Attachment 4(d)

National HIV Surveillance System (NHSS)

OMB # 0920-0573

Supplemental Surveillance Activity 2: Molecular HIV Surveillance (MHS) Technical Guidance
Formerly known as VARHS (Variant, Atypical, and Resistant HIV Surveillance)

Technical Guidance for HIV Surveillance Programs

Molecular HIV Surveillance (MHS)

HIV Incidence and Case Surveillance Branch
Atlanta, Georgia

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Notes

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CONTENTS — MOLECULAR HIV SURVEILLANCE (MHS)

Technical Guidance for HIV Surveillance Programs — Policies and Procedures for Molecular HIV Surveillance (MHS)

INTRODUCTION

The Centers for Disease Control and Prevention (CDC) maintains the National HIV Surveillance System and collects data on diagnoses of HIV infection for national, state, and local HIV program planning and evaluation. As a component of this system, Molecular HIV Surveillance (MHS) ─formerly referred to as Variant, Atypical, and Resistant HIV Surveillance (VARHS) ─ monitors trends in HIV-1 drug resistance and evaluates the genetic diversity of HIV-1 in the United States. Unless otherwise noted, all references to HIV in this document refer to HIV-1 infection.

Objectives

The primary objectives of MHS are as follows:

- Collect HIV nucleotide sequence data from laboratories that perform HIV genotype testing;
- Estimate the prevalence of and monitor trends in HIV drug resistance mutations, including transmitted drug resistance–associated mutations (TDRMs);
- Monitor the distribution of HIV genetic subtypes and recombinants, including circulating recombinant forms (CRFs) and unique recombinant forms (URFs);
- Use molecular HIV data to describe patterns of HIV transmission; and
- Disseminate the results of molecular HIV data analyses to assist HIV treatment, prevention, and program planning and evaluation.

MHS provides a unique perspective about HIV disease in the United States. MHS activities include applying an HIV drug resistance-associated mutation list, which was developed for public health surveillance purposes, to identify factors associated with HIV drug resistance and genetic diversity at the population level. MHS uses molecular epidemiology to help describe HIV transmission, clusters, and diversification. MHS data have been referenced in the development of recommended first-line antiretroviral drug regimens. MHS activities support the National HIV/AIDS Strategy goals of (1) reducing new HIV infections through the potential use of nucleotide sequence data to determine duration of infection and estimate incidence; (2) increasing access to care and improving health outcomes by using nucleotide sequence data as a marker for linkage to and quality of care, and (3) reducing HIV-related disparities and health inequities by using nucleotide sequence data to reveal transmission patterns and provide insight into prevention.

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Disease Surveillance Activity

In 2004, CDC determined that the collection of HIV nucleotide sequence data as a part of the National HIV Surveillance System was a non-research disease surveillance activity and that a review by the Institutional Review Board, pursuant to Title 45 Code of Federal Regulations Section 46: Protection of Human Subjects, was not required (Appendix A).

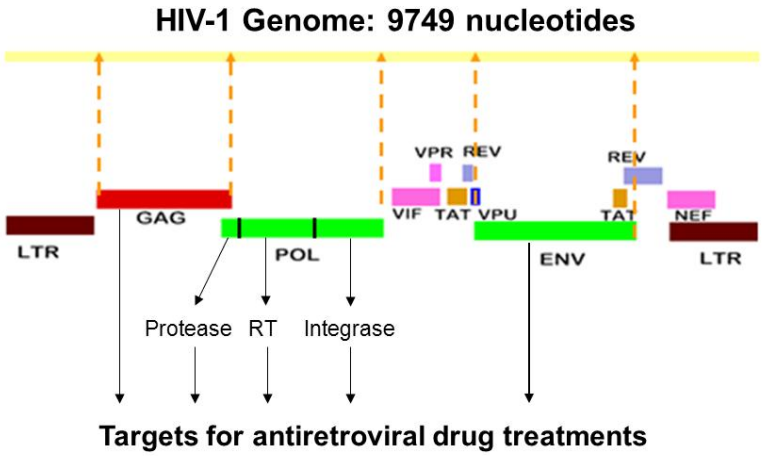
GENERAL CONCEPTS

Antiretroviral therapy (ART)

Current treatment of HIV disease has been designed and optimized for HIV-1 and includes five classes of antiretroviral drugs (ARVs). These ARVs have been approved by the Food and Drug Administration (FDA) for use in the treatment or prophylaxis of HIV infection and prevention of HIV replication at various stages of its life cycle (Figure 1). They include the following:

- Nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), which prevent the HIV reverse transcriptase (RT) from transcribing HIV RNA to viral DNA;
- Protease inhibitors (PIs), which prevent the maturation of HIV proteins by the HIV protease;
- Integrase strand transfer inhibitors (INSTIs), which block the HIV integrase from integrating viral DNA into the genome of host cells with CD4 receptors; and
- Entry/fusion inhibitors (EIs), which prevent the HIV envelope (env) from binding to and allowing the HIV genome to enter the human cell.

Figure 1. Map of HIV-1 Genome and ARV Targets



Appropriately timed and consistent use of ARVs can suppress viral loads, which can lead to better health outcomes and a much lower chance of passing HIV on to partners (1). Lists of ARVs and recommended HIV treatment regimens are available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.

HIV Drug Resistance and Transmitted Drug Resistance-associated Mutations

HIV has a rapid reproduction rate and a very high mutation rate. Because HIV lacks the mechanism to correct mistakes that occur as it reproduces, HIV in an infected person exists as a set of related, but non-identical viruses, some of which are intrinsically drug resistant even in the absence of ARV pressure (i.e., contain polymorphisms). Expanded and suboptimal uses of ART have also contributed to the emergence of drug-resistant strains of HIV, resulting in suboptimal virologic responses, treatment failures, and transmission of drug-resistant strains of HIV. CDC estimates that one in six individuals newly diagnosed with HIV infection and reported with nucleotide sequence data was infected with a strain that contained TDRMs associated with at least one antiretroviral drug class (2).

HIV Genotype Testing

HIV genotype testing is used to detect the presence of mutations associated with antiretroviral drug resistance. Standard HIV genotypic assays extract viral RNA from the blood plasma of an infected person and amplify regions of the HIV genome targeted by ARVs, mainly the PR and RT genes of the *pol* region (Figure 1). Other areas of the HIV genome, the integrase gene in the *pol* region and the envelope gene, can also be tested for mutations associated with antiretroviral drug resistance. A nucleotide sequence of the person's viral isolate is translated into corresponding amino acids and compared to a "wild-type" reference strain to identify mutations associated with drug resistance. A final report is generated that provides an interpretation of the level of resistance detected and can be used by health providers in the clinical management of patients.

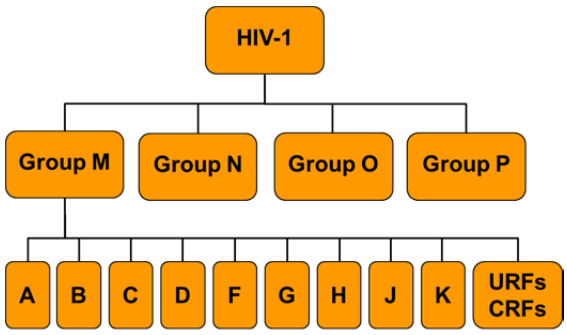
HIV genotype testing is a part of the standard of care for persons infected with HIV. The U.S. Department of Health and Human Services and the International Antiviral Society-USA (IAS-USA) recommend that HIV genotype testing be performed at entry into care, prior to initiation of ART, and upon treatment failure (3,4).

HIV-1 Subtypes

There are two types of HIV: HIV-1 and HIV-2. Most HIV infections in the United States and around the world are caused by HIV-1. More than 90% of HIV-1 infections belong to Group M, of which at least 9

genetically distinct subtypes (or clades) are known: A, B, C, D, F, G, H, J and K (Figure 2). There are also "circulating recombinant forms" (CRFs) derived from the merging of different subtypes, “unique recombinant forms” (URFs), and numerous unknown variants.

Figure 2. Genetic Diversity of HIV-1



Standard genotyping methods used to identify mutations associated with antiretroviral drug resistance can also be used to distinguish between subtype B and non-B variants of HIV. Phylogenetic analyses are used by CDC to classify potential non-B variants to the other subtypes, CRFs, and potential URFs.

STRUCTURAL REQUIREMENTS

Policies and Procedures

All persons diagnosed with HIV infection and all HIV-related laboratory test results (including, where applicable, results from HIV genotype tests) should be reported to HIV surveillance programs as required by local laws and regulations. Upon receipt, the local surveillance program should enter or import the information into eHARS in accordance with the *Technical Guidance for HIV Surveillance Programs, Vol. I: Policies and Procedures*. Because MHS is an extension of HIV case surveillance, MHS staff, in collaboration with CDC, should expand on the existing infrastructure to collect the information needed to achieve MHS objectives.

Before implementing MHS, local staff should consult with the assigned CDC epidemiologist and the CDC MHS project officer about an implementation plan, a timeline for implementation, and the incorporation of MHS policies and procedures into local guidance documents.

MHS-specific policies and procedures should include information related to the following elements:

- Staff responsibilities and requirements, including collaboration with case surveillance

- Security and confidentiality
- Collection of ARV use history data
- Laws and regulations regarding the reporting of HIV nucleotide sequence data
- Collection of HIV nucleotide sequence data from laboratories
- Data management practices
- Data transmissions to CDC
- Local analysis and dissemination
- Program evaluation

Staffing Needs

HIV case surveillance staff and MHS staff must collaborate to effectively integrate MHS into the local HIV surveillance system and to implement MHS successfully. The number of staff needed to conduct MHS activities at the local level depends on the phase of program implementation, HIV morbidity, and resource availability, but will typically include a partial full-time employee (FTE) for MHS coordination and a partial FTE for MHS data management.

MHS staff are expected to understand the local HIV surveillance system and MHS and work closely with case surveillance staff, laboratory and clinical service providers, HIV surveillance coordinators in other states, and CDC. MHS staff should also have expertise in three areas—programmatic, technical, and scientific—and ensure that the following activities related to project coordination, surveillance and epidemiology, and data management are conducted:

Programmatic: Project Coordination

- Overall management of MHS and collaboration with other surveillance staff to ensure integration of MHS into the local HIV surveillance system
- Coordination of efforts to establish the regulatory authority to obtain HIV nucleotide sequence data from laboratories
- Development and implementation of MHS activities, including local MHS guidance, policies, and procedures
- Compliance of MHS activities with CDC and local security and confidentiality requirements
- Collection of antiretroviral use history data for all new HIV diagnoses, including training of all data collectors and timely and accurate entry of these data on the Testing and Treatment History Document in eHARS

- Collaboration with laboratories to develop and implement procedures for the electronic transfer of HIV nucleotide sequence data to the health department
- Participation in CDC site visits, trainings, and workshops highlighting MHS activities as required
- Continued monitoring of MHS activities to ensure that process and outcome standards are achieved

Technical: Data Management

- Development, integration, and maintenance of data management systems for the receipt, storage, processing, and analysis of MHS data
- Development of processes to ensure that MHS meets or exceeds data quality outcome standards
- Ongoing proficiency in Base SAS software and other locally-required data management/analysis applications
- Preparation of MHS data for local analysis and transmission to CDC

Scientific: Surveillance and Epidemiology

- Analysis of HIV drug resistance and subtypes/CRFs in the jurisdiction
- Development and dissemination of MHS data reports and publications

PROCESS STANDARDS

MHS activities involve the following general processes:

- Secure and confidential reporting of HIV surveillance data
- Collecting antiretroviral use history data for all persons newly diagnosed with HIV infection
- Reviewing state or local HIV laws and regulations regarding the reporting of HIV nucleotide sequence data
- Collaborating with laboratories performing HIV genotype testing
- Obtaining HIV nucleotide sequence data for all persons diagnosed
- Storing and validating HIV nucleotide sequence data
- Linking HIV nucleotide sequence data with case surveillance information
- Ongoing monitoring of data quality and evaluation of local activities
- Preparing monthly data sets and transferring them to CDC
- Analyzing data, including transmitted drug resistance
- Developing and disseminating data reports and presentations

Secure and confidential reporting of HIV surveillance data

The secure and confidential transfer of any HIV-related data, including HIV nucleotide sequence data, is of utmost importance. Areas should review existing state and local policies on maintaining patient confidentiality and develop specific steps that will be taken to secure the data. These standard operating procedures should be reviewed and approved by the ORP and should be consistent with the guidelines and standards specified in *Data Security and Confidentiality Guidelines for HIV, Viral Hepatitis, Sexually Transmitted Disease, and Tuberculosis Programs: Standards to Facilitate Sharing and Use of Surveillance Data for Public Health Action*.

All staff responsible for the transmission and receipt of HIV surveillance data and MHS nucleotide sequence data must be trained in the security and confidentiality procedures for HIV surveillance.

Collecting antiretroviral use history data for all newly diagnosed persons

Information on the prior use of ARVs for all newly diagnosed persons is needed to estimate the prevalence of total HIV drug resistance, including transmitted drug resistance-associated mutations (TDRMs). MHS areas can collect ARV use history data using the CDC Adult HIV Confidential Case Report Form or other forms (e.g., state-based case report forms or National HIV Monitoring and Evaluation Program [NHM&E] form). Sources of the information may be patient self-reports; medical charts that contain physician's notes, laboratory reports, and pharmacy records; and the AIDS Drug Assistance Program (ADAP) records. Staff reporting ARV use data should comply with the jurisdiction's standard reporting procedures or other procedures that meet the routine security and confidentiality guidelines for HIV surveillance.

Information on ARV use should be entered into eHARS on the Testing and Treatment History (TTH) Document. To be consistent with the principles of document-based data entry, new eHARS documents should be used to enter data from multiple forms, from multiple sources, or to update previously entered information.

Information for all variables should be collected as close as possible to the HIV diagnosis date to identify persons with evidence of prior ARV use. The TTH variables related to ARV use in eHARS are listed below.

- **Ever Taken Any Antiretroviral Medications —** this variable is used to determine whether the patient took any ARVs at any time. The information collected should indicate whether antiretroviral drugs have ever been used (i.e., no time limit should be placed on the history of antiretroviral drug use) and the date on which that information was obtained.
- **Name(s) of ARV Medication Taken —** this variable lists at least one of the ARVs that the patient

has taken, but may not include all medications used, and verifies that at least one medication taken was an ARV. A list of current medications used to treat HIV is available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.

- **Date ARVs First Began —** this date represents the earliest date of any ARV use and determines whether the patient took any ARVs before the collection date of the specimen from which the nucleotide sequence was obtained.
- **Date of Last ARV Use —** this variable represents the date when ARVs were last taken by the patient.

Additional information about the collection of ARV use history data and entry of these data into eHARS can be found in the *Guidance for Collection and Data Entry of HIV Incidence Surveillance Information*.

Reviewing state or local HIV laws and regulations regarding the reporting of HIV nucleotide sequence data

MHS areas should review existing state laws and regulations regarding the reporting of HIV test results to the health department. If HIV nucleotide sequence data are not specifically referenced on the list of reportable HIV laboratory test results, areas should consult the state office of legal counsel to determine whether current laws and regulations can be interpreted to include the reporting of HIV nucleotide sequence data (e.g., "all tests indicative of HIV infection and care"). Otherwise, areas should consider modifying existing laws and regulations to ensure the reporting of HIV nucleotide sequence data for public health surveillance.

Additional information about reviewing reporting laws is available in the chapter on *Reporting* in the *Technical Guidance for HIV Surveillance Programs, Volume I: Policies and Procedures*.

Collaborating with laboratories performing HIV genotype testing

MHS relies on collaboration with laboratories performing HIV genotype testing. Each area should identify public, commercial, and private laboratories that perform HIV genotype testing for area residents. Sources of this information include Clinical Laboratory Improvement Amendments (CLIA) state and regional offices and state and local licensing boards for clinical laboratories.

Areas should consider developing a survey to collect information that will facilitate collaboration between the laboratories and the health department. Examples of topics to be addressed include the following:

- Contact information for key laboratory personnel, both administrative and technical

- Whether HIV genotype testing occurs on-site or at a reference laboratory, and document how their HIV genotype testing system can generate and export nucleotide sequence data in standard text-based file formats
- Level of information technology (IT) support available

Laboratory staff should be informed about the purpose of MHS and made aware of any laws or regulations that require the reporting of HIV nucleotide sequence data to the health department, and encouraged to partner with the health department to conduct MHS activities.

Additional information about laboratories and reporting of data is available in the chapter on *Reporting* in the *Technical Guidance for HIV Surveillance Programs, Volume I: Policies and Procedures*.

Obtaining HIV nucleotide sequence data for persons newly diagnosed with HIV infection and persons living with HIV infection who had HIV genotype tests done

MHS sites should work with commercial and private laboratories to obtain all HIV nucleotide sequence data, regardless of the person's date of diagnosis. In other words, collection of HIV sequence data should be collected for all persons diagnosed and living with HIV, not just for those who are newly diagnosed, who had HIV genotype tests done.

Laboratories that perform HIV genotype testing use HIV genotyping systems to analyze HIV nucleotide sequence data. The primary output of most of these systems is a genotype report that provides a drug resistance interpretation for clinical use. The HIV nucleotide sequence, which is the basis of MHS activities, is an intermediate product of these HIV genotype testing systems. MHS areas should work with laboratory staff to develop procedures for extracting HIV nucleotide sequence data from the HIV genotype testing system. Sequence data are often not stored with other laboratory test results, and the HIV genotype testing system that holds the sequence data may not be connected to the laboratory's main computer network. Procedures should also be developed that link the sequence data to standard patient demographic information and other data (e.g., collection date, ordering physician). Additional linking procedures may be necessary if a reference laboratory is used to conduct the HIV genotype testing, as the reference laboratory may not have access to standard patient and provider data available.

Close collaboration with the laboratory administration and technical staff, including IT staff, is needed to extract the HIV nucleotide sequence data from HIV genotype testing systems. If the laboratory staff are not familiar with the data export capabilities of the genotyping system, the manufacturer of the HIV genotype

testing system should be consulted.

MHS areas should determine the best method for receiving HIV nucleotide sequence data files from laboratories performing the HIV genotype testing. MHS areas should work with the laboratory staff to determine a standard file format (HL7 messaging, FASTA, ASCII, .txt) that will be used to transmit the HIV nucleotide sequence data and relevant information from the laboratories to the health department. Depending on the surveillance program's infrastructure, technical capabilities, and state reporting laws and regulations, programs might rely on a combination of the methods described below.

Electronic Laboratory-based Reporting (ELR)

Electronic Laboratory Reporting (ELR) is the electronic transfer of public health data from clinical laboratories to public health agencies in pre-established formats (e.g., HL7 messaging, ASCII, spreadsheet) that do not require extensive human manipulation, such as data entry, cutting and pasting, or translation to add to a database. Ideally, data transmitted by ELR should be automated and should use standardized codes for tests (e.g., Logical Observation Identifiers Names and Codes or LOINC) and results, allowing for timely, complete, and accurate reporting. Additional information about ELR is available in the chapter on *Reporting* of the *Technical Guidance for HIV Surveillance Programs, Volume I: Policies and Procedures*. Possible methods of receiving HIV nucleotide sequence data from laboratories include coordinated transmission with HIV case surveillance data, coordinated transmission with data from existing state systems, and transmission of sequence data from the laboratory directly using the Secure File Transfer Protocol (SFTP).

<u>Transmission with HIV case surveillance data</u>

Many HIV surveillance programs that use ELR to receive HIV serology data, CD4 data, and viral load data, may receive HIV nucleotide sequence data through this same mechanism. If the HIV surveillance program does not use ELR, other surveillance programs within the health department (e.g., general infectious diseases, TB, STDs) may use ELR to receive HIV nucleotide sequence data. MHS staff should consult with staff within these programs and with IT staff at the health department about the possibility of modifying existing ELR processes that ensure the secure and confidential receipt of HIV nucleotide sequence data.

<u>Transmission through existing state systems</u>

The CDC Public Health Information Network (PHIN) is a national initiative to improve the capacity of public health to use and exchange information electronically by promoting the use of standards and defining functional and technical requirements. As a component of PHIN, CDC has developed the National

Electronic Disease Surveillance System (NEDSS), an Internet-based infrastructure for public health surveillance data exchange. The NEDSS Messaging solution (NMS) supports electronic messaging between public health partners (e.g., commercial entities and local, state, and federal agencies) and relies heavily on industry standards (i.e., LOINC, SNOMED, and HL7), policy-level agreements on data access, and the protection of confidentiality.

MHS areas that are considering receiving HIV nucleotide sequence data through their state NEDSS program should coordinate with NEDSS program staff to make modifications in NEDSS. Upon meeting security and confidentiality guidelines, HIV nucleotide sequence data can be routed through NEDSS to the MHS program. Sites that have implemented a system that uses standards similar to NEDSS or have mobilized healthcare information electronically across different organizations through health information exchanges (HIE) can also consider the possibility of receiving HIV surveillance data via these mechanisms.

Additional information about NEDSS and HIE are available in the chapter on *Reporting* of the *Technical Guidance for HIV Surveillance Programs, Volume I: Policies and Procedures*.

Transmission using Secure File Transfer Protocol (SFTP)

A common method used by health departments to receive HIV surveillance data is the Secure File Transfer Protocol (SFTP). SFTP is a type of protocol that provides a set of rules that govern the syntax, semantics, and synchronization of communication across computer networks. SFTP encrypts both commands and data, requires certification on at least the sending or receiving end, and allows the secure transmission of passwords and sensitive information.

To establish SFTP transmission, both the host laboratory and the health department should maintain a SFTP server, preferably located within a secure area, behind a firewall, and with other physical security measures to prevent access by non-authorized staff. Authorized staff at the health department may be granted permission to log into a laboratory's host network, access the host server using a password, retrieve the sequence data files (e.g., HL7 file or FASTA file) and initiate the transfer of the files from the laboratory to a SFTP server located at the health department. Alternatively, the health department may grant permission for authorized laboratory staff to access and transfer the data files to the secure server at the health department. Regardless of the process chosen, close collaboration between the laboratory staff, MHS staff, and staff from both IT departments is essential.

Ideally, electronic data transfers should be conducted over a secure data network (SDN), virtual private network (VPN) connection with certificates on both the sending and receiving ends, or a similar secure connection. At a minimum, when transferring data electronically, programs should encrypt data using a secure application such as the SFTP described above. If either the sender or the recipient of the data is not part of a defined security zone appropriate for sensitive data, the data should also be encrypted by another method prior to being transmitted.

MHS areas that have not yet implemented ELR are strongly encouraged to do so, particularly for the collection of HIV nucleotide sequence data. Areas should contact their assigned CDC HIV Incidence and Case Surveillance Branch epidemiologist and request assistance in establishing ELR for their HIV surveillance program. Refer to the ELR section in the chapter on *Reporting* of the *Technical Guidance for HIV Surveillance Programs, Volume I: Policies and Procedures*.

Non-ELR methods

If ELR is not a feasible option, MHS areas can develop other methods of obtaining HIV nucleotide sequence data from the laboratory to the health department. Acceptable methods include using CDs, DVDs, or FIPS 140-2 compliant flash drives or external hard drives, provided that these portable and external storage components have encryption software that meets the federal Advanced Encryption Standards (AES). The selected procedures should also comply with security and confidentiality requirements at the state and CDC.

All removable or external storage devices containing identifiable public health data must include only the minimum amount of information necessary to accomplish assigned tasks as determined by the designated official or overall responsible party (ORP); must be encrypted or stored under lock and key when not in use; and must be sanitized immediately following a given task (except for those used as back-ups). Methods used to sanitize a storage device must ensure that any data on the device cannot be retrieved by using "undelete" or data retrieval software.

Storing and validating HIV nucleotide sequence data

Because the Laboratory Document in eHARS does not currently accommodate HIV nucleotide sequence data, MHS areas should develop procedures for processing and managing the data. Through the NEDSS program, CDC has provided most funded health departments with the Rhapsody Integration Engine (Orion Health, CA), a software tool that can be used to read laboratory data in various formats. MHS areas using

ELR methods can use this CDC-provided software, or an alternative software, to parse laboratory data reported through ELR and translate the laboratory results into a format that can be imported into a database or repository. All areas should develop processes for importing the data into a local MHS database, exporting these data from the MHS database, and using SAS software to merge these data with CDC-specific demographic and clinical variables from eHARS.

Until sequence data can be imported into eHARS, MHS areas should develop or modify a database that can hold a large volume of data (e.g., SQL database). At a minimum, the database should include a unique record ID (e.g., MHSID), STATENO, patient information, laboratory CLIA number, accession number, unique specimen ID, LOINC, specimen collection date, facility information, provider information, and HIV nucleotide sequence(s). Inclusion of LOINC is important to distinguish the type of HIV nucleotide sequence generated by the HIV genotype test. The data may exist as two separate nucleotide sequences from the PR and/or RT genes of the *pol* region, and the data may also exist as a single, combined PR and RT sequence. The paired vs. single-record format of the result depends on the genotyping system used by the laboratory performing the test. Though rare, the data may also represent the integrase gene of the *pol* region, and sequences may exist as separate or combined PR, RT, and integrase sequences.

Sequences should be stored in the database in their original format. Therefore, nucleotide sequences that are received as separate records should be stored as separate laboratory results for the same individual. The sequences can be concatenated during data analysis.

Data validation should be implemented to ensure that the data received and stored are reasonable. Reported nucleotide sequences vary in length among and within laboratories, and MHS areas should be able to identify potential problems. Protease sequences contain at most 297 base pairs and RT sequences contain at most 1,320 base pairs, for a combined protease-RT length of 1,617 possible base pairs. Integrase sequences contain at most 866 base pairs.

MHS areas should develop internal processes for validating the sequences, including:

- Using LOINC to compare the length of sequences received to expected lengths. Though length sequences vary according to the HIV genotyping system used, sequences outside of the system's expected length or outside of a laboratory's usual range of variation may indicate a problem with transmission.
- Assessing sequences for embedded, non-sequence characters. Some characters may be legitimate, while others are not and may interfere with proper interpretation of the sequence. Sequences that

contain numbers, letters other than ATUCGNRWYMKSHBVDX, and/or punctuation other than ~!#*-.()' might indicate a problem.

Linking HIV nucleotide sequence data with case surveillance information

Once the nucleotide sequence data have been validated, the data should be linked with case surveillance information. MHS areas should develop processes for merging the sequence data with selected demographic and clinical data from eHARS using the SAS software and storing the linked data. Unmatched sequence data may indicate a reporting delay in eHARS or may indicate a new case that has not been reported to the HIV surveillance system; additional follow-up or field investigation of the case may be warranted. Appendix B lists the minimum set of data elements required to meet MHS objectives.

Ongoing monitoring of data quality and evaluation of local data

MHS areas should review the minimum set of data elements (Appendix B) and determine the completeness and quality of the data elements used for analysis. Because all of the demographic and clinical data elements used are key elements for HIV case surveillance, areas should consider methods of increasing the reporting of these elements (e.g., adding specific elements, such as country of birth, to counseling and testing laboratory request forms).

Preparing monthly data sets and transferring them to CDC

Until the Laboratory Document in eHARS can accommodate HIV nucleotide sequence data, MHS areas are expected to transmit a complete MHS dataset (sequence data merged with eHARS data) to CDC before the 15th day of the next month via the SDN. Data transmitted to CDC must be encrypted and password protected and must not include personal identifiers as specified in *Data Security and Confidentiality Guidelines for HIV, Viral Hepatitis, Sexually Transmitted Disease, and Tuberculosis Programs: Standards to Facilitate Sharing and Use of Surveillance Data for Public Health Action*. All MHS areas must have encryption software and a CDC-approved SDN certificate. Symantec PGP Desktop Professional 10.2 is currently the preferred encryption product for CDC. If PGP is used, all staff should create password-protected, self-decrypting files or exchange encryption keys.

To track the quality of MHS data, area-specific reports are generated by the CDC MHS Data Manager on a monthly basis and shared with MHS areas via the SDN.

Analyzing data, including transmitted drug resistance

CDC uses a regularly updated program to analyze the HIV nucleotide sequence data submitted by

genotyping laboratories. HIV-1 *pol* sequences are screened for subtype B (cut-off 90%) and potential non-B variants using Sierra—The Stanford HIV Web Service, Version 1.0 (http://hivdb.stanford.edu/pages/webservices/). This program translates the nucleotide sequence data and incorporates information on individual mutations of interest, the level of resistance to each antiretroviral drug in common use, and HIV-1 subtype. Sequences classified to potential non-B variants are phylogenetically assigned to subtypes, CRFs, and URFs. Records that meet CDC data quality are aggregated for national analyses, including analyses on transmitted drug resistance-associated mutations (TDRMs).

Persons are classified as having sequences that contain transmitted drug resistance-associated mutations (TDRMs) based on the CDC HIV-1 surveillance mutation list if the following criteria are met:

- The nucleotide sequence is from a specimen that was drawn within three months after the date of collection of the diagnostic specimen (i.e., the HIV-positive specimen that led to the report in eHARS).

  and

- The person has no evidence of prior ARV use (as determined by ARV history use data).

On a semi-annual basis or as deemed appropriate, CDC will provide a local dataset and accompanying SAS program for MHS areas to conduct local data analyses. Alternatively, MHS areas that have staff with knowledge of Perl, Java, and XML can choose to process the sequence data reported from laboratories by installing and using the Sierra Web service (or a similar service meeting security and confidentiality guidelines). Staff should also have advanced SAS skills to locally develop their own SAS programs to read in outputs from processed sequences, apply surveillance mutation lists, and analyze the data.

Developing and disseminating data reports and presentations

As appropriate, results of national data analyses will be presented at conferences and published in peer-reviewed journals. Contributors representing the surveillance areas and those representing CDC will be determined for each presentation or paper. MHS areas should also disseminate the results of local analyses through surveillance reports and presentations to assist HIV treatment, prevention, and program planning and evaluation.

OUTCOME STANDARDS

Outcome standards described in the *Introduction to Policies and Procedures*, *Data Quality*, and *Reporting* chapters of *Technical Guidance for HIV Surveillance Programs, Vol. I: Policies and Procedures* should be

applied to MHS. Meeting the surveillance standards for case ascertainment, data quality, timeliness, and completeness are essential to the success of MHS. The outcome standards for MHS relate only to persons who resided in the surveillance area at the time of diagnosis.

For assessment at 12 months after the end of the diagnosis year,

- At least 50% of newly diagnosed HIV disease cases reported to the national HIV surveillance system for a calendar year should have an initial HIV nucleotide sequence from a specimen obtained within 3 months of HIV diagnosis, and
- At least 85% of newly diagnosed HIV disease cases with a nucleotide sequence reported to the national HIV surveillance system for a calendar year should have HIV treatment history data.

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Notes

Cleared by HICSB Management 10/15/2012

APPENDIX A

National Center for HIV, STD, and TB Prevention's Non-research Determination for HIV

NCHSTP
Research/Non-research Determination
(Request to Classify Project as Not Involving Human Subjects or Research)

This form should be used to submit to NCHSTP ADS materials for projects involving CDC investigations that are not subject to human subjects regulations. Projects are eligible for this classification either as "non-research" projects (primary intent is not to generate generalizable knowledge) or as research projects that do not involve identifiable human subjects. Such projects do not require submission to the CDC Human Subjects Office for IRB review. Do **NOT** use this form for IRB "EXEMPT" research.

Project Title: Surveillance of variant, atypical, and resistant strains of HIV
(under PA 1194, 4017, 4118, and future program announcements supporting genotyping for this purpose)

Project Locations/Sites Current sites: Piloted for feasibility under Protocol 3575 (as research, because of pilot status, but consent was waived by all involved IRBs) in Colorado, Illinois, Maryland, and Seattle/King County.
We now propose to reclassify this activity from pilot status to routine HIV surveillance. Departments of Health in Chicago, Colorado, Florida, Illinois, Indiana, Louisiana, Massachusetts, Michigan, New York City, New York State, North Carolina, Pennsylvania, Puerto Rico, Seattle/King County, South Carolina, and Virginia have received funding under PA 4017 for this HIV surveillance activity.
Departments of Health in all other states performing HIV surveillance are eligible under a new program announcement (4118).

Project Officer(s) Diane Bennett Division: DHAP-SE Telephone: 404-639-5349

Proposed Project Dates: Proposed Start (as non-research routine surveillance): 7/1/2004 Ending: ongoing HIV surveillance activity

Categories of data collection that do not constitute human subjects research include are listed below. Please check appropriate category:

___I. **Activity is not research** . Primary intent is a public health practice disease control activity.
___A. Epidemic/endemic **disease control** activity; collected data directly relate to disease control needs.
XB. Routine **disease surveillance** activity; data used for disease control program or policy purposes.
___C. **Program evaluation** activity; data are used primarily for that purpose.
___D. **Post-marketing surveillance** of efficacy and/or adverse effects a new regimen, drug or device.

NCHSTP ADS Review **Date rec'd in NCHSTP ADS Office:**_____

✓ **Concur, project does not constitute human subjects research**

or

___**Project constitutes human subjects research**, submission for Human Subjects review required

Additional Comments:
1. This form cannot be used to document "IRB Exempt Research," which must instead be submitted to the CDC IRB.
2. Although CDC Human Subjects (IRB) review is not required in this instance, investigators/project officers are expected to adhere to ethical principles and standards by respecting and protecting to the maximum extent possible the privacy, confidentiality and autonomy of participants. All applicable State and Federal privacy laws must be followed.
3. Although this project does not constitute human subjects research, informed consent may be appropriate. Information disclosed in the consent process should address the eight standard consent elements.
4. Other:

Signed: _____ 6-25-04
Andrew Vernon, MD, MHS
Associate Director for Science
National Center for HIV, STD, and TB Prevention
Date

APPENDIX B

MHS Data Elements

The following surveillance data elements are used to estimate the prevalence of HIV-1 drug resistance and distribution of HIV-1 subtypes in the United States.

Data Element	HIV-1 Drug Resistance Prevalence	HIV-1 Subtype Distributions
Demographic Data		
Age	X	X
Sex	X	X
Race/ethnicity	X	X
Transmission category for HIV infection	X	X
Country of origin	X	X
Current state of residence	X	X
State of residence at HIV diagnosis	X	X
Laboratory Data		
Specimen collection date associated with nucleotide sequence	X	X
HIV *pol* gene nucleotide sequence data	X	X
Mutation-specific assays	X	X
Previous HIV Testing Data		
Date of first HIV test	X	
Date of first positive HIV test (documented or self-reported)	X	
Date of last negative HIV test (documented or self-reported)	X	
Clinical Data		
Date of HIV diagnosis	X	
Date of AIDS diagnosis	X	
CD4 counts	X	
Dates of CD4 counts	X	
Viral load	X	
Dates of viral loads	X	
Antiretroviral agents used	X	
Start/end dates of antiretroviral agent use	X	
Opportunistic infection(s) diagnosed	X	
Date(s) of opportunistic infection diagnosis	X	

APPENDIX C

History and Timeline of MHS

2002: CDC funds four surveillance areas to conduct the Antiretroviral Drug Resistance Testing (ARVDRT) pilot project, which demonstrates the feasibility of using remnant sera from diagnostic testing to conduct HIV genotypic resistance testing.

2004: Through a four-year cooperative agreement, 22 CDC-funded HIV Incidence Surveillance (HIS) areas opt to also conduct Variant, Atypical, and Resistant HIV Surveillance (VARHS) using a protocol developed under ARVDRT.

CDC determines that VARHS is a non-research disease surveillance activity that does not require institutional review board approval or informed consent.

2007: CDC publishes first VARHS data in abstract presented at the 2007 Conference on Retroviruses and Opportunistic Infections.

2008: Through a five-year cooperative agreement, CDC funds 11 surveillance areas to conduct VARHS using the protocol developed in 2004.

CDC establishes a contract with the Stanford Clinical Virology Laboratory at Stanford University Medical Center (Palo Alto, CA) to conduct genotypic resistance testing for VARHS.

2009: CDC adapts the WHO global HIV-1 surveillance mutation list developed for interpreting transmitted drug resistance-associated mutations (TDRMs) for all HIV-1 subtypes and finalizes the CDC HIV-1 surveillance mutation list for evaluating the prevalence of TDRMs for subtype B, the predominant HIV-1 subtype in the United States.

2010: CDC publishes first VARHS analysis in peer-reviewed journal. (*AIDS*. 2010 May 15; 24(8):1203-12.)

2011: CDC does not renew the contract with the Stanford Laboratory and discontinues genotypic resistance testing through this laboratory. Genotypic resistance testing for VARHS transitions to a program reliant on VARHS-funded sites to collect nucleotide sequence data from commercial and private laboratories.

2012: CDC proposes expanding VARHS to include the use of molecular epidemiology approaches to describe the burden of HIV infection and supplement other HIV surveillance data. The VARHS program is renamed Molecular HIV Surveillance (MHS) to reflect these broader goals and objectives.

CDC also proposes expanding VARHS to include the collection of (1) ARV history use data for all new diagnoses of HIV infection and (2) nucleotide sequence data for all persons diagnosed with HIV infection, regardless of when the person was diagnosed or when the specimen (from which the sequence was obtained) was collected.

APPENDIX D

Glossary of Terms (unless otherwise noted, terms are limited to HIV)

Antiretroviral drug: a medication used to treat HIV infection and prevent HIV transmission.

Antiretroviral therapy: a combination of antiretroviral drugs administered consistently and therapeutically to treat HIV. It does not cure HIV infection, but controls HIV reproduction and transmission and boosts the immune system of the person in treatment.

Circulating recombinant form (CRF): an HIV strain with a mosaic structure of the genome consisting of two or more distinct subtypes that have been identified in at least three individuals who do not have direct, epidemiologically-linked infections. As of May 2012, 51 CRFs have been identified globally.

Drug resistance: the ability of HIV to continue to reproduce in the presence of antiretroviral drugs. Drug resistance can be acquired after exposure to antiretroviral drugs or transmitted from an HIV-infected person.

Drug resistance testing: testing the blood plasma of HIV-infected individuals to identify HIV drug resistance. Commonly used drug resistance tests include genotypic resistance testing (genotyping), phenotypic drug resistance testing (phenotyping), and virtual phenotypic drug resistance testing.

Enhanced HIV/AIDS Reporting System (eHARS): a browser-based HIV surveillance system deployed at state and local health departments. The data are collected in documents such as case reports, lab reports and death certificates. The health departments submit de-identified data electronically on a monthly basis to CDC's national database through a secure data network.

Electronic laboratory-based reporting (ELR): the electronic transfer of public health data from clinical laboratories to public health agencies in pre-established formats that do not require extensive human manipulation to add to a database. HL7 messaging is an example ELR format.

FASTA file: a standard, text-based format for nucleotide sequences. Each nucleotide sequence is preceded by a line starting with > and a description or name. Base pairs or amino acids are represented using single-letter codes.

Example:
>HumanATGGCACATGCAGCGCAAGTAGGTCTACAAGACGCTACTTCCCCTATCATAG
AAGAGCTTATCACCTTTCATGATCACGCCCTCATAATCATTTTCCTTATCTGCTTCCTA

Genotypic resistance testing: testing the blood plasma of HIV-infected individuals to detect the presence of mutations associated with drug resistance. Genotypic resistance assays compare the nucleotide sequences (e.g., the protease and reverse transcriptase genes of the *pol* region) of the infected person with a wild-type strain.

Health Information Exchange (HIE): the mobilization of healthcare information electronically across organizations within a region, community or hospital system. HIE provides the capability to electronically move clinical information among disparate health care information systems while maintaining the meaning

of the information being exchanged. The goal of HIE is to facilitate access to and retrieval of clinical data to provide safer, more timely, efficient, effective, patient-centered care.

HL7 messaging: a standard method of electronically transmitting laboratory results.

Molecular epidemiology of HIV: the application of molecular biology techniques (e.g. polymerase chain reaction-PCR, phylogenetic analyses of viral sequences) for the detection, characterization, and transmission of HIV to study the distribution and determinants of disease occurrence and health-related events in the human population.

Mutation: a genetic change that results in a viral strain that is different from the wild-type HIV strain. Mutations can occur naturally or in the presence of antiretroviral drugs. A mutation is described by a combination of letters and numbers (e.g., M41L). The first letter (M) represents the amino acid in the wild-type strain, the number (41) represents the amino acid position in the gene, and the last letter (L) represents the mutation.

Nucleotides: molecules that make up the structural basis of nucleic acids, such as DNA or RNA. Each nucleotide consists of a phosphate group, a sugar (ribose in RNA), and a set of nucleotide bases: adenine (A), cytosine (C), guanine (G), and thymine (T). Three nucleotides make up a codon, which represent a single amino acid, the building blocks of proteins.

Nucleotide sequence: the genetic code of nucleic acids (i.e., DNA and RNA).

Phylogenetic analysis: the process of studying the relationship between HIV strains through analysis of nucleotide sequences. Phylogenetic methods are used to detect closely related HIV strains (i.e., clusters) and graphically display them through phylogenetic trees.

Polymorphism: a genetic mutation that occurs naturally in the absence of antiretroviral drugs.

Recombinant form: a hybrid HIV strain created when two or more HIV strains of different subtypes are combined. See circulating recombinant form and unique recombinant form.

Secure data network (SDN): method of transmitting data across defined, secure boundaries.

Secure file transfer protocol (SFTP): a type of protocol that provides a set of rules that govern the syntax, semantics, and synchronization of communication across computer networks. SFTP encrypts both commands and data, requires certification on the sending or receiving end, and allows the secure transmission of passwords and sensitive information.

Transmitted HIV drug resistance: the transmission of a drug-resistant HIV strain from an infected person to an uninfected person, resulting in HIV drug resistance in the newly infected, drug-naïve person. The presence of mutations associated with transmitted drug resistance (i.e., transmitted drug-resistance–associated mutations, TDRMs) can be detected through genotypic resistance testing.

Transmitted drug resistance-associated mutations: HIV mutations that confer antiretroviral drug resistance.

Unique recombinant form (URF): a hybrid strain that is the result of recombination of two or more HIV subtypes that has not been identified elsewhere.

Viral load: an estimate of the amount of virus in an infected person's blood. For clinical HIV management, it is typically expressed as the number of HIV RNA copies calculated per milliliter of blood plasma.

Wild-type strain: an HIV strain that has not been exposed to antiretroviral drugs.

APPENDIX E

Acronyms

ACRF	Adult HIV Confidential Case Report Form
AES	Advanced Encryption Standard
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral therapy
ARV	Antiretroviral
ARVDRT	Antiretroviral Drug Resistance Testing
ASCII	American Standard Code for Information Interchange
CDC	Centers for Disease Control and Prevention
CD4	Cluster of differentiation 4
CLIA	Clinical Laboratory Improvement Amendments
CRF	Circulating Recombinant Form
CROI	Conference on Retroviruses and Opportunistic Infections
DFS	Dried fluid spots
DHAP	Division of HIV/AIDS Prevention
eHARS	Enhanced HIV/AIDS Reporting System
ELR	Enhancing Laboratory Reporting, Electronic laboratory reporting
HICSB	HIV Incidence and Case Surveillance Branch
HIS	HIV Incidence Surveillance
HIV	Human Immunodeficiency Virus
IAS-USA	International Antiviral Society-USA
INSTI	Integrase strand-transfer inhibitor
IRB	Institutional Review Board
LOINC	Logical Observation Identifiers Names and Codes
MHS	Molecular HIV Surveillance
NCHHSTP	National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
NEDSS	National Electronic Disease Surveillance System
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
ORP	Overall responsible party
PHIN	Public Health Information Network
PI	Protease inhibitor
S&C	Security and confidentiality
SDN	Secure data network
SFTP	Secure file transfer protocol
TDRM	Transmitted drug resistance-associated mutation
TTH	Testing and treatment history
URF	Unique recombinant form
VARHS	Variant, Atypical, Resistant HIV Surveillance
VL	Viral load
VPN	Virtual private network

The *Molecular HIV Surveillance* chapter of the *Technical Guidance for HIV Surveillance Programs* was revised and reviewed by staff within the CDC HIV and Incidence Case Surveillance Branch and the following health departments: Rory Angulo (Connecticut), Mary-Grace Brandt (Michigan), Mariama Gondo (Florida), Dan Gordon (New York), Tom Jaenicke (Washington), Michelle Porter (Texas), and Lucia Torian (New York City).

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