient capacity to respond to clusters and outbreaks

Methods of Reporting Data: Jurisdictions must submit their outbreak detection and response plans using the template provided by CDC by the end of the first year of PS18-1802 funding. They will also provide responses on their perceived level of preparedness and capacity when reporting through the SER and APR.

Data Source: APR, SER, HIV cluster and outbreak response plan

Frequency of Reporting: The HIV cluster an outbreak response plan will be submitted by the end of the first year of PS18-1802 funding, with significant updates to the plan (i.e. changes in staffing, training requirements, protocols, etc.) submitted each year thereafter. Jurisdictions will also be required to provide qualitative responses annually through the APR indicating that they continue to maintain sufficient capacity for cluster and outbreak response.

Figure 10a: Process flow for including newly-identified HIV-positive persons in PS18-1802 evaluation measures
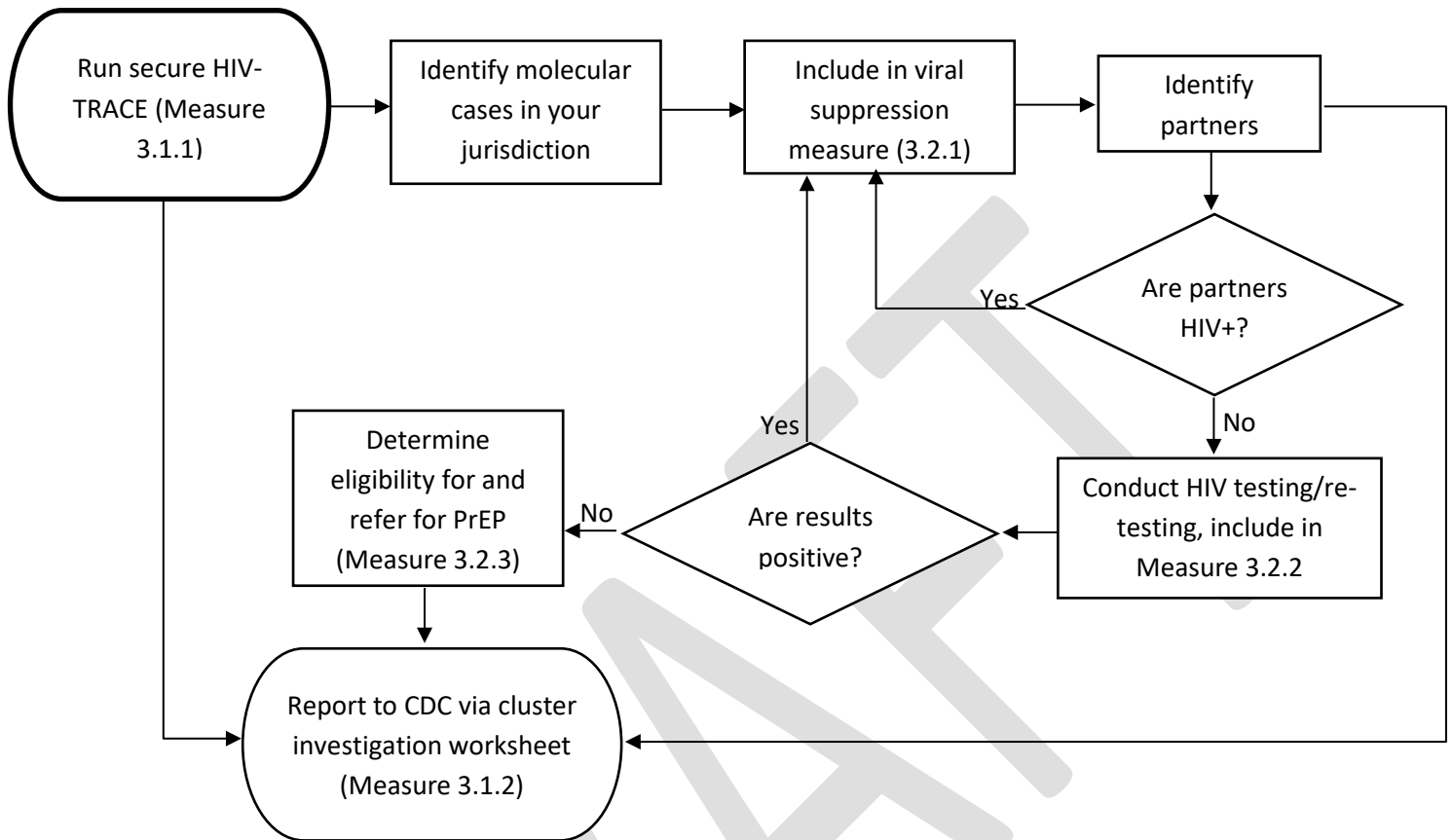
Note: This process applies to other methods of cluster detection in addition to molecular analysis.

Step 1: Run secure HIV-TRACE at least monthly (Measure 3.1.1) and report analysis outcomes to CDC quarterly using the cluster investigation worksheet (Measure 3.1.2).

Step 2: Identify molecular cases residing in your jurisdiction. You will be responsible for reporting outcome measures on all cases in your jurisdiction, not just those for which you are the primary jurisdiction at HIV diagnosis.

Step 3: Conduct interventions and report on viral suppression for all cases not virally suppressed at the time of identification as part of the cluster (Measure 3.2.1).

Step 4: Identify partners of molecular cases by reviewing available data and conducting cluster investigation activities. Report the outcomes of these investigations using the cluster investigation worksheet (Measure 3.1.2).

Step 5: HIV-positive persons identified who are partners of molecular cases (i.e., transmission cluster cases) should be included in interventions for and reports on viral suppression (Measure 3.2.1). Their partners should also be identified and evaluated for HIV status.

Step 6: Partners with unknown HIV status and HIV-negative partners should be tested/re-tested within six months of identification as part of the risk network (Measure 3.2.2). Any partners newly-identified as positive through testing/re-testing activities should be included in interventions for and reports on viral suppression (Measure 3.2.1), and should also be interviewed by partner services to identify other members of the risk network.

Step 7: Partners who are identified to be negative through testing/re-testing efforts should be referred to PrEP (Measure 3.2.3), and the outcomes of these and other cluster-based interventions should be reported to CDC quarterly via the cluster investigation worksheet (Measure 3.1.2).

Out of jurisdiction cases: Guidance for Strategy 3 measures

Overview

Strategy 3 of PS18-1802 contains measures that require jurisdictions to report on outcomes from cluster investigation and response activities. Often, clusters of concern will cross jurisdictional boundaries and contain one or more cases that reside in other jurisdictions (see Section 3, 'Identifying growing transmission clusters using surveillance data'). In order to stop cluster growth and interrupt the transmission of HIV, it is essential that jurisdictions collaborate and ensure that interventions are provided to all cases in a transmission cluster and risk network, regardless of the jurisdiction in which they reside. For the purposes of evaluating these efforts, jurisdictions should abide by the procedures outlined below.

Identifying Out-of-Jurisdiction Cases in Clusters

Below are possible scenarios in which out-of-jurisdiction cases in clusters may be identified:

- Through quarterly national cluster analysis at the CDC: Clusters newly identified through national analysis may have already been detected at the local level by the primary jurisdiction through running Secure HIV-TRACE, reviewing partner services data, or through other means. However, molecularly linked cases in these clusters that are residing in other jurisdictions may not have been identified prior

to running the national analysis. Additionally, quarterly national analysis may detect new cases located outside the primary jurisdiction for older clusters that continue to grow.

- <u>Through Secure HIV-TRACE</u>: an enhancement to incorporate multijurisdicital analysis into Secure HIV-TRACE is currently in delopment.
- <u>Through review of partner services and surveillance data</u>: During the course of conducting a cluster investigation, jurisdictions may find that cases have relocated to another jurisdiction. Additionally, they may find that partners of molecular cases are living outside the jurisdiction.
- <u>Reporting by multiple jurisdictions</u>: Some HIV-infected persons may live in geographic areas in which care is typically sought across jurisdictional boundaries. Alternatively, an HIV-infected person in a cluster might relocate frequently and seek care in multiple jurisdictions. RIDR or other secure data sharing process may also inform on whether cases have relocated and are in multiple jurisdictions.

In each of these scenarios, responsibility for follow up of HIV-infected persons who are molecular cluster, transmisison cluster, or risk network members belongs to the jurisdiction in which the individual is currently residing.

Coordinating with Other Jurisdictions

Coordination across jurisdictions is essential to ensure that out of jurisdiction cases in clusters are linked to care and partners are tested and referred to the appropriate prevention services. While CDC can identify out-of-jurisdiction cases during quarterly national molecular analyses, this process may be delayed, and thus it is essential that individual jurisdictions communicate with one another in a timely manner regarding HIV-positive persons who are members of a cluster that move to another jurisdiction and partners of that live in other jurisdictions that need testing and referral for PrEP. See Section 7, 'Approaching multijurisdictional clusters', for further guidance on communicating about clusters across jurisdictional boundaries.

Completing the Cluster Investigation Worksheet

Jurisdictions must report on data related to cluster investigation and response using the Cluster Investigation Worksheet (see Appendix E). For data related to testing of partners, jurisdictions should indicate on the form the number of individuals who are out of jurisdiction. Communication to the jurisdictions where these individuals reside should occur rapidly and securely to ensure that follow up occurs in a timely manner.

Reporting on Measures

Using the SER, jurisdictions must report on Strategy 3 outcomes for all cluster cases and partners that are currently residing in their jurisdiction, **regardless of whether they are the primary jurisdiction for the cluster**. Specific guidance for each measure is listed below.

- *Measure 3.2.1: Of all HIV-positive persons in transmission clusters who were not known to be virally suppressed at the time of identification as part of the cluster, percentage that achieved viral suppression within 6 months of identification as part of the cluster.*
  - o Viral load results must be entered into eHARS for all HIV-positive partners in the transmission cluster. Activities to promote viral suppression include linkage or re-linkage to care and follow up with providers as needed. Jurisdictions are responsible for reporting the viral suppression status of all transmission cluster members currently residing in their jurisdictions.
- *Measure 3.2.2: Of all partners of transmission cluster members who were not known to be HIV positive at the time of cluster identification, percentage tested or re-tested within 6 months of identification as part of the risk network.*
  - o Partners of HIV-positive persons in transmission clusters with unknown HIV status should be tested, and HIV-negative partners should be re-tested if their last negative HIV test occurred more than three months before the time in which they were identified as part of the risk

network (or re-tested according to other guidance timeframes, such as provider/physician recommendation). For evaluation purposes, jurisdictions are required to report on re-testing of HIV-negative persons who were last tested three or more months before identification as part of the risk network. Jurisdictions are responsible for reporting the outcomes of testing and re-testing efforts among all partners of molecular and transmission cluster members currently residing in their jurisdictions.

- o In some cases, an HIV-positive member of a cluster may have named and locatable partners who live in another jurisdiction. In such instances, the jurisdiction in which the HIV-negative or HIV-unknown partners reside, not the jurisdiction in which the HIV-positive cluster member resides, should report on outcomes of testing and re-testing efforts.

- *Measure 3.2.3: Of all partners of transmission cluster members who were determined to be HIV-negative and not on PrEP, percentage referred for PrEP within 6 months of identification as part of the risk network.*
    - o HIV-negative members of a risk network who were not on PrEP at the time of identification as part of the risk network and are eligible for PrEP should be referred for PrEP. As stated above, jurisdictions are responsible for reporting the outcomes of PrEP referrals for all HIV-negative partners who currently reside in their jurisdictions, regardless of whether the HIV-positive transmission cluster members also reside in their jurisdictions.

Appendix A: List of abbreviations and key definitions

AIDS Drug Assistance Program (ADAP) State and territory-administered program authorized under Part B of the Ryan White HIV/AIDS Treatment Extension Act of 2009 that provides FDA-approved medications to low-income people living with HIV who have limited or no health coverage from private insurance, Medicaid, or Medicare. ADAP funds may also be used to purchase health insurance for eligible clients and for services that enhance access to, adherence to, and monitoring of drug treatments *Source: Health Resources & Services Administration*

Community-based organization (CBO) Provides HIV prevention services, including HIV counseling and testing, to populations that are hard to reach and at high risk for transmitting or acquiring HIV. CBOs can act as a partner services entry point for clients who might not otherwise be offered these services, and staff members can promote partner services to the communities. CBOs also might be adept at gaining trust and establishing rapport with wary, untrusting, and fearful clients and their partners. CBO staff members might effectively elicit partner information from HIV-infected clients and provide counseling and testing to partners who come to the CBOs for services. Before partner services program managers determine how best to use CBOs in the partner services process, they should consider local laws and regulations. In certain jurisdictions, health departments and medical providers are the only entities with legal authority to notify persons of their exposure to HIV and other types of STDs.

Cluster investigation A systematic process to:

1) Identify the underlying transmission cluster and risk network (e.g., undiagnosed cases, diagnosed cases without a sequence, persons at risk for HIV)
2) Identify factors possibly associated with transmission
3) Understand possible connections between cases in a cluster
4) Assess potential risk for ongoing transmission
5) Determine what potential interventions might be effective

Cluster snapshot A document developed by the CDC HIV Incidence and Case Surveillance Branch to communicate cluster and case-level data on a molecular cluster to state and local health departments. An example of a cluster snapshot can be found in Appendix E.

Disease intervention specialists (DIS) Health department personnel who are specifically trained to provide partner services. Some health departments use different titles for persons providing partner services. In addition, in certain jurisdictions, other persons (e.g., HIV counselors or clinicians) either inside or outside of the health department provide certain or all elements of partner services.

Drug resistance testing	Conducted in order to identify mutations associated with viral resistance to antiretroviral medications and help the HIV care provider select an appropriate treatment regimen. Drug resistance testing is recommended for all persons with diagnosed HIV infection, with the recommendation that testing be conducted at entry to HIV care. Drug resistance testing is typically ordered by providers at entry to HIV care, but can also be ordered at later time points (for example, if a patient is on treatment but does not have a suppressed viral load). A nucleotide sequence is generated as an intermediate byproduct from a drug resistance test.
Engagement in care	Measured by whether a person with diagnosed HIV infection has a had at least one HIV medical care visit during the analysis period
Genetic distance threshold	The level of genetic similarity used to identify closely related pairs of sequences. The genetic distance threshold used can vary based on the goal of the analysis.
HIV TRAnsmission Cluster Engine (HIV-TRACE)	A bioinformatics tool developed by researchers at the University of California, San Diego to analyze nucleotide sequences and identify clusters representing recent and rapid transmission. A secure local installation of HIV-TRACE at CDC is used to run routine analyses on national surveillance datasets.
Molecular cluster	Identified through analysis of HIV genetic sequence data that is generated through HIV drug resistance testing. Molecular clusters contain only those people for whom molecular data is available and can be analyzed, and contains a subset of what is likely a larger underlying transmission cluster
Molecular data	See 'Nucleotide sequence'
Molecular HIV Surveillance (MHS)	A component of the National HIV Surveillance System. CDC funds selected state and local health departments to conduct molecular HIV surveillance activities.
Multijurisdictional cluster	A cluster in which coordination across jurisdictions is required for effective investigation and response. Often, multijurisdictional clusters will include cases reported from multiple states, however the jurisdictional issues involved could be relevant for clusters involving multiple counties within a single state, particularly if they include separately funded HIV surveillance or prevention programs.
National HIV Surveillance System (NHSS)	The primary source for monitoring HIV trends in the United States. The primary functions of the National HIV Surveillance System (NHSS) are (1) to provide accurate epidemiologic data to monitor the incidence and prevalence of HIV infection and HIV-related morbidity and mortality and (2) to use these data trends to assist in public health planning and policy. CDC provides federal funding to states and territories through surveillance cooperative

	agreements to achieve the goals of NHSS and also to assist states in developing their own surveillance programs in accordance with state and local laws and practices.
Nucleotide sequence	An intermediate byproduct of an HIV drug resistance test. Analysis of nucleotide sequences can identify pairs of sequences that are extremely similar and which may be closely related in transmission
Partner services	A broad array of services that should be offered to persons with HIV infection, syphilis, gonorrhea, or chlamydial infection and their partners. A critical function of partner services is partner notification, a process through which infected persons are interviewed to elicit information about their partners, who can then be confidentially notified of their possible exposure or potential risk. Other functions of partner services include prevention counseling, testing for HIV and other types of STDs (not necessarily limited to syphilis, gonorrhea, and chlamydial infection), hepatitis screening and vaccination, treatment or linkage to medical care, linkage or referral to other prevention services, and linkage or referral to other services (e.g., reproductive health services, prenatal care, substance abuse treatment, social support, housing assistance, legal services, and mental health services).
Pre-exposure prophylaxis (PrEP)	A way for people who do not have HIV but who are at substantial risk of getting it to prevent HIV infection by taking a pill every day
Primary jurisdiction	The jurisdiction with the majority of cases in a molecular cluster
Priority cluster	A molecular cluster that has met certain criteria and which should be flagged for preliminary investigation. Currently, CDC-defined priority clusters for high and medium morbidity jurisdictions are clusters identified at a 0.5% genetic distance threshold with ≥5 cases in the most recent 12-month period. For low morbidity jurisdictions, CDC-defined priority clusters are those identified at a 0.5% genetic distance threshold with ≥3 cases in the most recent 12-month period. Analyses of clusters meeting the abovementioned criteria indicates similar transmission rates that are approximately 7 - 8 times greater than the transmission rate among HIV infected individuals in the US. In addition to using criteria for CDC-defined priority clusters, jurisdictions may also develop criteria to identify additional locally-defined priority clusters.
PWID	Persons who inject drugs
Ryan White HIV/AIDS Program	Provides a comprehensive system of care that includes primary medical care and essential support services for people living with HIV who are uninsured or underinsured. *Source: Health Resources & Services Administration*

Second-generation interview   A partner services interview strategy that involves interviewing partners of partners, regardless of HIV infection status

Secure HIV-TRACE   A web-based bioinformatics tool developed by researchers at the University of California, San Diego and Temple University to analyze HIV nucleotide sequences and identify molecular clusters. Secure HIV-TRACE is available to individual public health institutions to facilitate real-time analysis by state and local health departments to better understand and respond to their specific HIV burden.

Social network testing strategy   A recruitment approach for reaching and providing HIV counseling, testing, and referral services to persons who are unaware of their HIV infection by using existing social connections

Time-space cluster   A time-space cluster occurs when the number of diagnoses of HIV infection in a particular geographic area is elevated above levels expected given previous patterns.

Transmission cluster   A group of HIV infected persons who are connected by HIV transmission. A transmission cluster represents a subset of an underlying risk network

(Underlying) risk network   Includes the group of persons among which HIV transmission has occurred and could be ongoing. This network includes persons who are not HIV-infected but may be at risk for infection, as well as the HIV infected persons in the transmission cluster

Appendix B. HIV Molecular Evolution

HIV-1 Genome and Structure

The HIV-1 RNA genome is comprised of approximately 10,000 nucleotides that are the code for 9 to 10 genes that encode for 16 proteins. Tgroup specific antigen (*gag*), polymerase *(pol)* and envelope (*env)* genes encode the information needed to make the structural proteins for new viral particles. The *pol* gene also codes for enzymes for viral replication (reverse transcriptase (RT)) and integration into the host genome (integrase (IN)). The other genes encode for regulatory or accessory proteins that control replication and infectivity.
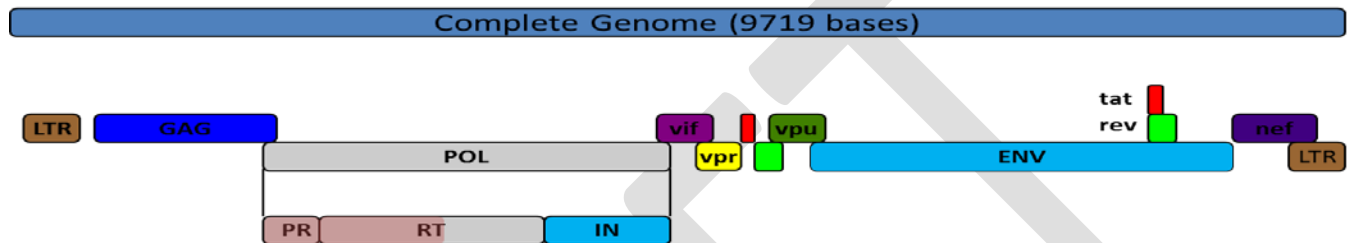
HIV-1 Genetic Evolution

HIV-1 replicates rapidly, generating about 10 billion viral particles every day in an untreated person. HIV-1 also has a high genomic evolutionary rate ranging from 1.3×10^{-3} to 3.5×10^{-3} nucleotide substitutions/site/year depending on the HIV-1 subtype and specific gene region examined. For pol, this corresponds to a rate of evolution of 1% every 10 years. The genetic distance that reflects the relative change between HIV sequences can be used as a proxy for the number of years since the HIV sequences diverged from a common ancestor or transmission event. The genetic distance applied can vary based on the goal of the analysis. For example, to identify cases related by recent and rapid transmission, a very close genetic distance threshold should be used—for example, 0.5% (which, for a sequence that is 1000 nucleotides long, corresponds approximately to 5 different nucleotides). A genetic threshold of 0.5% corresponds to approximately a maximum of 5 years of viral evolution (2-3 years for each person, because the virus is evolving in each person) separating these strains (which may correspond to time since a common transmission event). By contrast, if the goal is to identify all possible cases that could be related to a given case, a larger genetic distance threshold should be used—for example, 1.5%. A 1.5% threshold corresponds to a maximum of 15 years of viral evolution separating these strains.

The high substitution rate is believed to be caused by the low fidelity of the RT enzyme during replication and by HIV-1 genome interactions with other cellular enzymes. RT is the enzyme used by HIV to convert single-stranded HIV RNA into double-stranded cDNA allowing integration into the host genome. Because RT does not have a proofreading mechanism, transcription from viral RNA to DNA is error prone. HIV's fast replication cycle and high substitution rate of HIV-1 leads to high genetic diversity enabling the virus to evade the immune system and also to develop antiretroviral drug resistant mutations.

Mutations have been found in all HIV-1 genes. When considering only the *pol*, *gag*, and *env* genes, there are small sequence regions in each that are considered genetically conserved, because mutations in those regions negatively affect the virus's ability to survive or replicate. In general, the *pol* gene is considered the most conserved gene and *env* is considered the least conserved gene likely due to *env* having a higher substitution rate. Therefore, analyses of regions other than pol may need to consider different genetic distance thresholds.

HIV-1 Subtypes and Minority Strains

HIV-1 can be classified into four groups; of which M is associated with the majority of infections worldwide. Within group M, many distinct subtypes exist (e.g., A, B, C, D, F, G, H, J and K). The sequences within any one subtype are more similar to each other than to sequences from other subtypes. These subtypes represent different lineages of HIV, and have some geographical associations. Additionally, different subtypes can combine genetic material to form a hybrid virus, known as a 'circulating recombinant form' (CRF).

Although most persons are infected with a single variant of HIV-1, rapid error-prone replication over time leads to HIV-1-positive individuals being infected with an enormous pool of genetically related strains called "quasispecies". These quasispecies or variants are closely related viruses with different nucleotide sequences. Within an infected individual, HIV-1 diversity typically consists of a major, dominant strain and other less frequent genetic variants, which can change due to viral fitness, changes in immune response or drug pressure.

Minority strains are normally defined as those variants that are present in less than 20% of the total quasispecies pool. Sanger or bulk sequencing, the most common approach used for HIV drug resistance testing in clinical settings, detects variants with a frequency of at least 20% of the total viral population. Hence, most minority strains will not be detected when testing for HIV drug resistance using Sanger sequencing. The clinical significance of minority HIV-1 strains for development of drug resistance is not clear at the present time. About 10-15% of newly diagnosed patients are infected with strains containing at least one drug resistant mutation.

HIV gene regions analyzed for detecting antiretroviral drug resistance

Testing for HIV drug resistance mutations consists of sequencing of only positions of the *pol* gene that encode enzymes targeted by antiretrovirals, including RT, protease (PR), and integrase (INT). Currently, the PR and RT sequences are analyzed in programs such as Secure HIV-Trace to identify molecular clusters.. Commercial drug resistance detection assays were developed using HIV-1 subtype B and may not perform well with other subtypes.

Sanger Sequencing vs Next Generation Sequencing (NGS)

Sanger or "bulk" sequencing is the most common method used for HIV drug resistance testing in clinical settings. This testing is available at commercial labs but HIV researchers also perform this testing using in-house assays and analysis. Sanger sequencing was developed by Dr. Frederick Sanger in the 1970s and involves the termination of DNA synthesis by selective incorporation of chain terminating dideoxynucleotides by DNA polymerase during DNA replication and separation and visualization of the resulting fragments by capillary electrophoresis and laser detection.

Currently, NGS, deep sequencing or massively parallel sequencing is predominantly used in HIV research studies. NGS methods are based on the "sequencing by synthesis" principle where nucleotides incorporated into a strand of DNA provide a unique signal. The unique signal in most NGS platforms is a fluorescent molecule but can also be a change in pH. NGS can sequence myriad DNA fragments simultaneously in a short period of time and uses bioinformatics programs to piece together and analyze the synthesized sequences. There are several NGS platforms, each with their own synthesis and detection methods.

Sanger Sequencing	Next Generation Sequencing
DNA synthesis and signal detection are two separate processes and only one DNA strand (forward or reverse) can be read at a time	Synthesis and signal detection occur simultaneously using multiple DNA templates
Cost per sample is more expensive; one sample per sequencing reaction No special bioinformatics infrastructure and storage capacity required Sequence reads are longer (~700-900 bases per read per sample)	Cost is lower and process is faster; can sequence many samples simultaneously Bioinformatics infrastructure and storage capacity to store and analyze millions of sequence fragments is required Higher error rate but getting better Sequence reads are shorter (< 400 bases per read depending on platform), but many more reads per sample per run are possible
Detects variants with prevalence of/greater than ~20%	Detect minority variants at a prevalence of/less than 1%
Most common method used for HIV drug resistance testing in clinical settings	Mostly used in research settings

Appendix C. Frequently asked questions about HIV-TRACE and transmission network analysis

Excerpted from 'Secure HIV-TRACE: a guide for public health departments to reconstructing HIV-1 transmission clusters,' courtesy of Joel Wertheim.

Why pairwise alignment?

Secure HIV-TRACE was designed to detect transmission clusters using the 1497 nucleotide region spanning the HIV-1 *pro/rt* region common in public health surveillance activities, drug resistance screening, and research studies. This genomic region is from a conserved genomic region with very limited length variation (unlike, say, *env*) across all major HIV-1 subtypes and circulating recombinant forms. The absence of insertions and deletions permits robust pairwise alignment to a reference sequence. This approach is a timesaving measure compared with the more computational intensive approach of multiple sequence alignment, because it has linear complexity in the number of sequences; popular multiple sequence alignment algorithms all have superlinear complexity. **Secure HIV-TRACE** uses a modified version of the Smith-Waterman algorithm, which aligns nucleotide sequences by considering amino-acid translations of constituent codons; this approach allows us to make full use of amino-acid conservation to preserve alignment accuracy for divergent sequences (e.g., those from different subtypes).

Why genetic distance?

Genetic distance provides a measure of epidemiological relatedness, because it increases as a function of time since transmission (in a linear fashion, as a first order approximation). This increase in genetic distance, due to an underlying molecular clock provides us with a proxy for the amount of time that has passed since two viral strains diverged from one another. The molecular clock in HIV, however, is highly imprecise because of factors like latency and natural selection due to immune escape and anti-retroviral treatment. Furthermore, the virus evolves in both the donor and recipient, so the distance between two strains is not simply a multiplier for the time since transmission. That being said, genetic distance serves as a useful proxy for epidemiological relatedness.

Why use a fixed distance cutoff?

HIV *pro/rt* diverges from the founder strain at a rate of about 0.1% per site per year, which indicates that a cutoff of 0.015 is about 5-15 years of combined evolution (in the source and the recipient). Distributions of pairwise distances in large sets of sequences (i.e., local, national, regional, and global) have the characteristic property of resembling a mixture of two distributions (see **FIGURE 24**): a component near 0 (i.e., closely/recently related sequences) and a component near 0.06 (i.e., two random sequences of the same subtype). Distance cutoffs of 0.01 to 0.02 segregate the two components nicely. See more below: **How do I select a genetic distance threshold?**). Further, our recent work in named partners in New York City has demonstrated that genetic distance alone provides better insight into who are potential transmission partners than partner tracing alone. In a sense, using genetic distances allows one to perform contact tracing among all persons in a surveillance cohort, asking each pair if they have an epidemiological connection.

What is TN93 genetic distance?

TN93 is the name of a nucleotide substitution model developed by Koichiro Tamura and Masatoshi Nei, published in 1993. Hence, TN93. Nucleotide substitution models are used in evolutionary analyses to correct for multiple substitutions and/or reversions at a given site. Highly divergent sequences, with a greater number of substitutions separating them, are more likely to require complicated evolutionary models to properly estimate

the level of divergence. The simplest evolutionary model, JC69, has a single parameter governing mutation rates among different nucleotides, and assumes equal frequencies for all nucleotides. In contrast, a more complex evolutionary model like general time reversible model with gamma rate variation (GTR+Γ) allows all nucleotide substitutions to occur at a unique rate, unique equilibrium base frequencies, and rate variation across sites. Importantly, over relatively short evolutionary distances (i.e., <0.05 substitutions/site), GTR+Γ does not improve distance estimation accuracy for simpler models like JC69 (CITE), because not enough time has elapsed for a substantial number of multiple substations and/or reversions. In basic calculus terms, most curves resemble straight lines if you zoom in closely enough.

For **Secure HIV-TRACE**, we wanted an evolutionary model that optimizes both realism and computational efficiency. Simple models like JC69 and K2P (Kimura 2-parameter) have obvious shortcomings when applied to HIV: these models do not permit unequal nucleotide base frequencies, and HIV has notorious high frequencies of adenine (A) and low frequencies of uracil/thymine (U/T). The TN93 substitution model allows for unequal base frequencies and three different rates of substitutions between nucleotide bases: transitions between purines (i.e., A and G), transitions between pyrimidines (i.e., C and U/T), and transversions between purines and pyrimidines. Furthermore, distances estimated under TN93 can be represented by a closed form solution (i.e., computed without numerical optimization, simply from pairwise differences in nucleotide counts), which permits rapid computation of pairwise distances. More complex models require relatively expensive numerical optimization, especially because it will have to be done hundreds of millions or billions of times, to find all relevant distances. Therefore, when using genetic distances to identify potential transmission partners, which are expected to be between 0.01 and 0.02 substitutions/site divergent, a substitution model more complicated than TN93 is not needed, and there are no appreciable computational savings to be had by using cruder models. As an example, our implementation can compute approximately 10 million TN93 distances per second on a single server node.

Why not phylogenetics?

Phylogenetics in an extraordinary powerful tool for understanding viral evolutionary history and dynamics. That being said, its strength lies in its ability to say that two strains, Virus A and Virus B, are more closely related to each other (i.e., share a common ancestor more recently) than they are to a third strain, Virus C. This statement is relative and applies only to the viruses being considered. Moreover, this statement says <u>nothing</u> about whether the relatedness of Viruses A and B is epidemiologically meaningful. For example, any two subtype B sequences are more closely related to each other than either one is to a subtype D virus; to say that two subtype B sequences have a meaningful epidemiological linkage, would be saying that we care about events that had happened more than 50 years ago. Although there have been studies that used only phylogenetic relatedness to establish HIV transmission clusters, our position is that just because something *was* done, does not mean it *should* have been done.

In fact, many HIV transmission network studies that used phylogenies **also needed a genetic distance** component: looking for groups of sequences that have low genetic divergence **and** high phylogenetic support (i.e., bootstrap, aLRT, or posterior probability). A bound on genetic distances establishes recency, whereas phylogenetics establish relatedness (relative to the rest of the sequences in the analysis). A major problem with relying on these support values to define what can be in a single cluster, is that they are highly contingent on the data, and change in counterintuitive ways. For example, as more sequences are added, bootstrap values can decrease, resulting in the breakdown of formerly robust transmission clusters. When the goal is tracking transmission network growth over time while adding more and more sequence data, this is a highly undesirable feature. Sequences that are clustered using **Secure HIV-TRACE** will always be clustered using **Secure HIV-TRACE**, if the underlying parameters stay the same. And adding more data can only increase the size of clusters, not break them apart.

Another issue with the phylogenetic approach is that it takes a lot of computational time, especially for big datasets with tens or hundreds of thousands of HIV sequences. Most of the time is spent determining the evolutionary relationships deep in the phylogenetic tree, which will never be considered in a study of transmission clusters anyway. And when a few new sequences are added, the whole process needs to begin again. With our genetic distance approach, only the new sequences need to be considered, and all the previous computational work can be kept: like adding new pieces to a jigsaw puzzle.

Finally, while there exist approaches that estimate times along with trees (e.g., relaxed clock methods), they are so computationally expensive that they simply do not scale past about 1000 sequences, Moverover, they will typically give you essentially the same answer as **Secure HIV-TRACE** (e.g., **clusterpicker**).
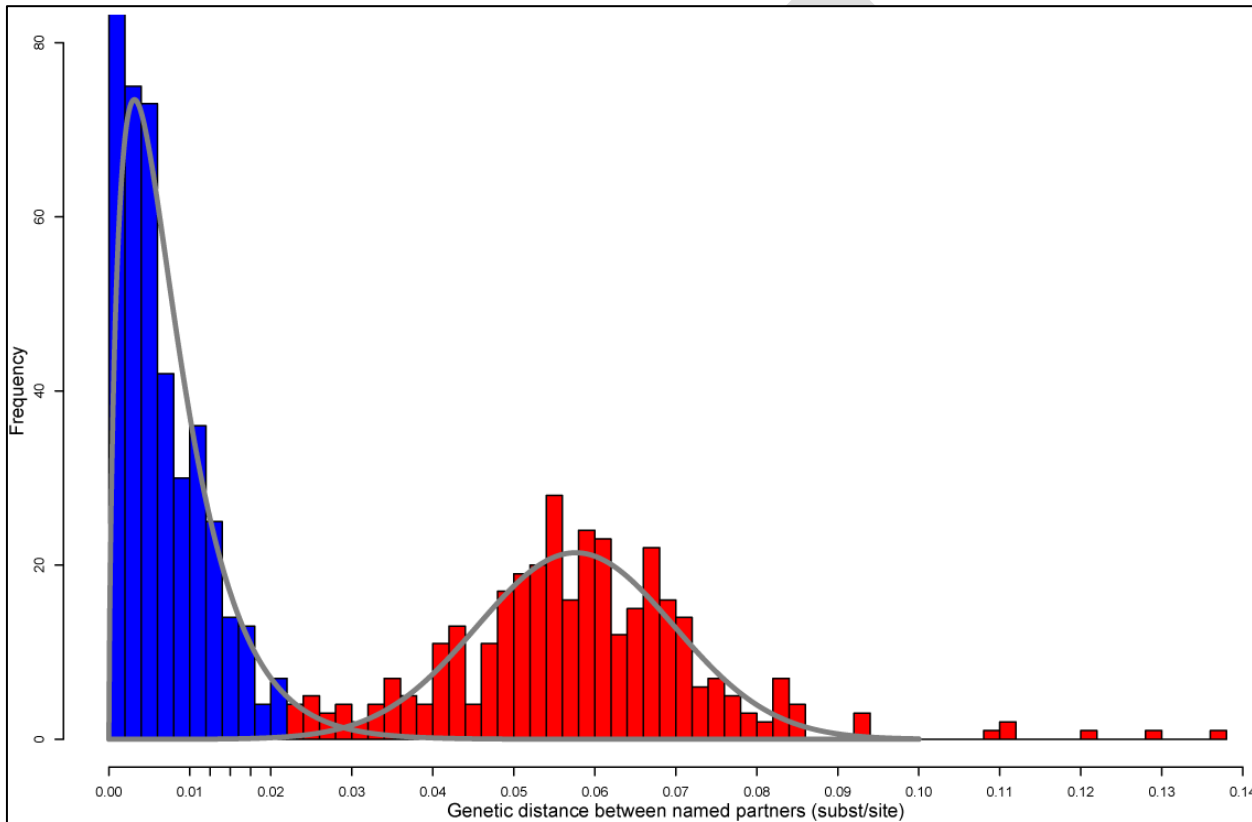
Figure 24. Distribution of genetic distances separating named partners in New York City. Potential transmission are shown in blue. Random within subtype variation is shown in red.

How do I select a genetic distance threshold?

An epidemiologically meaningful genetic distance threshold should link people who are potential transmission partners (i.e., close in the true transmission network) but not link people who are unlikely to have been involved in direct viral transmission. The best guide we have for determining a genetic distance threshold for identifying potential transmission partners in a U.S. surveillance setting comes from the analysis of 749 named partner pairs in New York City interviewed during 2006 through 2012. We analyzed the genetic distance separating baseline virus from named partners (reported sexual contact or shared injection drug use in the previous 12 months). When we plot these genetic distances, we observe two distinct modes: potential transmission partners (highlighted in blue) and partners who are HIV-infected, but have a genetic distance comparable to random within subtype variation (red). The potential transmission partners tend to have genetic distance ≤0.02 substitutions/site. To minimize the likelihood of spurious links in a surveillance cohort of thousands or tens of

thousands of people, we recommend a slightly more conservative threshold: around 0.015 substitutions/site. More conservative genetic distance thresholds can also be applied to improve the probability that potential transmission partners share a meaningful epidemiological connection.

What are ambiguous nucleotides? Or ambiguities?

When HIV infects an individual, it forms genetically diverse and potentially complex populations within that person. Currently in the National HIV Surveillance System overseen by MHS, a single genetic sequence representing this circulating population is produced using bulk Sanger sequencing. This bulk sequence commonly reports diversity at polymorphic sites as common nucleotide IUPAC ambiguity codes [e.g., R (A or G), Y (C or T), N (any nucleotide)]. In standard phylogenetic inference, nucleotide ambiguities are "partially missing data" (e.g., Y is either C or T, but not A or G). When using pairwise distances (as in **Secure HIV-TRACE**) to construct genetic transmission networks, these nucleotide ambiguities have the potential to greatly complicate inference (see **FIGURE 25A**). The most conservative approach is to average the distance between ambiguities and resolved bases (e.g., Y is 0.5 differences from either C or T), and this is the approach we took when inferring the HIV-1 global transmission network. But averaging ambiguities in transmission network analysis penalizes sequences from chronically infected individuals—who are likely to have a more diverse viral population—and this averaging of distances makes these sequences less likely to cluster in the network. Therefore, resolving ambiguities (so that Y would be 0 differences from either C or T, and 1 difference from A or G) appears to be an attractive option. However, if we are too permissive in our tolerance of ambiguities, unrelated viruses can become connected in our network.

For example, if sequences from two people differ at 5% of sites, their viruses represent random intra-subtype variation and are not likely potential transmission partners. However, if within one of these people, most of this variation is polymorphic, and ambiguities are resolved in the genetic distance calculation, the genetic distance separating these viruses may fall below the distance threshold. Since variable sites are not uniformly distributed across the HIV genome, the highly polymorphic sequence is also likely to link to many other 'unrelated' viruses as well. The result is a large transmission cluster in which most sequences are connected to a hub (the high ambiguity sequence) but not to each other.

In an example from the San Diego Primary Infection Cohort (**FIGURE 25A**), the genetic transmission network is affected by handling of nucleotide ambiguities. When ambiguities are fully resolved, the largest cluster in this cohort contains 119 people. However, when this cluster was mapped onto a maximum likelihood phylogenetic tree, its members are dispersed across the tree, encompassing the genetic diversity of the entire city of San Diego. Furthermore, the majority of nodes in the cluster are connected via two nodes acting as hubs (highlighted in red in **FIGURE 25**) which have 5.8% and 7.6% ambiguities and represent the two highest degree nodes in the network. The nodes connected through the spokes on these hubs rarely share an edge with each other. This feature, along with the phylogenetic dispersion, suggests that this cluster is an artifact of nucleotide ambiguity resolution. When these two hubs are excluded from the analysis, the cluster breaks apart, resulting in several distinct clusters and unconnected nodes (**FIGURE 25B**).
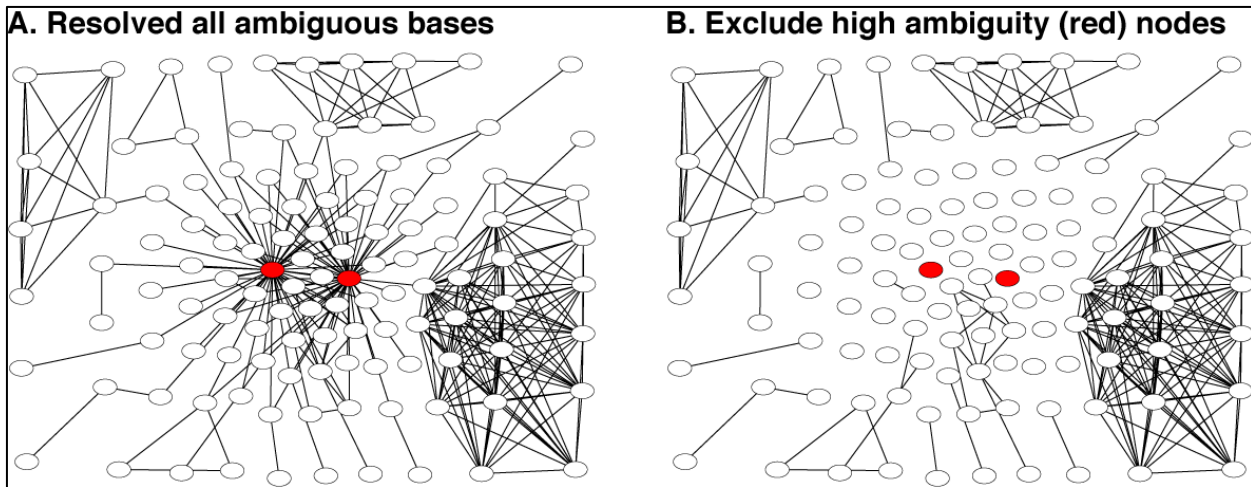
Figure 25. Example in which two contaminant sequences with high numbers of nucleotide ambiguities (shown in red) can create artificial clustering among unlinked singletons and unrelated clusters. (A) The inferred cluster resolving all ambiguous nucleotides. (B) The same cluster where the two hubs (shown in red) are excluded from the analysis.

Clusters that resemble **FIGURE 25A** should be interpreted with extreme caution. They are almost always spurious and the result of erroneous inference due to high levels of nucleotide ambiguities (or contamination with "reference" strains).

How does Secure HIV-TRACE handle ambiguous bases?

We recommend that nucleotide ambiguities be fully resolved when calculating genetic distance only when (i) the sequences have a low proportion of ambiguities or (ii) if the size of the dataset is small. When constructing a transmission network for datasets of thousands or tens of thousands of sequences, we recommend penalizing sequences with high levels of ambiguities. The "Ambiguity Fraction" parameter (**TABLE 2**) governs this penalty. The default "Ambiguity Fraction" value of 0.015 resolves the genetic distance between ambiguous nucleotides when calculating the distance between sequences with ≤1.5% ambiguities and averages the genetic distance between ambiguous nucleotides when calculating the distance between sequences with >1.5% ambiguities.

Sequences with >5% ambiguous nucleotides will be flagged as problematic sequences and removed from the analysis. This protocol follows the guide set forth by the Los Alamos National Laboratory (LANL) HIV Sequence Database (https://www.hiv.lanl.gov/components/sequence/ HIV/search/help.html#bad_seq). Extremely high proportions of ambiguities can be the result of poor quality sequencing, contamination, or dual infection. Including these sequences can adversely affect the performance of **Secure HIV-TRACE**.

Why should I screen for laboratory contaminants?

Although the protocols for generating HIV-1 *pro/rt* genetic sequences are well validated, occasionally laboratory contamination with other genetic material is known to occur. This contamination is most often with the lab strain HXB2, but it can happen with any strain of HIV. Importantly, this contamination often results in a mixed sample where the resulting sequence is a combination of the isolate and the laboratory contaminant. This mixed sample often has high levels of ambiguous nucleotides and could compromise HIV-TRACE analysis if it were to be included, especially because mixing two unrelated strains will create ambiguities at many sites that tend to vary between strains, thereby enabling a "connection" through this sequence if ambiguous nucleotides are resolved (see above). Furthermore, if multiple contaminant sequences are included in the same analysis, they

will erroneously be inferred to be part of the same cluster. Therefore, we screen every run for HXB2 linked sequences. Any sequence that links to HXB2 is excluded from further analysis.

What about drug resistance associated mutations (DRAMs)?

DRAMs often arise in HIV found in people taking anti-retroviral therapy; they can be found in virus from both treatment-naive and treatment-experienced people who were initially infected with a drug-resistant virus. DRAMs typically occur at a select set of sites that are not polymorphic in the absence of prior anti-viral therapy. This type of convergent evolution at the amino acid-level has the potential to negatively affect phylogenetic inference [CITE]. The genetic distance separating two viruses that undergone convergent evolution will theoretically be lower than two viruses that have not experienced convergent evolution. In practice, however, we find little to no effect of excising DRAM sites from network inference. Specifically, transmission networks built at the city, national, global level are robust to inclusion of DRAM sites. For example, when analyzing a cohort of named partner pairs in New York City, only a small fraction of partners become either linked or unlinked when DRAMs are excluded (red in **FIGURE 25**). Therefore, we do not recommend excising DRAMs from transmission network analyses using HIV-TRACE. An exception to this recommendation is for studies focusing on the effect of DRAMs on network characteristics; in these instances, DRAM site should be excised prior to network construction.
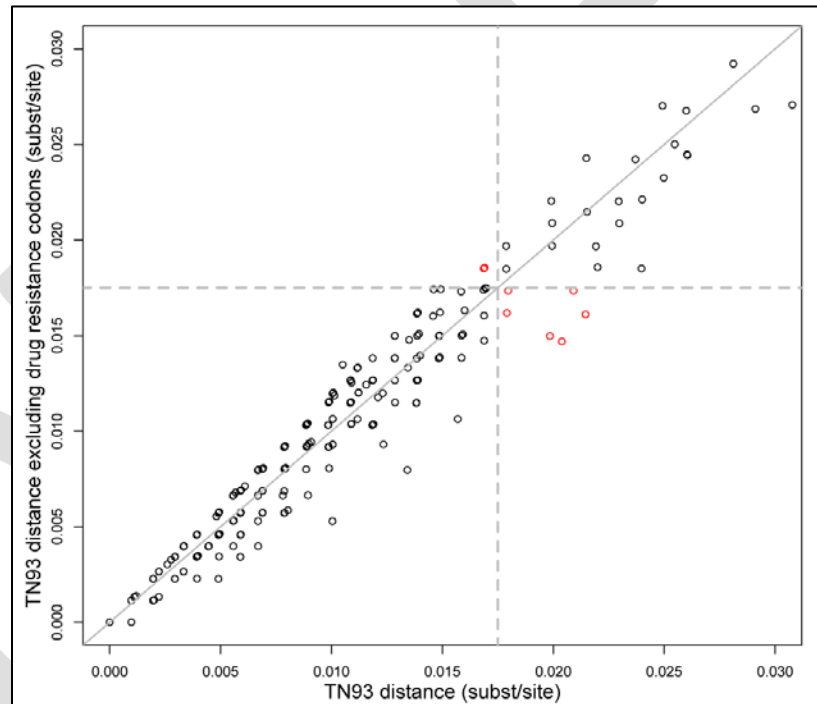
Figure 26. Genetic linkage including/excluding codons associated with drug resistance mutations in a New York City surveillance cohort. Nodes in red change linkage depending on inclusion/exclusion of DRAMs.

Appendix D. Cluster snapshot companion document

**HIV Molecular Cluster Snapshots:
A Companion Document**

HIV Incidence and Case Surveillance Branch
Division of HIV/AIDS Prevention
Centers for Disease Control and Prevention

March 2018

PURPOSE OF COMPANION DOCUMENT

This document serves as a companion guide to the HIV molecular cluster snapshot generated by the HIV Incidence and Case Surveillance Branch (HICSB) at CDC. The snapshot provides summary information about a specific HIV molecular cluster that CDC has identified through analysis of the national HIV surveillance data, specifically HIV nucleotide sequences.

The snapshot is generated for use by HIV surveillance programs to understand a specific HIV molecular cluster. Because the snapshot includes personally identifiable information, it should only be shared with health department colleagues on a 'need-to-know' basis and handled in accordance with NCHHSTP Data Security and Confidentiality Guidelines (www.cdc.gov/nchhstp/programintegration/docs/pcsidatasecurityguidelines.pdf).

KEY CONCEPTS

HIV Molecular Clusters

An HIV molecular cluster is defined as a group of persons with diagnosed HIV infection that have genetically similar HIV strains. The cluster represents a subset of an underlying risk network that can include persons with undiagnosed HIV infection, persons with diagnosed HIV infection who may or may not be in care, or HIV-negative persons at risk for acquiring HIV infection.

Cluster Identification

CDC has developed criteria to identify, using national HIV surveillance data, a subset of clusters with recent, rapid transmission that may require rapid and complete investigation and action. These clusters of concern are currently selected based on the following criteria:

1. Clustering of HIV nucleotide sequences at a low genetic threshold (0.5%), suggestive of recent transmission (pairs of sequences with very few genetic differences represent sequences that are very closely related)
2. At least 5 cases in the cluster diagnosed in the most recent 12 months, indicating rapid and recent growth

NOTE: A molecular cluster represents a subset of an underlying sexual/risk network in which transmission has occurred and could be ongoing. However, the molecular clusters cannot reveal which cases are directly related by transmission or determine the direction of transmission. This is because two persons with genetically similar HIV strains are not necessarily directly linked by transmission: the relationship could be indirect, and there could be unidentified persons involved in transmission relationships. Readers can refer to the guidance document "Detecting, Investigating, and Responding to HIV Transmission Clusters" for more detailed information on interpretation of HIV cluster data.

Information on Cases Reported by Other Jurisdictions

The amount of information provided in the snapshot on cases reported by other jurisdictions depends on whether the primary jurisdiction and the other jurisdiction have agreed, in accordance with their respective reporting and data sharing laws and regulations, to the reciprocal sharing of HIV surveillance data. When an agreement is in place, detailed case-level information for cases reported by other jurisdictions will be provided in the snapshot. Otherwise, only limited information will be shown.

(1)

HIV MOLECULAR CLUSTER SNAPSHOT: CLUSTER YYYYMM_####

(2) PRIMARY JURISDICTION: _____   (3) DIAGNOSIS DATES INCLUDED: MM/DD/YYYY–MM/DD/YYYY

Table 1: Overall information about analysis and data completeness.

(4) Dataset date: Month YYYY	(5) Date of Analysis: Month YYYY	(6) Threshold for cluster inclusion: #.#%

(7) % of diagnoses with HIV sequencing data available in primary jurisdiction, by year:
YYYY: ##% (##/##)   YYYY: ##% (##/##)   YYYY: ##% (##/##)   YYYY: ##% (##/##)

(8) % of diagnoses with HIV sequencing data available in previously-funded MHS jurisdictions, by year:
YYYY: ##%   YYYY: ##%   YYYY: ##%   YYYY: ##%

% of diagnoses with HIV sequencing data available in all jurisdictions, by year:
YYYY: ##%   YYYY: ##%   YYYY: ##%   YYYY: ##%

(9) Complete lab reporting of CD4+ and VL for primary jurisdiction during YYYY–YYYY? Yes

Total case count at #.#% threshold: 11 (10)

Dataset in which cluster was first identified: MONTH YYYY (11)

Figure 1. Map(s) with number of cases by residence at diagnosis

UNITED STATES

(12)

State 1

☐ 0   ☐ 1   ☐ 2-5   ■ >5
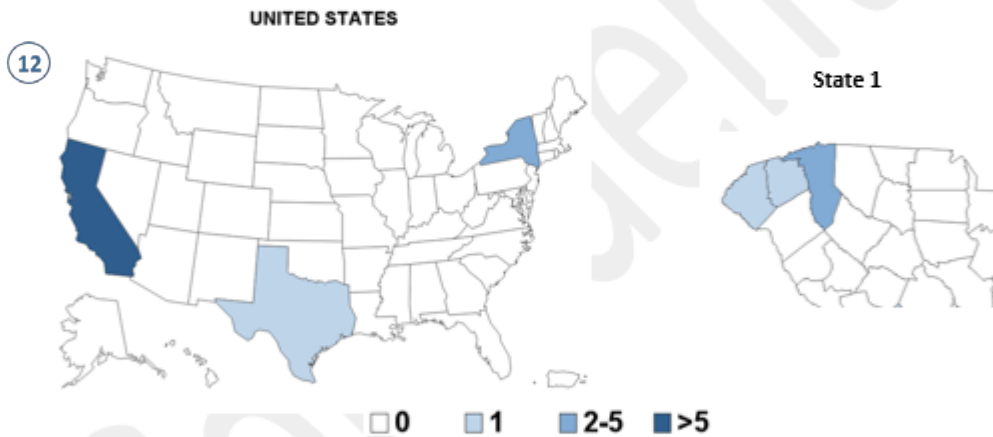
Table 2. Residence at diagnosis.

(13)

Residence at diagnosis	N = 11
STATE 1	N = 7
County 1	5 (78%)
County 2	1 (11%)
County 3	1 (11%)
STATE 2	N=3
STATE 3	N=1

Figure 2. Epidemiologic curve of cases in cluster and percent of diagnoses with sequencing data by quarter, Year1–Year4 (N=11).

(14)

■ Number of cases   —— % of diagnoses with sequencing data in primary jurisdiction

87
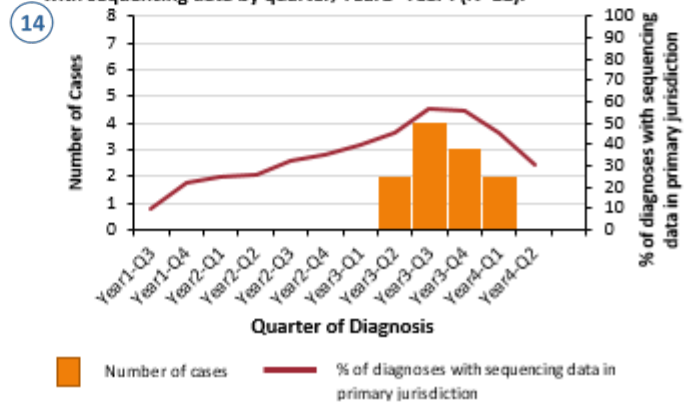
DESCRIPTION of PAGE 1 of SNAPSHOT

Header:

1. The cluster number is a unique number assigned to identify each cluster. This number is composed of the year and month of the dataset in which the cluster was first identified as a priority cluster, followed by an arbitrary number.

2. The primary jurisdiction is the jurisdiction in which the majority of cases identified in the cluster reside at diagnosis.

3. The cluster analysis includes data from the most recent three years of diagnoses, ending with the last day of the month of the dataset used for analysis. Limiting the analysis to the most recent three years assists in focusing efforts on identifying recent transmission.

Table 1:

4. This is the CDC dataset that was used to identify the cluster and generate the snapshot. All sequences of sufficient quality and ≥500 nucleotides in length collected for persons diagnosed in the years of interest were included.

5. The month and year that the cluster analysis was conducted by HICSB.

6. A very low threshold (≤0.5% genetic distance) was used to identify extremely similar sequences. Although the calculation of genetic distance involves evolutionary models, the details of which are beyond this document, a genetic distance of 0.5% for two sequences that are each 1,000 base pairs long equates to a difference of approximately 5 nucleotides.

7. Completeness of sequence data for the primary jurisdiction, by year of diagnosis, is presented. The numerator is the number of cases with an eligible sequence for transmission network analysis, and the denominator is all cases residing in that jurisdiction at diagnosis. All eligible sequences, regardless of the time between the date of diagnosis and the date of specimen collection, are included. Because of reporting delay, completeness might be lower in later years compared to earlier years.

8. Completeness of sequence data for all previously-funded MHS jurisdictions, by year of diagnosis, along with completeness of sequence data overall, is presented for comparison.

9. Completeness of CD4+ and VL reporting for the primary jurisdiction is provided.

10. The total number of cases that clustered at 0.5% genetic threshold. The total number includes all cases in the cluster reported to the national HIV surveillance system by any jurisdiction.

11. The dataset in which the cluster was first identified.

Figure 1:

12. Jurisdictions with at least one case that clustered at the 0.5% genetic threshold are highlighted on a national map. A map highlighting the counties of the primary jurisdiction is also included in the snapshot.

Table 2:

13. The number and percent of cases identified in the cluster by county of residence at diagnosis for the primary jurisdiction are presented. These data correspond to the maps shown in Figure 1.

Figure 2:

14. The example epidemic curve displays the number of all cases (orange bars) that clustered at the 0.5% genetic threshold throughout the analysis, by year and quarter. The red line shows the completeness of sequence data by diagnosis year (same data shown in 7 above) and is independent of the number of identified cases indicated by the orange bars. Low sequence completeness suggests that the cluster could include additional cases not captured by sequence data.

Table 3. Demographic, risk, and clinical characteristics of HIV cases in cluster

Characteristic	Cases reported (N=7*)	
	n	Col %
(15) Age at HIV diagnosis (in years)		
<13	0	0
13–19	3	43
20–29	4	57
30–39	0	0
40–49	0	0
50–59	0	0
≥60	0	0
(16) Vital Status		
Alive	7	100
Dead	0	0
Unknown	0	0
(17) Sex		
Male	7	100
Female	0	0
(18) Race/ethnicity		
American Indian/Alaska Native	0	0
Asian	0	0
Black/African American	0	0
Hispanic/Latino	0	0
Native Hawaiian/Other Pacific Islander	0	0
White	7	100
Other/Multiple race	0	0
(19) Transmission category		
Male-to-male sexual contact (MSM)	7	100
Injection drug use	0	0
Heterosexual-Male	0	0
Heterosexual-Female	0	0
Male-to-male sexual contact and injection drug use	0	0
Other/No identified risk	0	0
(20) Stage zero at HIV diagnosis		
Yes	1	14
No	6	86
(21) AIDS status at diagnosis		
AIDS at HIV diagnosis	1	14
AIDS within 6 months of HIV diagnosis	0	0
AIDS greater than 6 months after HIV diagnosis		
(22) Evidence of viral suppression in past 12 months††		
Yes	3	43
No	4	57
(23) Drug resistance		
Yes	2	29
No	2	39
Not determined	3	43

*Data reported by at least one other jurisdiction suppressed in this table, unless jurisdictions have agreed to share data

†† Viral suppression defined as most recent viral load <200 cp/mL collected ≤12 months before end of dataset among those still alive at end of dataset (MMDDYYYY)

DESCRIPTION of PAGE 2 of SNAPSHOT

Table 3:

The demographic, risk, and clinical characteristics of the cases included in the cluster are shown in the table. These data are based on analysis of the national datasets. All cases reported exclusively by the primary jurisdiction will be included in the table. Cases that were not reported by the primary jurisdiction, or reported by both the primary jurisdiction and another jurisdiction, will only be included in the table if all reporting jurisdictions agreed to share data on the cases identified in the cluster.

(15) The number and percent of cases by age group. Age is based on age at diagnosis.

(16) The number and percent of cases by vital status.

(17) The number and percent of cases by sex at birth.

(18) The number and percent of cases by race/ethnicity.

(19) The number and percent of cases by transmission category.

(20) The number and percent of cases with stage zero at HIV diagnosis.

(21) The number and percent of cases with AIDS at HIV diagnosis, within 6 months of HIV diagnosis, or greater than 6 months of HIV diagnosis.

(22) The number and percent of cases with any evidence of viral suppression in the past 12 months. Evidence of viral suppression was defined as most recent viral load <200 cp/mL collected ≤12 months before the end of the dataset among those still alive at the end of the dataset.

(23) The number and percent of cases with any HIV drug resistance identified. Sierra, the Stanford HIV Web Service (Version 1.1), was used to assess the presence of mutations associated with FDA-approved antiretroviral drugs that target the protease, reverse transcriptase and integrase enzymes of the HIV-1 *pol* region.

Table 4. Line list (sorted by descending date of diagnosis)

Reporting jurisdictions ± (24)	StateNo (25)	Vital status (26)	Date of HIV diagnosis (27)	NHSS quarterly dataset the person was identified as part of the cluster (28)	Type of facility at HIV diagnosis (29)	Residence at diagnosis (30)	Current residence (31)	Date last known to be residing in the current residence (32)	Transmission category (33)	Sex (34)	Age (35)	Race / Ethnicity (36)	Stage zero at diagnosis (37)	AIDS status at diagnosis (38)	Date of last negative HIV test* (39)	Viral load range for most recent viral load (40)	Most recent VL date (41)	Whether drug resistance detected (42)	Number of mutations (43)	Specific drug resistance mutations (44)
STATE 1	######	Alive	4/4/YYYY	Sep YYYY	(F02.03)OP Fac/Prvt Physician's Office	County 1, State 1	County 1, State 1	8/5/YYYY	Male-to-male sexual contact	Male	20–29	White	No		2/YYYY	10001-100000	8/5/YYYY	Not determined	0	
STATE 1	######	Alive	5/21/YYYY	Sep YYYY	(F02.03)OP Fac/Prvt Physician's Office	County 1, State 1	County 1, State 1	7/13/YYYY	Male-to-male sexual contact	Male	13–19	White	No	AIDS at HIV diagnosis		>500000	7/27/YYYY	Not determined	0	
STATE 1	######	Alive	7/7/YYYY	Sep YYYY	(F01.01)IP Fac/Hospital	County 1, State 1	County 1, State 1	5/20/YYYY	Male-to-male sexual contact	Male	20–29	White	No		4/YYYY	<200	5/20/YYYY	Not determined	0	
STATE 1	######	Alive	7/28/YYYY	Sep YYYY	(F02.OTH)OP Fac/Other	County 1, State 1	County 1, State 1	5/15/YYYY	Male-to-male sexual contact	Male	13–19	White	Yes		6/YYYY	<200	5/15/YYYY	Yes	1	NNRTI_K103N
STATE 1	######	Alive	9/27/YYYY	Sep YYYY	(F04.05)SDR/ HIV Counseling, Testing Site	County 1, State 1	County 1, State 1	4/2/YYYY	Male-to-male sexual contact	Male	13–19	White	No		5/1/YYYY	<200	4/2/YYYY	Yes	1	NNRTI_K103N
STATE 1	######	Alive	9/21/YYYY	Sep YYYY	(F04.04)SDR/ HIV Case Mgmt Agency	County 2, State 1	County 2, State 1	2/12/YYYY	Male-to-male sexual contact	Male	20–49	White	Yes			200-1000	2/12/YYYY	No	0	
STATE 1	######	Alive	10/14/YYYY	Sep YYYY	(F04.05)SDR/ HIV Counseling, Testing Site	County 3, State 1	County 3, State 1	1/16/YYYY	Male-to-male sexual contact	Male	20–29	White	No		3/18/YYYY	<200	1/16/YYYY	No	0	
STATE 2				Sep YYYY		STATE 2	STATE 2													
STATE 2				Sep YYYY		STATE 2	STATE 2													
STATE 2				Sep YYYY		STATE 2	STATE 2													
STATE 3				Sep YYYY		STATE 3	STATE 3													

± List of all jurisdictions that have reported any data about this case

* Date of last negative HIV test is based on self-reported TTH information or a lab documented negative HIV test before HIV diagnosis. If dates from both sources are available, the date from the lab documented negative HIV test is chosen.

DESCRIPTION of PAGE 3 of SNAPSHOT

Table 4:
The line list provides detailed information about each case identified in the cluster. These data are based on analysis of the national datasets. Detailed information for all cases reported exclusively by the primary jurisdiction will be included in the table. However, information on cases that were not exclusively reported by the primary jurisdiction will be limited and highlighted in grey if the other jurisdictions do not agree to share data with the primary jurisdiction. The line list is sorted by descending date of diagnosis. NOTE: These data should be handled in accordance with security and confidentiality guidelines.

(24) All jurisdictions that reported this case will be listed.

(25) The StateNo assigned by the primary jurisdiction for each case will be displayed. StateNos assigned by other jurisdictions for the same case will be shared if that jurisdiction agreed to share data with the primary jurisdiction.

(26) Vital status was based on national data. If all the reporting jurisdictions for a case have agreed to share data, then vital status will be shown.

(27) Date of HIV diagnosis was calculated based on national data. The date of HIV diagnosis will be shown for a case if all the reporting jurisdictions for a case have agreed to share data.

(28) The NHSS quarterly dataset in which each case in the cluster was identified as being part of the cluster will be shown, regardless of reporting jurisdiction.

(29) Type of facility at HIV diagnosis was based on national data. If all the reporting jurisdictions for a case have agreed to share data, then facility at HIV diagnosis will be shown.

(30) Residence at diagnosis was based on national data. County and state at residence of diagnosis will be provided for cases reported by the primary jurisdiction and/or other jurisdiction(s) that agreed to share data with the primary jurisdiction. Otherwise, state at residence of diagnosis will be provided.

(31) Current residence was based on national data. County and state of current residence will be provided for cases reported exclusively by the primary jurisdiction and/or other jurisdiction(s) that agreed to share data with the primary jurisdiction. Otherwise, state of current residence will be provided.

(32) The date the case was last known to be residing in the current residence was based on national data. If all the reporting jurisdictions for a case have agreed to share data, then this date will be shown.

(33) Transmission category was based on national data. If all the reporting jurisdictions for a case have agreed to share data, then transmission category will be shown.

(34) Sex at birth was based on national data. If all the reporting jurisdictions for a case have agreed to share data, then sex at birth will be shown.

(35) Age was based on national data. If all the reporting jurisdictions for a case have agreed to share data, then the age group will be shown.

(36) Race/ethnicity was based on national data. If all the reporting jurisdictions for a case have agreed to share data, then race/ethnicity will be shown.

(37)

Indicates if the infection was stage zero at HIV diagnosis

(38) Indicates if the infection was Stage 3 (AIDS) at HIV diagnosis, within 6 months of HIV diagnosis, or greater than 6 months after HIV diagnosis.

(39) Date of last negative HIV test is based on self-reported testing and treatment history (TTH) information or a lab documented negative HIV test before HIV diagnosis. If dates from both sources are available, the date from the lab documented negative HIV test is chosen.

(40) Most recent viral load (copies/mL) was based on national data. If all the reporting jurisdictions for a case have agreed to share data, then the most recent viral load range will be shown.

(41) Date of the most recent viral load was based on national data. If all the reporting jurisdictions for a case have agreed to share data, then the corresponding date of the most recent viral load result will be shown.

(42) Drug resistance was determined using Sierra, the Stanford HIV Web Service (Version 1.1).

(43) Indicates the number of drug resistant-associated mutations were identified. This column will not be included if no drug resistant-associated mutations were detected.

(44) Indicates the specific mutations associated with nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and integrase stand-transfer inhibitors (INSTIs). This column will not be included if no drug resistant-associated mutations were detected.

Appendix E. Example cluster investigation worksheet and companion document

Cluster Investigation Worksheet	
General Cluster Investigation Information	
Jurisdiction Name: Click or tap here to enter text. Person Completing Report: Click or tap here to enter text. Contact Information: Click or tap here to enter text.	
1. Date Worksheet Submitted	Click or tap here to enter text.
2. eHARS Cluster ID	Click or tap here to enter text.
3. Date of detection	Click or tap here to enter text.
4. Initial cluster detection method that identified this cluster (please select one):	Molecular Analysis: ☐ State/Local ☐ National Time-Space Analysis: ☐ State/Local ☐ National Notification: ☐ Provider ☐ Partner Services ☐Other (specify: Click or tap here to enter text.)
5. Additional cluster detection method(s) (select all that apply and include the cluster ID and date detected): ☐State/Local Molecular Analysis: Cluster ID: Click or tap here to enter text. Date Detected: Click or tap here to enter text. ☐National Molecular Analysis: Cluster ID: Click or tap here to enter text. Date Detected: Click or tap here to enter text. ☐State/Local Time-Space Analysis: Cluster ID: Click or tap here to enter text. Date Detected: Click or tap here to enter text. ☐National Time-Space Analysis: Cluster ID: Click or tap here to enter text. Date Detected: Click or tap here to enter text. ☐Provider Notification: Cluster ID: Click or tap here to enter text. Date Detected: Click or tap here to enter text. ☐Partner Services Notification: Cluster ID: Click or tap here to enter text. Date Detected: Click or tap here to enter text. ☐Other (specify: Click or tap here to enter text.): Cluster ID: Click or tap here to enter text. Date Detected: Click or tap here to enter text.	
6. Please indicate what data were reviewed for cases identified in the cluster (select all that apply):	Partner Services Data: ☐ HIV ☐ STD Partner Services Interview Notes: ☐ HIV ☐ STD Surveillance Data: ☐ HIV ☐ STD ☐ Viral Hepatitis ☐Ryan White HIV/AIDS Program Data (including ADAP) ☐Data From Other Jurisdictions ☐Correctional Databases ☐Social Network Sites ☐Discussions with DIS Who Interviewed Cases ☐Other (specify: Click or tap here to enter text.)

Time-Space Clusters: Existing Data Review	
7. Describe the geographic area in which the time-space cluster was detected	Click or tap here to enter text.
8. Describe the subpopulations involved in the time-space cluster	Click or tap here to enter text.
9. Number of HIV-positive persons in the time-space cluster at time of detection (subset by diagnoses identified in the recent period and the baseline period)	# in recent period (define timeframe: Click or tap here to enter text.) = Click or tap here to enter text. # in baseline period (define timeframe: Click or tap here to enter text.) = Click or tap here to enter text.
10. Current number of HIV-positive persons in the time-space cluster for the recent period (based on any subsequent data analysis)	# in recent period (define timeframe: Click or tap here to enter text.) = Click or tap here to enter text.
11. How many HIV-positive persons in the cluster had been interviewed by partner services prior to cluster detection?	# = Click or tap here to enter text.
12. How many individuals had been claimed as partners (excluding members of the time-space cluster) through DIS interview conducted prior to cluster detection?	Named: # = Click or tap here to enter text. Marginal: # = Click or tap here to enter text. Anonymous: # = Click or tap here to enter text.

13. How many HIV-positive persons in the time-space cluster were known to be connected to at least one other HIV-positive person in the cluster through existing partner services data?	# = Click or tap here to enter text.
14. How many additional HIV-positive persons were identified through review of partner services data?	HIV+ partners of cluster members: # = Click or tap here to enter text. HIV+ partners of partners: # = Click or tap here to enter text. HIV+ social contacts (not partners) of cluster members: # = Click or tap here to enter text. HIV+ social contacts of HIV+ partners of cluster members: # = Click or tap here to enter text.

15. Of named partners of HIV-positive persons in the time-space cluster, how many did partner services data show as:
(Do not include initial cases in the time-space cluster even if they were named partners too)

Tested: # = Click or tap here to enter text.		Not Tested: # = Click or tap here to enter text.	
New Positive:	# = Click or tap here to enter text.	Previous Positive:	# = Click or tap here to enter text.
Acute:	(subset: # = Click or tap here to enter text.)	Refused:	# = Click or tap here to enter text.
Negative:	# = Click or tap here to enter text.	Not Located:	# = Click or tap here to enter text.
Referred for PrEP:	(subset: # = Click or tap here to enter text.)	Outside Jurisdiction:	# = Click or tap here to enter text.
Unknown:	# = Click or tap here to enter text.	Deceased:	# = Click or tap here to enter text.
		Other:	# = Click or tap here to enter text.

16. How many HIV-positive persons in the cluster had evidence of recent viral suppression (most recent viral load <200 cp/mL and occurred in the past 12 months), and how many were unsuppressed?	Evidence of recent viral suppression: # = Click or tap here to enter text. No evidence of recent viral suppression: # = Click or tap here to enter text.

Molecular Clusters: Existing Data Review	
17. Number of HIV-positive persons in the molecular cluster at time of detection	# = Click or tap here to enter text.
18. Current number of HIV-positive persons in the molecular cluster (based on any subsequent data analysis)	# = Click or tap here to enter text.
19. How many HIV-positive persons in the molecular cluster had been interviewed by partner services prior to cluster detection?	# = Click or tap here to enter text.
20. How many individuals had been claimed as partners (excluding molecular members of the cluster) through DIS interview conducted prior to cluster detection?	Named: # = Click or tap here to enter text. Marginal: # = Click or tap here to enter text. Anonymous: # = Click or tap here to enter text.
21. How many HIV-positive persons in the molecular cluster were known to be connected to at least one other HIV-positive person in the molecular cluster through existing partner services data?	# = Click or tap here to enter text.
22. How many additional HIV-positive persons in the transmission cluster were identified through review of partner services data?	HIV+ partners of molecular cluster members: # = Click or tap here to enter text. HIV+ partners of partners: # = Click or tap here to enter text. HIV+ social contacts (not partners) of molecular cluster members: # = Click or tap here to enter text. HIV+ social contacts of HIV+ partners of molecular cluster members: # = Click or tap here to enter text.

23. Of named partners of HIV-positive persons in the molecular cluster, how many did partner services data show as:
(Do not include molecular cases in the cluster even if they were named partners too)

Tested: # = Click or tap here to enter text.		Not Tested: # = Click or tap here to enter text.	
New Positive[1]:	# = Click or tap here to enter text.	Previous Positive:	# = Click or tap here to enter text.
Acute:	(subset: # = Click or tap here to enter text.)	Refused:	# = Click or tap here to enter text.

Negative:	# = Click or tap here to enter text.	Not Located:	# = Click or tap here to enter text.
Referred for PrEP:	(subset: # = Click or tap here to enter text.)	Outside Jurisdiction:	# = Click or tap here to enter text.
Unknown:	# = Click or tap here to enter text.	Deceased:	# = Click or tap here to enter text.
		Other:	# = Click or tap here to enter text.

[1]These persons should be included as members of the larger transmission cluster

24. How many HIV-positive persons in the transmission cluster had evidence of recent viral suppression (most recent viral load <200 cp/mL and occurred in the past 12 months), and how many were unsuppressed?	Evidence of recent viral suppression: # = Click or tap here to enter text. No evidence of recent viral suppression: # = Click or tap here to enter text.

Existing Data Review Commonalities and Summary

25. Were any common venues or other virtual or physical sites identified? (select all that apply)	☐Bar ☐Bath house ☐Specific park ☐Social Media/Apps ☐Internet sites ☐Other (specify): Click or tap here to enter text. ☐None
26. Were any common facilities of diagnosis identified (e.g., ER screening, jail screening, health center, plasma center)?	☐Yes (describe): Click or tap here to enter text. ☐No

Key findings from review of partner services, surveillance, and other available data

Click or tap here to enter text.

27. Based on your initial review of the data, what is your level of concern for this cluster?	☐High: additional response is needed ☐Medium: additional information about the cluster is needed ☐Low: no additional investigation activities are needed at this time

Actions Taken To Date

28. To date, have partner services interviews been initiated for cluster members, partners, and/or contacts who had not been previously interviewed? *(If yes, complete supplemental questionnaire)*	☐Yes ☐No
29. To date, have partner services re-interviews been initiated for cluster members, partners, and/or contacts who had been previously interviewed? *(If yes, complete supplemental questionnaire)*	☐Yes ☐No
30. To date, have social network interviewing and/or testing been conducted? (If yes, complete supplemental questionnaire)	☐Yes ☐No
31. To date, have targeted testing events been conducted (e.g., venue-based testing)? *(If yes, complete supplemental questionnaire)*	☐Yes ☐No
32. To date, have linkage to or re-engagement in care efforts been prioritized for persons in the cluster?	☐Yes (fill in numbers below) ☐No Initiated linkage to/re-engagement in care: # = Click or tap here to enter text. Successfully linked to/re-engaged in care: # = Click or tap here to enter text. Achieved viral suppression within 6 months: # = Click or tap here to enter text.

33. Of persons who were HIV-negative or had unknown HIV status at the time of identification as part of the risk network, what are the results of testing or re-testing efforts to date?

Tested: # = Click or tap here to enter text.		Not Tested: # = Click or tap here to enter text.	
New Positive[1]:	# = Click or tap here to enter text.	Refused:	# = Click or tap here to enter text.
Acute:	(subset: # = Click or tap here to enter text.)	Not Located:	# = Click or tap here to enter text.
Negative:	# = Click or tap here to enter text.	Outside Jurisdiction:	# = Click or tap here to enter text.
Referred for PrEP:	(subset: # = Click or tap here to enter text.)	Deceased:	# = Click or tap here to enter text.
Unknown:	# = Click or tap here to enter text.	Other:	# = Click or tap here to enter text.

[1]These persons should be included as members of the larger transmission cluster

34. What messaging activities have been initiated to date? (select all that apply)	☐Health alerts to providers ☐Targeted messaging through apps/venues ☐Press releases ☐Advertisements (mass media) ☐Dear colleague letters ☐Other (specify): Click or tap here to enter text. ☐None
35. Have any other intervention activities been conducted as a result of this cluster investigation? If so, please describe.	☐Yes (describe): Click or tap here to enter text. ☐No
36. Were additional resources required to investigate and respond to this particular cluster (i.e. surge staff, partnership with CBOs, etc.)? If so, please describe.	☐Yes (describe): Click or tap here to enter text. ☐No
37. What is your current level of concern for this cluster?	☐High: additional response is needed ☐Medium: additional information about the cluster is needed ☐Low: no additional investigation activities are needed at this time

Additional Comments

Click or tap here to enter text.

Cluster Closeout	
38. Date cluster investigation and response activities were closed	Click or tap here to enter text.
39. Size of cluster at closeout	Transmission cluster: # = Click or tap here to enter text. Risk network: # = Click or tap here to enter text.
40. Reason(s) for closeout (describe):	Click or tap here to enter text.
41. Briefly describe how you will continue monitoring the cluster for future growth.	Click or tap here to enter text.

Cluster Investigation Worksheet: Supplemental Questionnaire
Additional Investigation and Intervention Actions Taken

Jurisdiction Name: Click or tap here to enter text. Person Completing Report: Click or tap here to enter text. Contact Information: Click or tap here to enter text. Date Supplemental Questionnaire Completed: Click or tap here to enter text.

42. How many partner services interviews have been initiated to date for cluster members, partners, and/or contacts who had not been previously interviewed? *(If no new interviews have been conducted, put '0' in each response category.)*	Cluster Members: # = Click or tap here to enter text. Sexual and/or drug-sharing partners: # = Click or tap here to enter text. Social contacts: # = Click or tap here to enter text.
43. How many partner services re-interviews have been initiated to date for cluster members, partners, and/or contacts who had been previously interviewed? *(If no re-interviews have been conducted, put '0' in each response category.)*	Cluster Members: # = Click or tap here to enter text. Sexual and/or drug-sharing partners: # = Click or tap here to enter text. Social contacts: # = Click or tap here to enter text.

44. Were additional partners identified through additional partner services interviews and/or re-interviews? *(Complete this question only if the responses to #42 and/or #43 were >0.)*

☐Yes (fill in numbers below)

☐No

Total # of new partners named: # = Click or tap here to enter text.

Previously named but not previously interviewed: # = Click or tap here to enter text.

Newly named: # = Click or tap here to enter text.

Tested: # = Click or tap here to enter text.		Not Tested: # = Click or tap here to enter text.	
New Positive[1]:	# = Click or tap here to enter text.	Previous Positive:	# = Click or tap here to enter text.
Acute:	(subset: # = Click or tap here to enter text.)	Refused:	# = Click or tap here to enter text.
Negative:	# = Click or tap here to enter text.	Not Located:	# = Click or tap here to enter text.
Referred for PrEP:	(subset: # = Click or tap here to enter text.)	Outside Jurisdiction:	# = Click or tap here to enter text.
Unknown:	# = Click or tap here to enter text.	Deceased:	# = Click or tap here to enter text.
		Other:	# = Click or tap here to enter text.

[1]These persons should be included as members of the larger transmission cluster

45. Were second generation interviews (interviews of partners of partners) conducted?	☐Yes (fill in numbers below) ☐No Cluster Members: # = Click or tap here to enter text. Sexual and/or drug-sharing partners: # = Click or tap here to enter text. Social contacts: # = Click or tap here to enter text.
46. If social network interviewing and/or testing was conducted, fill in the values to the right and answer question #45. *(If no social network interviews were conducted, put '0' in each response category.)*	Tested: # = Click or tap here to enter text. New Positive: # = Click or tap here to enter text. Acute: (subset: # = Click or tap here to enter text.) Negative: # = Click or tap here to enter text. Referred for PrEP: (subset: # = Click or tap here to enter text.) Unknown: # = Click or tap here to enter text.
47. How was this strategy (social network interviewing/testing) implemented? Select all that apply. *(Complete only if the response to #46 was >0.)*	☐Incentives for testing If so, how much for: The recruiter? $ Click or tap here to enter text. The recruitee? $ Click or tap here to enter text. ☐Incentives for interview If so, how much for: The recruiter? $ Click or tap here to enter text. The recruitee? $ Click or tap here to enter text. ☐ Clinical service or intervention offered If so, what? Click or tap here to enter text.

	☐Other (describe: Click or tap here to enter text.)

48. If targeted testing events were conducted, fill in the values to the right. *(If no targeted testing events were conducted, put '0' in each response category.)*	Tested: # = Click or tap here to enter text.
	  New Positive: # = Click or tap here to enter text.
	   Acute: (subset: # = Click or tap here to enter text.)
	  Negative: # = Click or tap here to enter text.
	   Referred for PrEP: (subset: # = Click or tap here to enter text.)
	  Unknown: # = Click or tap here to enter text.

49. Were other investigation activities conducted, such as medical chart review or qualitative interviews?	☐Yes (describe): Click or tap here to enter text. ☐No
50. Were any enhancements made to your regular HIV prevention and treatment processes for cluster and/or risk network members? If so, please describe. (select all that apply)	☐Linkage to/re-engagement in care (describe: Click or tap here to enter text.) ☐Patient navigation (describe: Click or tap here to enter text.) ☐Case management (describe: Click or tap here to enter text.) ☐Expansion of PrEP resources (describe: Click or tap here to enter text.) ☐Expansion of SSP or MAT resources (describe: Click or tap here to enter text.) ☐Health insurance assistance (describe: Click or tap here to enter text.) ☐Housing assistance (describe: Click or tap here to enter text.) ☐Expansion of HIV testing (describe: Click or tap here to enter text.) ☐Provider education (describe: Click or tap here to enter text.) ☐Referrals to substance abuse and mental health services (describe: Click or tap here to enter text.) ☐Other (describe: Click or tap here to enter text.) ☐No enhancements made
51. As a result of cluster response, how did communication within the health department (e.g., between surveillance and prevention) change? How did interaction between local and state jurisdictions change?	Click or tap here to enter text.
52. Was the existence of the cluster used to advocate for any policy changes? If so, please describe.	☐Yes (describe): Click or tap here to enter text. ☐No

Instructions for Completing the Cluster Investigation Worksheet

<u>Overview</u>

The cluster investigation worksheet has been designed to assist jurisdictions with tracking the relevant steps of the roadmap to investigating and intervening in transmission clusters (see Guidance Document: Detecting and Responding to HIV Transmission Clusters). One form should be completed per quarter for each cluster in which investigation and response activities are ongoing. This form is intended for use with molecular clusters that meet CDC's definition of a priority cluster, whether the cluster was first identified through local or through national analysis, as well as with additional clusters of concern identified through alternative means (i.e. time-space analysis).

Instructions for completing the cluster investigation worksheet are outlined below according to each subsection of the form.

<u>General Cluster Investigation Information</u>

- Complete the first row with the name of the jurisdiction and the name of the person completing the cluster investigation worksheet. The person completing the form should also list their contact information (phone and email).
- Question #1, 'Date Worksheet Submitted': Fill in the final date the worksheet was completed prior to submission to CDC. This worksheet should be completed after the jurisdiction has had time to gather enough information for at least a preliminary desk review shortly after the cluster was detected (Question #3), but not necessarily the same date. The cluster should also be entered into eHARS prior to completing this form.
- Questions #2, 'eHARS Cluster ID', and #3, 'Date of detection': In completing this form, use the eHARS cluster ID from whichever source first detected the cluster. The date of detection should be the date the cluster was first identified through any of the sources listed in Question #4.
- Question #4, 'Initial cluster detection method that identified this cluster': Select the method that initially detected this cluster. Only one option should be selected. This should match the method of cluster detection that is reported in eHARS.
- Question #5, 'Additional cluster detection method(s)': If the cluster was eventually identified through multiple detection methods, select all additional methods of cluster detection. Include the cluster ID and date detected for each method of detection.
- Question #6, 'Please indicate what data were reviewed for cases identified in the cluster': Select all sources of data that were reviewed for cases in the cluster (i.e. the number of cases listed in Question #10 or #18).

<u>Time-Space Clusters: Existing Data Review</u>

(Complete this section only if you indicated in Question #4 or #5 that this cluster was detected through state/local or national time-space analysis.)

- Question #7, 'Describe the geographic area in which the time-space cluster was detected': Provide a brief description of the geographic area in which the time-space cluster was detected. For example, you can note whether the time-space cluster identified in one single county, a group of adjacent counties, a metropolitan statistical area, a specific region of the state, etc.
- Question #8, 'Describe the subpopulations involved in the time-space cluster': Indicate which subpopulations were involved in the time-space cluster at the time of detection (for example, persons who inject drugs, persons who reported both male-to-male sexual contact and intravenous drug use, etc.).
- Question #9, 'Number of HIV-positive persons in the time-space cluster at time of detection': List the total number of HIV-positive persons known to be in the time-space cluster at the time of detection. Subset your

response by the number of diagnoses in the most recent period and the number of diagnoses in the baseline period. Make sure to specify the timeframes used for each period. For example, if this cluster was detected using the default parameters in the CDC Time Space Alert SAS program, you would enter the 12-month timeframe analyzed next to "# in recent period" and the subsequent 36 months included in the baseline period next to "# in baseline period".

- Question #10, 'Current number of HIV-positive persons in the time-space cluster for the recent period': List the total number of HIV-positive persons in the time-space cluster at the time the form is being completed. This number should include the number of cases reported in Question #9, plus any additional cases identified through subsequent analysis.
- Question #11, 'How many HIV-positive persons in the cluster had been interviewed by partner services prior to cluster detection?': Based on data review, list the number of time-space cluster members that had been interviewed by partner services after HIV diagnosis and before identification as part of the cluster.
- Question #12, 'How many individuals had been claimed as partners (excluding members of the time-space cluster) through DIS interview conducted prior to cluster detection?': Report the total number of individuals claimed as partners by time-space cluster members through interviews conducted prior to cluster detection. This number should be divided into three categories: 1. the number of named partners, 2. the number of marginal partners (e.g., some identifying information given, but not enough to locate the person), and 3. the number of anonymous partners (e.g., no identifying information given). Note: If any of the time-space cluster members named each other, this should be excluded from the total (time-space cluster members that named each other will be accounted for in question #13).
- Question #13, 'How many HIV-positive persons in the time-space cluster were known to be connected to at least one other HIV-positive person in the cluster through existing partner services data?': List the total number of time-space cluster members that were known to be connected to at least one other person in the molecular cluster through existing partner services data. Count each person that was named only once. For example, if Person A named Person B as a partner and Person B also named Person A as a partner, you would count both persons. Likewise, if Person A named Person B as a partner but Person B did not name Person A, you would still count both persons.
- Question #14, 'How many additional HIV-positive persons were identified through review of partner services data?': Indicate the total number of additional HIV-positive persons that were identified through existing data review. This should be divided into the following four categories: 1. HIV-positive partners of time-space cluster members, 2. HIV-positive partners of partners, 3. HIV-positive social contacts (not partners) of time-space cluster members, and 4. HIV-positive social contacts of HIV+ partners of the time-space cluster members.
- Question #15, 'Of named partners of HIV-positive persons in the time-space cluster, how many did partner services data show as…': Fill in testing information based on your existing data review for named partners of time-space cluster members. The total number of named partners reported in Question #12 should be used to answer this question. Do not include testing information on initial time-space cluster members, whether or not they were named as partners by other members of the cluster.
  - Testing status should be divided between "tested" and "not tested" for each named partner reported in Question #12.
  - For those who were tested, indicate the number that newly tested as positive (based on patient report and no evidence of prior positive result in the state HIV surveillance system) and those who tested as negative, as well as any with unknown testing results. If the number of acute positive persons and PrEP referral information for negative persons is available, report those as well.
  - For those not tested, indicate the appropriate response for why testing was not done, if that information is available. Persons not tested due to being previously diagnosed with HIV infection should meet one of the following criteria: 1. self-report of having previously tested HIV-positive or 2. had been previously reported to the health department's surveillance registry as being infected with HIV.

- Question #16, 'How many HIV-positive persons in the cluster had evidence of recent viral suppression (most recent viral load <200 cp/mL and occurred in the past 12 months), and how many were unsuppressed?': Indicate the number of cluster members with evidence of recent viral suppression (most recent viral load <200 cp/mL and occurred in the past 12 months) and those who were unsuppressed.

Molecular Clusters: Existing Data Review

(Complete this section only if you indicated in Question #4 or #5 that this cluster was detected through state/local or national molecular analysis.)

- Question #17, 'Number of HIV-positive persons in the molecular cluster at time of detection': List the total number of HIV-positive persons known to be in the molecular cluster at the time of detection. (Diagnoses that had been made prior to cluster detection but were not yet known to be part of the cluster would not be included.)
- Question #18, 'Current number of HIV-positive persons in the molecular cluster': List the total number of HIV-positive persons in the molecular cluster at the time the form is being completed. This number should include the number of cases reported in Question #17, plus any additional cases identified through subsequent analysis.
- Question #19, 'How many HIV-positive persons in the molecular cluster had been interviewed by partner services prior to cluster detection?': Based on data review, list the number of molecular cluster members that had been interviewed by partner services after HIV diagnosis and before identification as part of the cluster.
- Question #20, 'How many individuals had been claimed as partners (excluding molecular members of the cluster) through DIS interview conducted prior to cluster detection?': Report the total number of individuals claimed as partners by molecular cluster members through interviews conducted prior to cluster identification. This number should be divided into three categories: 1. the number of named partners, 2. the number of marginal partners (e.g., some identifying information given, but not enough to locate the person), and 3. the number of anonymous partners (e.g., no identifying information given). Note: If any of the molecular cluster members named each other, this should be excluded from the total (molecular cluster members that named each other will be accounted for in question #21).
- Question #21, 'How many HIV-positive persons in the molecular cluster were known to be connected to at least one other HIV-positive person in the molecular cluster through existing partner services data?': List the total number of molecular cluster members that were known to be connected to at least one other person in the molecular cluster through existing partner services data. Count each person that was named only once. For example, if Person A named Person B as a partner and Person B also named Person A as a partner, you would count both persons. Likewise, if Person A named Person B as a partner but Person B did not name Person A, you would still count both persons.
- Question #22, 'How many additional HIV-positive persons in the transmission cluster were identified through review of partner services data?': Indicate the total number of transmission cluster members that were identified through existing data review. This should be divided into the following four categories: 1. HIV-positive partners of molecular cluster members, 2. HIV-positive partners of partners, 3. HIV-positive social contacts (not partners) of molecular cluster members, and 4. HIV-positive social contacts of HIV+ partners of the molecular cluster members.
- Question #23, 'Of named partners of HIV-positive persons in the molecular cluster, how many did partner services data show as…': Fill in testing information based on your existing data review for named partners of molecular cluster members. The total number of named partners reported in Question #20 should be used to answer this question. Do not include testing information on molecular cluster members, whether or not they were named as partners by other members of the cluster.
  - Testing status should be divided between "tested" and "not tested" for each named partner reported in Question #20.

- o For those who were tested, indicate the number that newly tested as positive (based on patient report and no evidence of prior positive result in the state HIV surveillance system) and those who tested as negative, as well as any with unknown testing results. If the number of acute positive persons and PrEP referral information for negative persons is available, report those as well.
  - o For those not tested, indicate the appropriate response for why testing was not done, if that information is available. Persons not tested due to being previously diagnosed with HIV infection should meet one of the following criteria: 1. self-report of having previously tested HIV-positive or 2. had been previously reported to the health department's surveillance registry as being infected with HIV.
- Question #24, 'How many HIV-positive persons in the transmission cluster had evidence of recent viral suppression (most recent viral load <200 cp/mL and occurred in the past 12 months), and how many were unsuppressed?': Indicate the number of transmission cluster members with evidence of recent viral suppression (most recent viral load <200 cp/mL and occurred in the past 12 months) and those who were unsuppressed.

Existing Data Review Commonalities and Summary

(Complete this section for all clusters, regardless of method of detection.)

- Question #25, 'Were any common venues or other virtual or physical sites identified?': Indicate whether any common venues or sites (physical or virtual) were identified among persons in the cluster through existing data review. Select all that apply.
- Question #26, 'Were any common facilities of diagnosis identified (e.g., ER screening, jail screening, health center, plasma center)?': Indicate whether any common facilities of diagnosis were identified among persons in the cluster through existing data review. If common facilities were identified, please describe.
- Question #27, 'Based on your initial review of the data, what is your level of concern for this cluster?': Indicate your level of concern about this cluster based on initial data review: High (additional response is needed), Medium (additional information about the cluster is needed), or Low (no additional investigation activities are needed at this time).
- Space is provided at the end of this section to report key findings and other observations not captured above from your review of partner services, surveillance, and other available data.

Actions Taken To Date

(Complete this section for all clusters, regardless of method of detection, once response activities have been initiated.)

- For Questions #28-31, complete the supplemental questionnaire at the end of the Cluster Investigation Worksheet if your response to any of the questions is "yes."
  - o Question #28, 'To date, have partner services interviews been initiated for cluster members, partners, and/or contacts who had not been previously interviewed?': Indicate whether additional partner services interviews have been initiated for members of the cluster, partners, and/or social contacts.
  - o Question #29, 'To date, have partner services re-interviews been initiated for cluster members, partners, and/or contacts who had been previously interviewed?': Indicate whether partner services re-interviews have been initiated for members of the cluster, partners, and/or social contacts.
  - o Question #30, 'To date, have social network interviewing and/or testing been conducted?': Indicate whether social network interviewing and/or testing have been conducted.
  - o Question #31, 'To date, have targeted testing events been conducted (e.g., venue-based testing)?': Indicate whether targeted testing events such as venue-based testing have been conducted in response to cluster investigation efforts.
- Question #32, 'To date, have linkage to or re-engagement in care efforts been prioritized for persons in the cluster?': Indicate whether linkage to or re-engagement in care efforts have been prioritized for persons in the

cluster who were identified through existing data review as being out of care. If so, fill in the number of persons for whom linkage to/re-engagement in care was initiated, the number successfully linked to or re-engaged in care, and the number that achieved viral suppression within six months of identification as part of the cluster. Note that per PS18-1802, jurisdictions are expected to report viral suppression for all members unsuppressed at the time of identification as part of a national priority cluster, even if jurisdictions indicate in Question #27 above that the cluster is considered a low level of concern after initial data review.

- Question #33, 'Of persons who were HIV negative or had unknown HIV status at the time of identification as part of the risk network, what are the results of testing or re-testing efforts to date?': Indicate the number of persons who were HIV-negative or had unknown HIV status at the time of identification as part of the risk network who have been re-tested or tested since the time of identification as part of the cluster.
    o Testing status for all HIV-negative persons or person with unknown HIV status should be divided between "tested" and "not tested".
    o For those who were tested, indicate the number that newly tested as positive (based on patient report and no evidence of prior positive result in the state HIV surveillance system) and those who tested as negative, as well as any with unknown testing results. If the number of acute positive persons is available, report those as well. The number of persons who tested as negative for HIV and were referred for PrEP should also be reported.
    o For those not tested, indicate the appropriate response for why testing was not done, if that information is available.
    o Note that per PS18-1802, jurisdictions are expected to report testing/re-testing for all persons who had unknown HIV status or were HIV-negative at the time of identification as part of a priority cluster, even if jurisdictions indicate in Question #27 above that the cluster is considered a low level of concern after initial data review. Similarly, PrEP referral status for all HIV-negative persons in the risk network should also be reported per PS18-1802.
- Question #34, 'What messaging activities have been initiated to date?': Indicate whether any messaging activities have been initiated as a part of cluster response activities. Select all that apply.
- Question #35, 'Have any other intervention activities been conducted as a result of this cluster investigation?': Indicate whether any additional interventions have been conducted for this cluster as a result of the investigation, and if so, describe those activities.
- Question #36, 'Were additional resources required to investigate and respond to this particular cluster (i.e. surge staff, partnership with CBOs, etc.)?': Indicate whether additional resources have been required to investigate and respond to this cluster, and if so, describe.
- Question #37, 'What is your current level of concern for this cluster?': Indicate your current level of concern for this cluster based on actions taken to-date: High (additional response is needed), Medium (additional information about the cluster is needed), or Low (no additional investigation activities are needed at this time).
- Space is provided at the end of this section to report key findings and other observations not captured above.

Cluster Closeout

(Complete this section only after you have closed investigation and response activities for the cluster.)

- Question #38, 'Date cluster investigation and response activities were closed': Provide the date that cluster investigation and response activities were closed.
- Question #39, 'Size of cluster at closeout': Indicate the size of the cluster at closeout. The total number should be divided into two categories: transmission cluster members and risk network members.
- Question #40, 'Reason(s) for closeout': Briefly describe the reason for closing out the cluster investigation.
- Question #41, 'Briefly describe how you will continue monitoring the cluster for future growth': Provide a brief description of how you plan to continue monitoring the cluster for future growth. Indicate the person(s) who

will be responsible for this activity and their role(s), and how CDC will be notified if the cluster experiences additional growth in the future.

Supplemental Questionnaire: Additional Investigation and Intervention Actions Taken

(Complete this section only if you have answered "yes" to Questions #28-31 above and/or have engaged in extended investigation and response activities not already captured in the main portion of the worksheet.)

- Complete the first row with the name of the jurisdiction and the name of the person completing the supplemental questionnaire. The person completing the form should also list their contact information. Indicate the date the supplemental questionnaire was completed.
- Question #42, 'How many partner services interviews have been initiated to date for cluster members, partners, and/or contacts who had not been previously interviewed?': Provide the number of partner services interviews that have been initiated for cluster members, partners, and/or contacts who had not been previously interviewed. Report the numbers according to the following categories: 1. Cluster members, 2. Sexual and/or drug-sharing partners, and 3. Social contacts. Note: If no new interviews have been conducted, put "0" in each response category.
- Question #43, 'How many partner services re-interviews have been initiated to date for cluster members, partners, and/or contacts who had been previously interviewed?': Provide the number of partner services re-interviews that have been initiated for cluster members, partners, and/or contacts who had been previously interviewed. Report the numbers according to the following categories: 1. Cluster members, 2. Sexual and/or drug-sharing partners, and 3. Social contacts. Note: If no re-interviews have been conducted, put "0" in each response category.
- Question #44, 'Were additional partners identified through additional partner services interviews and/or re-interviews?': (Complete this question only if the responses to Questions #42 and/or #43 were greater than "0".) Indicate whether additional partners have been identified through the additional partner services interviews and/or re-interviews. If yes, provide the total number of new partners named, then subset the information by those previously named but not previously interviewed and those who have been newly named. Note: "New partners" refer to individuals not previously named, whether or not that person was a pre-existing partner not previously disclosed or a new contact since the last interview.
  - Testing status for all newly-identified partners should be divided between "tested" and "not tested".
  - For those who were tested, indicate the number that newly tested as positive (based on patient report and no evidence of prior positive result in the state HIV surveillance system) and those who tested as negative, as well as any with unknown testing results. If the number of acute positive persons is available, report those as well. The number of persons who tested as negative for HIV and were referred for PrEP should also be reported.
  - For those not tested, indicate the appropriate response for why testing was not done, if that information is available. Persons not tested due to being previously diagnosed with HIV infection should meet one of the following criteria: 1. self-report of having previously tested HIV-positive or 2. had been previously reported to the health department's surveillance registry as being infected with HIV.
- Question #45, 'Were second generation interviews (interviews of partners of partners) conducted?': Indicate whether second generation interviews (interviews of partners of partners) were conducted for members of the cluster. If so, report the total number of second generation interviews according to the following categories: 1. Cluster members, 2. Sexual and/or drug-sharing partners, and 3. Social contacts.
- Question #46, 'If social network interviewing and/or testing was conducted, fill in the values to the right and answer question #47': Provide information about social network interviews and/or testing activities that may have been conducted. Report the total number of persons tested, then subset by the number of persons with positive, negative, and unknown test results. If the number of acute positive persons is available, report those as

well. The number of persons who tested as negative for HIV and were referred for PrEP should also be reported. Note: If no new interviews have been conducted, put "0" in each response category.

- Question #47, 'How was this strategy (social network interviewing/testing) implemented?' should only be completed if the response in Question #46 is greater than "0".
    - For Question #47, check the appropriate boxes for the strategies used to implement social network interviewing/testing. If incentives were used, indicate the amount provided to the recruiter and/or the recruitee. If clinical services or interventions were offered, indicate what they were. If other strategies were utilized, briefly describe. Select all options that apply.
- Question #48, 'If targeted testing events were conducted, fill in the values to the right': Provide information about targeted testing events that may have been conducted. Report the total number of persons tested, then subset by the number of persons with positive, negative, and unknown test results. If the number of acute positive persons is available, report those as well. The number of persons who tested as negative for HIV and were referred for PrEP should also be reported. Note: If no new interviews have been conducted, put "0" in each response category.
- Question #49, 'Were other investigation activities conducted, such as medical chart review, or qualitative interviews?': Indicate whether any other investigations were conducted for this cluster, and if so, describe.
- Question #50, 'Were any enhancements made to your regular HIV prevention and treatment processes for cluster and/or risk network members?': Describe whether any enhancements were made to the regular processes for HIV prevention and treatment for cluster and/or risk network, and if so, what those enhancements were. Select all options that apply.
- Question #51, 'As a result of cluster response, how did communication within the health department (e.g., between surveillance and prevention) change? How did interaction between local and state jurisdictions change?': Briefly describe how communication within the health department (e.g., between surveillance and prevention programs) and/or interactions between state and local jurisdictions changed as a result of cluster response efforts.
- Question #52, 'Was the existence of the cluster used to advocate for any policy changes?': Indicate whether cluster response efforts led to the opportunity to advocate for policy changes, and if so, describe.

Securely Submitting the Document

Jurisdictions should submit one cluster investigation worksheet per quarter for each cluster in which ongoing investigation and response activities are occurring. It is not necessary to repeat information that has already been reported in previous quarters. Jurisdictions are encouraged to save an electronic version of each cluster worksheet and add to the most recent copy when submitting for the next quarterly reporting period.

Jurisdictions should submit their worksheets securely using SAMS. Filepaths should follow this nomenclature so that they can easily be distinguished by CDC: "JURISDICTION NAME_CIW_CLUSTER ID_REPORTING QUARTER AND YEAR." For issues submitting files through SAMS, or to request SAMS access, please contact the SAMS helpdesk.

Cluster investigation worksheets should be submitted by the final business day of the last month of each quarter (March, June, September, and December).

Appendix F. Suggested variables to capture during a cluster investigation

Once the known transmission cluster and risk network have been ascertained, the next step is to extract and review existing data for these persons. A list of suggested variables is below. Please note that, depending on the specific fields collected in a jurisdiction, some of these variables may be easily extracted from existing data sets, while others may only be captured through review of partner services comments fields and notes.

Variable	Molecular cluster members	Other transmission cluster members (i.e., HIV-positive partners)	Other risk network members (i.e., HIV-negative or status unknown partners)
StateNo	X*	X*	
Partner services ID	X*	X*	X*
Other reporting jurisdictions (per RIDR, CDC cluster snapshot or other communication)	X	X	X
Category (confirmed, probable, possible, risk network member)	X	X	X
Last name	X*	X*	X*
First name	X*	X*	X*
Aliases	X	X	X
DOB	X	X	X
Current address	X	X	X
Current city	X	X	X
Current county	X	X	X
Current state	X	X	X
Current zip code	X	X	X
Current address type	X	X	X
Census tract of residence	X	X	X
Country of birth	X	X	
Date of HIV diagnosis	X	X	
Facility at HIV diagnosis	X	X	
Residence at diagnosis	X	X	
Transmission category	X	X	
Sex at birth	X	X	X
Current gender	X	X	X
Age	X	X	X
Race/ethnicity	X	X	X
Acute HIV infection?	X*	X*	
Symptoms of acute HIV?	X*	X*	
If yes, date of symptom onset	X*	X*	
Stage zero at diagnosis?	X*	X*	

Recency (if available from STARHS testing)	X*	X*	
AIDS at diagnosis?	X	X	
Date of last negative HIV test (self report)	X*	X*	X*
Date of last documented negative HIV test	X*	X*	X*
Date of first CD4/viral load after diagnosis (Linkage)	X	X	
Testing history	X	X	X
Reason for receiving HIV test that resulted in their HIV diagnosis	X	X	
Most recent care facility/provider	X*	X*	
Are they receiving care from a Ryan White provider?	X*	X*	
Most recent VL value	X*	X*	
Most recent VL date	X*	X*	
Trend in viral load	X	X	
Date of next appointment	X*	X*	
Facility of next appointment	X*	X*	
Currently on ART?	X	X	
Whether a genotype test was ordered/conducted?	X	X	
Genotype in eHARS? (Y/N)	X	X	
Whether drug resistance detected	X	X	
Specific drug resistance mutations	X	X	
PS interview ever completed?	X*	X*	X*
Date of most recent PS interview	X*	X*	X*
Named partners (list StateNo or partner services ID	X	X	
Named social network members (list StateNo or partner services ID)	X	X	
Number of partners initiated	X*	X*	
Anonymous partners	X	X	
Number of partners located	X	X	
Number of partners tested	X	X	
Number of partners positive	X	X	
Number of social contacts named	X	X	
Number of partners last 12 months	X	X	X
Sex while drunk/high	X	X	X
Sex for drugs/$	X	X	X
Any recreational drugs	X	X	X
Any IDU	X	X	X
Meth use?	X	X	X
Sex with IDU			X
Sex with males			X
Sex with females			X
Sex with MSM			X
Sex with transgender persons			X

History of travel to other jurisdictions	X	X	X
Reported sex partners from other jurisdictions	X	X	X
Sex without condom	X	X	X
Reported places to meet partners	X	X	X
History of incarceration	X	X	X
Employment Status	X	X	X
History of military service	X	X	X
Current student	X	X	X
On PrEP prior to diagnosis	X	X	
# of STIs in the past 12 months	X	X	
Prior syphilis infection	X	X	X
Last syphilis date	X	X	X
Prior gonorrhea infection	X	X	X
Last gonorrhea date	X	X	X
Prior chlamydia infection	X	X	X
Last chlamydia date	X	X	X
# STIs after HIV diagnosis	X	X	
Partner services disposition			X*
Partner services test result			X*
Referred for PrEP			X*
On PrEP			X*
Notes of pertinent other findings	X	X	X

*Indicates variables from the above data sets that can be extracted to prioritize and initiate persons for linkage to care and partner services.

Appendix G. Additional resources

Example publications using HIV-TRACE

- Wertheim JO, Leigh Brown AJ, Hepler NL, Mehta SR, Richman DD, Smith DM, Kosakovsky Pond SL (2014) The global transmission network of HIV-1 J Infect Dis 209(2): 304–313.
- Little SJ, Kosakovsky Pond SL, Anderson CM, Young JA, Wertheim JO, Mehta SR, May S, Smith DM (2014) Using HIV networks to inform real time prevention interventions PLOS ONE 9(6): e98443.
- Oster AM, Wertheim JO, Hernandez AL, Ocfemia MC, Saduvala N, Hall HI (2015) Using Molecular HIV Surveillance Data to Understand Transmission Between Subpopulations in the United States J Acquir Immune Defic Syndr 70(4):444–451.
- Whiteside YO, Song R, Wertheim JO, Oster AM (2015) Molecular analysis allows inference into HIV transmission among young men who have sex with men in the United States AIDS 29(18): 2517–2522.
- Wertheim JO, Oster AM, Hernandez AL, Saduvala N, Bañez Ocfemia MC, Hall HI (2016) The international dimension of the U.S. HIV transmission network and onward transmission of HIV recently imported into the United States. AIDS Res Hum Retroviruses.

Security and Confidentiality

- Data Security and Confidentiality Guidelines for HIV, Viral Hepatitis, Sexually Transmitted Diseases, and Tuberculosis Programs (available at https://www.cdc.gov/nchhstp/programintegration/docs/PCSIDataSecurityGuidelines.pdf).

Social Network Testing Strategy

- Kimbrough LW, Fisher HE, Jones KT, Johnson W, Thadiparthi S, Dooley S. Accessing social networks with high rates of undiagnosed HIV infection: The social networks demonstration project. Am J Public Health. 2009 Jun;99(6):1093-9.
- CDC. Use of social networks to identify persons with undiagnosed HIV infection—Seven U.S. cities, October 2003–September 2004. MMWR Weekly (2005). 54(24);601–605. Available at https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5424a3.htm
- McCree DH1, Millett G, Baytop C, Royal S, Ellen J, Halkitis PN, Kupprat SA, Gillen S. Lessons learned from use of social network strategy in HIV testing programs targeting African American men who have sex with men. AJPH 2013 Oct;103(10):1851-6.

Appendix H. Additional resources for cluster investigation

Tools for investigation, and considerations for when to do patient re-interview

Selected tools for cluster investigation developed by jurisdictions (or CDC and jurisdictions in collaboration) can be found on the [HICSB SharePoint site](#). These tools can be used as starting points when considering what and how best to capture information related to cluster investigation. Since investigations can differ depending on characteristics of the cluster and underlying networks, not all tools may be appropriate for every investigation.

Partnering with relevant stakeholders is crucial to developing and implementing tools that are most appropriate for cluster investigation. For example, if a substantial portion of HIV-positive individuals in a cluster receive care through Ryan White, involving Ryan White case managers and other staff who have established relationships with HIV-positive individuals in the cluster when developing and implementing tools for patient re-interview can be extremely helpful.

Cluster investigation management tool

- A cluster investigation will generate a large amount of information, and developing a database to input, organize, and maintain this information will be critical to effectively assessing the data. A simple excel spreadsheet may be sufficient for many investigations, though a more complex relational database could also be useful, particularly when managing data on connections between patients.
- Considerations for developing a database for cluster investigation:
  - Use one table that includes a de-duplicated list of all persons in the investigation (e.g., HIV-positive individuals, HIV-negative individuals, and those with unknown HIV status).
    - Surveillance data for HIV positive individuals can be imported from eHARS. Data for HIV-negative individuals or those with unknown HIV status can be imported or hand-entered from other systems.
    - A de-duplicated list in which each individual only appears once can be helpful to efficiently manage and summarize data. Consequently, it is crucial to develop an ID that will retain uniqueness at the individual level throughout the lifespan of the database and can be used as a relational key to other tables to support database normalization. To reduce duplication and circumvent common pitfalls, avoid the use of names, social security numbers or other similar IDs as the primary ID for a person. Instead, it is recommended to use an auto incremented number as the primary ID for a person.
    - It's important to have a core group of variables (e.g., age, race/ethnicity) using standard formats to be able to easily summarize demographic information across the entire cluster.
  - Use a second, separate table that lists relationships between individuals (e.g., links identified through review of partner services data).
    - An individual may be listed on multiple rows since he/she could have linkages to more than one person.
    - Given the importance of distinguishing type of relationship, jurisdictions are encouraged to add a column with values for valid types of relationships (e.g., sex partner, injection drug use partner, social contact.

- This table could be used by a variety of applications to visualize the network identified through partner services or other interview data.
- Suggested variables to capture during a cluster investigation that could be entered into a database are listed in Appendix F.
- In some instances, such as when partner services data is scarce or factors facilitating transmission remain unclear, it may be helpful to conduct a medical chart review on a portion of HIV-positive persons in the cluster. A template of variables to consider collecting during review of medical charts or partner services records are listed in Appendix F.

Patient re-interview

Considerations for conducting additional interviews or re-interviews
Although partner services data often offers a rich source of information on potential partners and routes of transmission, not everyone is interviewed and not everyone who is interviewed names partners. Thus, partner services initial interviews may not always yield useful information, and in certain circumstances, it may be beneficial to consider a re-interview.

When would additional interviews or re-interviews be most useful to an investigation?
1) If persons in the cluster were not interviewed initially, more information could be gained by interviewing these persons
2) If the cluster continues to grow and existing links identified from initial interviews have been exhausted
3) If "cluster interviewing," or elicitation of social contacts, was not incorporated in additional interviews
4) If persons in the cluster are not virally suppressed, additional partners may be at risk who were not elicited in initial interviews
   a. If an individual is out of care and will be receiving a reengagement visit/encounter, it may be helpful to incorporate re-interview questions at the time of this visit.
5) To better understand the context of risk behaviors and prevention needs (e.g., enhance interviews among PWID cluster members could provide nuanced information about drug use behaviors)

Examples of re-interview tools used by jurisdictions in cluster investigations
Documents on the HICSB SharePoint site provide sample scripts and protocols for
- Re-interviewing HIV-positive and/or negative persons part of an HIV cluster
- Approaching providers when discussing viremic, HIV-positive persons part of an HIV cluster

Since the type of questions to include in a re-interview will strongly depend on the characteristics of the persons in the cluster, the questions in the provided examples may not always be appropriate for a given cluster investigation but should be viewed as a starting point.

Additional resources when considering re-interviewing persons in a cluster

DIS surge support

- Within the state
    - o Ideally, a health department determines the capacity of its DIS staff before an outbreak occurs:
        - ▪ Maximum number of open cases (short- and long-term or mixture of short- and long-term cases) that staff can manage at any given time
        - ▪ Amount of travel time required to locate and follow-up persons with diagnosed infection
    - o After determining current capacity, a health department should establish the point at which to request additional DIS staff.
    - o During an outbreak, a health department may increase DIS capacity by shifting internal staff (e.g., by deploying current staff who previously worked as DIS), or by deploying DIS from a different part of the state.
- Outside the state: Requesting assistance from other states, CDC and/or HRSA
    - o If responding to an outbreak starts to exceed the state's current DIS resources, the state can request additional DIS support from other states, CDC and/or HRSA. Before requesting additional DIS support, a state should consider the following:
        - ▪ How many DIS are needed, and how long will additional DIS support be needed?
        - ▪ What skill sets are needed? Will responding DIS need advanced interviewing skills, phlebotomy skills, ability to conduct rapid HIV or HCV testing?
        - ▪ What are the expectations of responding staff? What are the expected responsibilities and duties, work hours, and command structure (i.e., to whom will the DIS report)?
        - ▪ How will travel and other costs be funded?
        - ▪ What are the health department's plans after responding DIS leave?
    - o States can request additional DIS support from other states through the Emergency Management Assistance Compact (EMAC). The Emergency Management Assistance Compact (EMAC) is a mutual aid agreement between all 50 states, the District of Columbia, Puerto Rico, Guam, and the U.S. Virgin Islands. During a governor-declared state of emergency, states can use EMAC to request personnel, equipment, supplies, and services from other states to assist in the emergency.
        - ▪ For more information on requesting additional DIS support through EMAC, refer to page 27 of 'Managing HIV and Hepatitis C Outbreaks Among People Who Inject Drugs—A Guide for State and Local Health Departments'.
    - o For steps on requesting additional DIS support from CDC, refer to page 26 of 'Managing HIV and Hepatitis C Outbreaks Among People Who Inject Drugs—A Guide for State and Local Health Departments'.
    - o States can request assistance from HRSA-funded staff to support cluster investigation by leveraging expertise of Ryan White case managers and other staff to serve as an additional source for contacting cluster members in the event that contact through DIS is not successful. For clusters involving neighboring jurisdictions, regional HRSA funds may also be available to programmatically support cluster investigations.

Appendix I. Cluster and Outbreak Detection and Response Plan Template

Cluster and Outbreak Detection and Response Plan Template
Jurisdiction Name
Version Number and Date

Version History

Version #	Implemented by	Revision date	Date submitted to CDC	Reason

DRAFT

Please answer the following questions for your jurisdiction. Indicate if and when procedures will differ from recommendations outlined in the technical guidance document for detecting, investigating, and responding to HIV transmission clusters.

I. Identifying growing transmission clusters using surveillance data (pp.10-19)		
a. Collection of molecular sequence data (pp.13-14)		
Activity	**Plan**	**Responsible Party**
Describe your jurisdiction's process for routinely collecting nucleotide sequences via ELR. Indicate who is responsible for assessing completeness and timeliness of the data and addressing issues as they arise.		
b. Analysis of sequence data to identify molecular clusters (pp.12-13, 15-17)		
Activity	**Plan**	**Responsible Party**
Describe how often HIV nucleotide sequence data will be analyzed using Secure HIV-TRACE or another CDC-approved method to detect clusters and monitor the growth of previously identified clusters. *Note: Per PS18-1802, jurisdictions are required to conduct local analysis to detect clusters at least monthly.*		
Provide any additional criteria you will use for identifying additional priority clusters within your jurisdiction beyond those detected with CDC's priority criteria (clusters with at least 5 cases diagnosed within the most recent 12-month period, or, for lower-burden jurisdictions clusters with at least 3 cases diagnosed within the most recent 12-month period.		
Describe the circumstances under which a genetic distance threshold other than 0.5% and/or a time period greater than		

Activity	Plan	Responsible Party
three years will be utilized to identify molecular cluster members.		
For jurisdictions partnering with academic institutions or other partners to analyze sequence data: List the name(s) of academic institution(s) and parties involved, their roles and responsibilities, and describe the data sharing and security/confidentiality agreements in place.		
c. Time-space and other clusters (pp.17-19)		
Activity	**Plan**	**Responsible Party**
Describe how your jurisdiction will use the CDC-provided SAS program and/or other methods to identify time-space clusters. Include the geographic areas (i.e. counties, MSAs, regions) that will be examined using these methods. Explain how often time-space cluster analysis will be conducted.		
Provide the criteria you will use for flagging time-space clusters for further investigation. Indicate whether this analysis will be used for any sub-populations of interest (e.g., IDU, reproductive age women)		
Describe any procedures you will use to routinely identify clusters detected through partner services.		
d. Reporting clusters to CDC (Appendix E)		
Activity	**Plan**	**Responsible Party**
Describe how locally-identified clusters will be entered into eHARS and reported to CDC. Indicate who will generate the data to be entered and upload it to eHARS.		

Describe how you will complete the CDC Cluster Investigation Worksheet and transmit this to CDC each quarter		

II. Assessing, prioritizing, and responding to clusters (pp.19-50)		
a. Cluster assessment and prioritization (pp.23-35)		
Activity	**Plan**	**Responsible Party**
Based on Section 4 of the cluster guidance document, describe your jurisdiction's process for completing Step 1 of the roadmap to investigating and intervening in transmission clusters: *Identify known transmission cluster and risk network*. Indicate who will be involved in collecting data for the desk review (Partner Services staff, etc.).		
Describe how the information gathered from a review of existing data will be stored, managed, and maintained at your site. Indicate what limitations exist in these systems and what opportunities there are to address these limitations. *Note: If a system for storing, managing, and maintaining information about clusters does not currently exist, your jurisdiction will be responsible for developing one.*		
Describe your jurisdiction's algorithm/process for completing Step 2a of the roadmap to investigating and intervening in transmission clusters: *Assess level of concern and need for enhanced investigation and response*. Describe the local epidemiology of HIV in your jurisdiction and how that impacts cluster prioritization. Explain how the decision to initiate an enhanced		

response for a cluster will be made, and who will be involved in making the decision.		
Describe your method(s) and timeframe for reviewing the data collected and using it to prioritize interventions (i.e. case conferences, communication with local health departments, communication with other jurisdictions, etc.).		
Describe how an assessment of factors specific to the cluster (e.g., factors facilitating transmission, or cluster-specific intervention points) will be integrated into your approach to reviewing data.		

b. Initiate critical initial interventions (pp.35-39)		
Activity	**Plan**	**Responsible Party**
Describe your jurisdiction's process for ensuring viral suppression among all persons in the transmission cluster (see Step 2b of the roadmap). Explain any enhancements to your typical processes (i.e. data-to-care) that will be provided for persons in the cluster who are identified to be out of care and/or virally unsuppressed.		
Describe your jurisdiction's process for testing/re-testing persons with unknown or HIV-negative status who are identified to be in the risk network (see Step 2b of the roadmap).		
Describe your jurisdiction's process for evaluating and referring HIV-uninfected persons in the risk network for PrEP and other prevention services (see Step 2b		

Activity	Plan	Responsible Party
of the roadmap). Identify current PrEP resource considerations.		
Describe how outcomes of linkage to care and viral suppression, testing/re-testing, and/or referral to PrEP for persons in the transmission cluster/risk network will be monitored, and who will be responsible for the monitoring and reporting. Include the role of partnering agencies and CBOs, if applicable. *Note: Per PS18-1802, jurisdictions will report on the proportion of transmission cluster members who were virally unsuppressed at identification as part of the cluster who achieved viral suppression within 6 months, the proportion of persons with negative or unknown HIV status who were tested/re-tested within 6 months, and the proportion of HIV-negative partners who were referred to PrEP within 6 months.*		
c. Conduct enhanced investigation and intervention activities, as appropriate (pp.39-47)		
Activity	**Plan**	**Responsible Party**
Indicate which additional response activities (described in Section 4 and Step 3 of the roadmap) will be considered for priority clusters, as needed (i.e. additional partner services interviews/re-interviews, venue testing, social network testing, etc.). Explain who will be responsible for these activities, and which additional health department personnel will be involved. Include the role of partnering agencies and CBOs, if applicable.		
d. Monitor progress and determine when a cluster response should be closed (pp.47-50)		
Activity	**Plan**	**Responsible Party**

Describe your process for reviewing and re-prioritizing clusters as new information becomes available and as clusters grow or change over time (see Step 4 of the roadmap). Explain the criteria you will use to determine under which circumstances the addition of new cases to clusters warrants additional actions and interventions. Indicate who will be involved in making the decision to respond to re-prioritized clusters.		
Describe how your jurisdiction will track this process and how you will continue to monitor lower priority clusters for future growth.		
Describe the methods you will take to determine the effectiveness of cluster response activities (i.e. Plan Do Study Act, after action review, etc.).		
Describe your jurisdiction's process for determining when to close an investigation (see Step 4 of the roadmap). Identify key persons involved in making the decision to close an investigation.		

Complete the table below with information about how HIV and other data is stored at your jurisdiction and your ability to access it in conducting a cluster investigation (see page 27-28 for data sources to consider).

Type of data	Database name	Who has access	How readily available is it?	Variables included	Data limitations

III. Communicating about HIV transmission clusters (pp.50-53)		
a. Developing a cluster communication plan (pp.50-53)		
Activity	**Plan**	**Responsible Party**
Describe your jurisdiction's communication plan for cluster and outbreak response (or submit a copy as an appendix). Indicate what actions, if any, are specific to regular communications processes in the context of a cluster investigation and which are specific to outbreak response.		

IV. Facilitating collaboration while protecting cluster data (pp.53-54)		
b. Data collection (pp.53-54)		
Activity	**Plan**	**Responsible Party**
Describe procedures for collecting, tracking, and synthesizing data from cluster investigation and response activities (including data from both local and national analyses). Indicate how you will organize and manage this data.		
c. Data security (pp.53-54)		
Activity	**Plan**	**Responsible Party**
Describe procedures for securely storing data related to cluster analysis, investigation, and response and maintaining patient privacy and confidentiality.		
d. Data sharing and communication about clusters (pp.53-54)		
Activity	**Plan**	**Responsible Party**
Describe how data related to cluster investigation and response activities will be shared between the local and state		

Activity	Plan	Responsible Party
health departments within your jurisdiction.		
Describe data sharing and security/confidentiality procedures for staff involved across multiple departments (e.g. HIV surveillance, HIV prevention, STD, DIS, etc.).		
Describe data sharing and security/confidentiality procedures for external organizations involved in cluster identification, investigation, and response (e.g. academic institutions, healthcare providers, CBOs).		
Describe your strategies for communicating with persons involved in transmission clusters for re-interviews and re-engagement in care.		

V. Approaching multi-jurisdictional clusters (pp.54-57)		
a. Situations in which your jurisdiction is the primary jurisdiction but cases reside in another jurisdiction (pp.54-57)		
Activity	**Plan**	**Responsible Party**
Describe procedures for communicating with other jurisdictions regarding cases in the cluster that reside in their jurisdictions. Identify methods of securely sharing data about clusters and cases. If there is more than one PS18-1802 funded jurisdiction in your state, describe how communication will occur across those entities as well.		
b. Situations in which another jurisdiction is the primary jurisdiction but cases reside in your jurisdiction (pp.54-57)		
Activity	**Plan**	**Responsible Party**
Describe procedures for communicating with other jurisdictions regarding cases in their clusters that reside in your jurisdiction. Identify methods of securely sharing data about clusters and cases. If		

there is more than one PS18-1802 funded jurisdiction in your state, describe how communication will occur across those entities as well.		

c. Multi-jurisdictional clusters involving cases in your jurisdiction (pp.54-57)		
Activity	**Plan**	**Responsible Party**
Describe procedures for communicating with other jurisdictions regarding cases that reside in your jurisdiction for multi-jurisdictional clusters identified by CDC. Identify methods of securely sharing data about clusters and cases. If there is more than one PS18-1802 funded jurisdiction in your state, describe how communication will occur across those entities as well.		

VI. Operationalizing cluster and outbreak detection and response (pp.57-60)		
a. Identify key staff and partners, establish roles, and provide training (p.58)		
Activity	**Plan**	**Responsible Party**
Describe training procedures and requirements for onboarding new staff involved in cluster detection, investigation, and response, including security and confidentiality.		
Describe training provided to outbreak staff not regularly involved in HIV cluster detection and response who may be called upon when surge capacity is needed.		
Describe annual training requirements for staff, including data security and confidentiality.		
Describe your plan to ensure that key activities can continue if key staff involved in cluster work leave the health department		

Activity	Plan	Responsible Party
Identify key stakeholders and partners that may need to be informed or involved in cluster or outbreak investigation and response.		
Describe the process for engaging partners prior to cluster detection and response.		
For states: Comment on your role in guiding local health departments to identify key stakeholders and partners in their service areas.		
b. Identify potential local resources that could be mobilized for investigation/response if needed (p.58)		
Activity	**Plan**	**Responsible Party**
Identify which of the partners listed above can be mobilized to assist with cluster interventions if needed. Include community providers that can provide HIV testing, prevention, and treatment services in case of an escalated response.		
For states: Comment on your role in guiding local health departments to develop capacity and partnerships for an escalated response in their service areas.		

Complete the table below identifying all staff involved in HIV cluster and outbreak detection, investigation, and response. Include outbreak response staff that are not regularly involved in cluster detection and response but may be called upon when surge capacity is needed. Indicate Incident Command System roles where applicable.

Name	Job title	Department/Division	Roles and responsibilities in cluster/outbreak work	Percent of time devoted to cluster/outbreak work

VII. Initiating an escalated response (pp.60-62)		
a. Determining a threshold for initiating an escalated response (p.61)		
Activity	**Plan**	**Responsible Party**
Indicate your process for notifying CDC HICSB and PPB project officers once the decision to initiate an escalated response has been made. *Note: This process is distinct from the regular cluster notification process that occurs quarterly per PS18-1802 requirements.*		
b. Assess local policies that might impact cluster investigation and potential intervention (p.61)		
Activity	**Plan**	**Responsible Party**
Describe any policies or state or local laws in place that may hinder cluster investigation and response. Indicate opportunities that may be available to revise policies.		
c. Scaling back and ending the cluster response activities (p.62)		
Activity	**Plan**	**Responsible Party**
Identify the threshold for reducing and demobilizing an escalated response.		

Appendix A: Documentation of annual staff training

To be submitted to CDC yearly, as evidence that the jurisdiction is maintaining capacity for cluster and outbreak detection and response.

Name	Position title	Department/Division	Training title	Date completed

Appendix B: Staffing vacancies log

To be submitted to CDC yearly, as evidence that the jurisdiction is maintaining capacity for cluster and outbreak detection and response.

Position	Department/Division	Date of vacancy	Date filled*

*For vacancies lasting longer than two months, please submit a brief explanation of roles and responsibilities that have been assumed by other staff members and how this has impacted overall capacity for cluster and outbreak detection and response.

Appendix J. Summary of key components to address in the Cluster and Outbreak Detection and Response Plan Template for operationalizing routine cluster detection.

For details, please refer back to topic-specific sections of this document.

Identifying growing transmission clusters

- Identifying growing transmission clusters starts with having a process in place for routinely collecting nucleotide sequence information in the ELR. It is also recommended that jurisdictions apply CDC-approved methods to identify time-space clusters.
- Currently, CDC conducts quarterly analyses of surveillance data to identify clusters meeting CDC priority criteria, which are then communicated to states.
- Under PS18-1802, Jurisdictions are required to conduct their own analyses of sequence data locally at least monthly. While CDC has standard criteria to identify priority clusters (current criterion is ≥5 cases in the most recent 12-month period in a cluster defined at a 0.5% threshold, or ≥3 cases in the most recent 12-month period for lower-burden jurisdictions), programs might want to consider alternate criteria. Such criteria could include lower thresholds for recent growth (e.g., 3 or fewer newly diagnosed cases in the most recent 12 month period), or criteria that focuses on particular risk groups (e.g., a demographic group with recent increases in diagnoses).
  - Newly identified clusters should be entered promptly into eHARS. Details related to clusters identified through local and national analysis should be reported to HICSB quarterly via SAMS using the Cluster Investigation Worksheet (see Appendix E).
- Determine the frequency with which local analyses will be conducted, if more often than monthly. More frequent analyses will allow more rapid detection of growing clusters and therefore greater opportunity for effective investigation and intervention. The advantages of more frequent analysis should be balanced with staffing and resource availability to determine the frequency for a given program.
- For more information on strategies to identify growing transmission clusters, refer to Section 3.

Assessing molecular clusters and prioritizing response efforts

- Complete Step 1 of the roadmap to investigating and intervening in transmission clusters: Identify known transmission cluster and risk network. This entails the following:
  - Identify readily available data for 'desk review' of clusters, and develop processes for accessing and linking that data to cluster information. This includes reviewing data from partner services as well as surveillance data.
  - Develop a system for storing, managing, and maintaining this data at your site.
- Complete Step 2a of the roadmap to investigating and intervening in transmission clusters: Assess priority level and need for enhanced investigation and response. This entails the following steps:
  - Develop methods and timeframes for reviewing the data collected and using it to prioritize interventions (i.e. case conferences, communication with local health departments, communication with other jurisdictions, etc.).
  - Review available data to determine whether additional investigation and response activities are needed in addition to the critical interventions that are required of all priority clusters detected.

- Key questions for consideration include: 1) How effectively have the transmission cluster and risk network been identified through partner services?, 2) What is the likelihood of or potential for ongoing transmission in the cluster?, 3) What is the potential for poor outcomes?, and 4) Does the cluster appear to be under control with activities already conducted?
- Prioritization may be an iterative process that evolves over the course of months or years as the cluster grows or new information becomes available or the cluster.
- Complete [Step 2b] of the roadmap to investigating and intervening in transmission clusters: Initiate critical initial interventions. This entails:
  - Ensure viral suppression among all persons in the transmission cluster. This may involve developing enhancements to typical processes for linking persons with HIV who are out of care an unsuppressed (i.e. data-to-care) for members of the cluster.
  - Test and/or re-test persons with unknown or HIV-negative status who are identified to be in the risk network.
  - Evaluate and refer HIV-uninfected persons in the risk network for PrEP and other prevention services. Consider whether PrEP availability needs to be expanded to reach targeted populations.
  - Develop processes for monitoring and reporting on the outcomes of linkage to care and viral suppression, testing/re-testing, and/or referral to PrEP for persons in the transmission cluster/risk network.
  - Per PS18-1802, jurisdictions must report on the proportion of transmission cluster members who were virally unsuppressed at identification as part of the cluster who achieved viral suppression within 6 months, the proportion of persons with negative or unknown HIV status who were tested/re-tested within 6 months, and the proportion of HIV-negative partners who were referred to PrEP within 6 months.
- Complete [Step 3] of the roadmap to investigating and intervening in transmission clusters: Conduct enhanced investigation and intervention activities, as appropriate. This entails:
  - Determining which additional response activities will be considered for priority clusters, as needed. These may include, but are not limited to, the following:
    - Initiating partner services interviews for persons in the cluster who were not previously interviewed
    - Re-interviewing persons in the cluster who are out of care or who are not virally suppressed
    - Initiating interviews of partners of transmission cluster members (partners of partners) and/or social contacts
    - Conducting social network interviewing and testing
    - Conducting targeted outreach at identified venues
    - Conducting general messaging campaigns through apps or internet sites
    - Conducting medical record reviews
    - Conducting population-level interventions
  - Consider whether population-level interventions may be needed, such as expanding PrEP resources to affected populations, conducting media campaigns, conducting targeted outreach, providing provider education, etc.
- Complete [Step 4] of the roadmap to investigating and intervening in transmission clusters: Monitor progress and determine when a cluster response should be closed. This entails:
  - Developing a process to review and re-prioritize clusters when new information becomes available and as clusters grow or change over time.
    - o As new cases are identified, include them in the cluster investigation to determine if there is new information that increases understanding of factors

facilitating transmission or provides a refined understanding of opportunities for intervention.
- Develop criteria for determining under which circumstances the addition of new cases to clusters warrants additional actions and interventions.
- Developing a system for tracking this process.
- Exploring methods to determine the effectiveness of cluster response activities, such as utilizing the Plan Do Study Act cycle or after action review.
- Developing a process to determine when to close a cluster investigation. Key considerations in making this decision include:
  - Whether transmission in the cluster is under control
  - Whether persons in the transmission cluster without evidence of viral suppression have been successfully linked to care
  - Whether persons in the risk network have been tested/re-tested and referred for PrEP
  - Whether new diagnoses have been identified through active investigation and intervention
  - Whether the rate of new diagnoses identified suggests that more testing is warranted
- For more details regarding prioritizing, investigating, intervening in, and monitoring clusters, refer to of this document.