Attachment G. *Supplemental Surveillance Activity 2:* Variant, atypical and Resistant

HIV Surveillance (VARHS) Data Elements

Status: new
Description: These data elements will be an electronic extension of the case report forms **(Attachment C)**; as such, there is no new form for this activity.

Standard Variant, Atypical, and Resistant HIV Surveillance (VARHS) Data Elements OMB No. 0920-0573 Exp. XX/XX/XX

Name	Type	Lengt	Valid Value	Label
PrimaryIDType	Text	50	Text	Primary ID Type
PrimaryID	Text	14	Text	Primary ID
AlternateIDType	Text	50	PEMS_ClientID PEMS_FormID PCN HARS_CityNo Code-base Stateno Other Local ID	AlternateID Type
AlternateID	Text	50	Text	AlternateID
INELIG	Text	1	0 = Eligible (default) 1 = Confirmatory tests non-reactive or negative 2 = Diagnosed before specified time period 3 = ARV drugs 4 = Other	Eligibility of Case
ANONYM	Text	1	1=yes; 0=no	Anonymous Tester?
SITENUM	Text	50	Text; list of valid site numbers will be provided by each project area	Site Number
SITEEXT	Text	50	Text; for areas that have extensions, otherwise blank	Site Extention
YEAR	Text	50	YY	Year of Blood Draw
SEQNUM	Text	50	Text	Sequence Number
SPECIMENID	Text	50	Text	SpecimenTracking ID 14 character field, left zero filled positions 1-4 = area number positions 5-8 = site number positions 9-10 = last 2 digits of year of draw date positions 11-14 = consecutive numbers for each participant enrolled, zero filled on left The last four digits need to be in ascending order for a given year, but not necessarily consecutive.
ACCESNUM	Text	15	Text	Laboratory Accession Number
DRAWDTTM	Text	50	YYYYMMDDHHMM	Date and Time of Draw Date
TUBETYPE	Text	1	1 = Clot tube (Red top tube - for serum) 2 = SST tube (Red and gray tiger top tube - for serum) 3 = EDTA tube (Purple top tube - for plasma) 4 = ACD tube (Yellow top tube - for plasma) 5 = PPT tube (White top tube - for plasma) 6 = CPT tube (Blue and black tiger top tube - for cells or plasma) 7 = Finger stick - no tube 9 = Other 0 = No information provided	Type of Tube Used for Blood Collection
BLDCOMP	Text	1	1= Serum 2= Plasma 3= Whole anticoagulated blood 4= Dried Blood Spot 5= Cells 6= Dried Serum Spot	Type of Specimen Sent from Collection Site

Name	Type	Lengt	Valid Value	Label
			7= Dried Plasma Spot 8= Clotted blood	
BLDLAB	Text	1	0= No information provided 1= Serum 2= Plasma 3= Whole anticoagulated blood 4= Dried Blood Spot 5= Cells 6= Dried Serum Spot 7= Dried Plasma Spot 8= Clotted blood	Type of Specimen Sent for Resistance Testing
COURDTTM	Text	50	YYYYMMDDHHMM	Date and Time of Courier Pick-up From Collection
DRECDTTM	Text	50	YYYYMMDDHHMM	Date and Time of Receipt in Diagnostic Lab
CENTDTTM	Text	50	YYYYMMDDHHMM	Date and Time of Centrifugation
SEPDTTM	Text	50	YYYYMMDDHHMM	Date and Time of Separation
VOLUME	Text	3	Text	Volume of Serum/Plasma After Separation
COND	Text	1	Enter highest relevent number 0= no hemolysis 1= low hemolysis 2= moderate hemolysis 3= high hemolysis 4= lipemic 5= contaminated	Condition of the Serum/Plasma
SpecimenFrozen	Text	50	1=yes; 0=no	Was the Specimen Frozen Before Aliquoting?
FREZ1DTM	Text	50	YYYYMMDDHHMM	Date and Time of First Freeze of Specimen before Aliquoting
THAW1DTM	Text	50	YYYYMMDDHHMM	Date and Time of First Thaw of Specimen before Aliquoting
FREZ2DTM	Text	50	YYYYMMDDHHMM	Date and Time of Second Freeze of Specimen before Aliquoting
THAW2YN	Text	1	1=yes; 0=no	Were There Two or More Thaws of Specimen before Aliquoting?
EIADTTM	Text	50	YYYYMMDDHHMM	Date and Time of First Reactive EIA
ALIQDTTM	Text	50	YYYYMMDDHHMM	Date and Time of Aliquoting
VOLGENO	Text	3	Text	Volume Aliquoted for Genotyping
GFRZ1DTM	Text	50	YYYYMMDDHHMM	Date and Time of First Freeze of Genotyping Aliquot
GTHW1DTM	Text	50	YYYYMMDDHHMM	Date and Time of First Thaw of Genotyping Aliquot
GFRZ2DTM	Text	50	YYYYMMDDHHMM	Date and Time of Second Freeze of Genotyping Aliquot
GTHAW2YN	Text	1	1=yes; 0=no	Were there 2 or More Thaws of Specimen Before Aliquoting? (Specimen for Genotyping)
VOLBACK	Text	3	Text	Volume Aliquoted for Back-up Specimen
BFRZ1DTM	Text	50	YYYYMMDDHHMM	Date and Time of First Freeze of Back-up Specimen
BTHW1DTM	Text	50	YYYYMMDDHHMM	Date and Time of First Thaw of Back-up Specimen
BFRZ2DTM	Text	50	YYYYMMDDHHMM	Date and Time of Second Freeze of Back-up
BTHAW2YN	Text	1	1=yes; 0=no	Were there 2 or More Thaws Before Aliquoting?
CNPOSDAT	Text	50	YYYYMMDDHHMM	Date of Western Blot or Other Confirmatory Positive Test
GSHPDATE	Text	50	YYYYMMDD	Date of Shipment to Geno Lab
GRESDATE	Text	50	YYYYMMDDHHMM	Date and Time Genotyping Results Received at
NOTSENT	Text	1	0= Specimen was sent (default) 1= QNS 2= Viral Load Not detectable	If Specimen was not sent for genotyping, what was the reason for this?

Name	Type	Lengt	Valid Value	Label
			3= Low Viral Load 4= Lost 5= Other	
AMPLIFY	Text	50	0= Yes (default) 1= No 8= Not attempted or unavailable for attempt 9 = Unknown	Did the Specimen Amplify?
SPOTDTTM	Text	50	YYYYMMDDHHMM	Date and Time of Spotting
DRYTIME	Text	4	Text	Length of Drying Time (Hours)
DRYLOC	Text	50	1 = Standard Laboratory 2 = Mobile Laboratory 3 = Field 4 = Clinic 5 = Other	Drying Location:
SPECIFYLOC	Text	50	Text	Specify the drying location if DRYLOC = Other
DIAGDFS	Text	4	1 = HIV Diagnostic Lab 0 = Site other than HIV Diagnostic Lab	Where was dried fluid spot made?
RNALATER	Text	50	1 = Yes 2 = No 9 = Unknown	Was Specimen Collection Card Pretreated with RNALater?
LocationType	Long	4	1 = DFS Collection Site 2 = Public Health Laboratory 3 = Other Laboratory 4 =Storage Facility 5 = Hospital 6 = Other 9 = Unknown	Type of Site Where Specimen Was Handled
StoreTemp	Long	4	1 = Room Temperature 2 = 4ºC 3 = -20ºC 4 = -70ºC	Storage Temperature at Site
StoreDTM	Text	50	YYYYMMDDHHMM	Date and Time of Refrigeration or Freeze and Desiccant Addition at Site
StoreDes	Long Integer	4	1=yes; 0=no	Was Desiccant Changed Before or After Transport from This Site to Next Site?
TransMeth	Long Integer	4	1 = US Mail 2 = FedEx/UPS/DHL 3 = Local Courier 4 = Lab/Health Department Staff 5 = Other	Method of Transport from This Site to Next Site
TransDTM	Text	50	YYYYMMDDHHMM	Date and Time of Removal from Refrigeration or Freeze at Site
TransCool	Long Integer	4	1=yes; 0=no	Was cooler or dry ice used for transport?
Nucleic Acid Sequence	Text	3000	Text	Nucleic Acid Sequence

Public reporting burden of this collection of information is estimated to average 5 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to CDC, Project Clearance Officer, 1600 Clifton Road, MS D-74, Atlanta, GA 30333, ATTN: PRA (0920-0573). Do not send completed form to this address.

Guidance for Variant, Atypical, and Resistant HIV Surveillance

October 31, 2006

DRAFT

HIV Incidence and Case Surveillance Branch
Division of HIV/AIDS Prevention
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention

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1.0 Variant, Atypical, and Resistant HIV Surveillance Overview

1.1 Objectives

1. Incorporate surveillance of transmitted strains of variant, atypical, and resistant HIV into routine HIV surveillance activities by:
    a. amplifying and sequencing relevant regions of the HIV *pol* gene from remnant HIV diagnostic specimens to evaluate mutations associated with HIV drug resistance and HIV-1 subtypes among all persons newly diagnosed with HIV
    b. evaluating mutations associated with resistance and HIV-1 subtype in the subset of diagnostic specimens with evidence of recent infection determined by laboratory testing using the serologic testing algorithm for recent HIV seroconversion (STARHS) or another CDC-approved method

2. Provide HIV drug resistance data and HIV-1 subtype data to assist local HIV prevention and treatment program planning and evaluation.

1.2 Methods

Variant, atypical, and resistant HIV surveillance (VARHS) evaluates the prevalence of HIV drug resistance and HIV-1 subtypes among individuals newly diagnosed with HIV in public health settings and other clinical and diagnostic settings collaborating with the state, county, or large city Departments of Health. Ideally, specimens from all individuals newly diagnosed with HIV in the state, county, or large city should be included. If sufficient volume is available, aliquots of remnant sera will be set aside for HIV drug resistance testing from each blood specimen drawn for HIV diagnosis from eligible persons in participating sites. For individuals meeting VARHS criteria, HIV genetic sequencing (genotyping) will be performed on the reverse transcriptase and protease regions of the HIV *pol* gene to detect the presence of mutations associated with HIV drug resistance. HIV-1 subtype will also be identified based on the *pol* gene sequence.

The CDC Office of the Director awarded a non-research determination to variant, atypical, and resistant HIV surveillance (VARHS) on June 25, 2004 (see Appendix A); VARHS was incorporated nationally into routine HIV surveillance as of July 1, 2004. The document that serves as the basis for the Federal Regulations for protecting human research participants is Title 45 of the Code of Federal Regulations part 46 (45 CFR 46, available at http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm). Subpart A, subsection 46.101c states, “the (Federal) Department or Agency heads retain final judgment as to whether a particular activity is covered by this policy”. “This policy” refers to the requirements for human

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subjects protection review for research protocols under the 45 CFR 46 regulations. *Disease surveillance* is one of the four major public health practice activities that usually involve data collection, but are not research and do not need review by an Institutional Review Board (IRB) according to 45 CFR 46. VARHS was determined to be a disease surveillance activity by CDC, the appropriate federal agency, and thus does not require IRB review. This finding does not supersede state or local laws or regulations that may require IRB review, or notification to an IRB, for public health surveillance activities.

HIV drug resistance testing for VARHS is performed utilizing standard tests that are widely used clinically. These tests are not experimental and do not require specific informed consent. The use of a remnant diagnostic specimen for drug resistance testing is routinely performed without informed consent for tuberculosis, urinary tract infections, and sexually transmitted diseases, and drug resistance results are collected as part of public health surveillance for these and other conditions.[3,5,7] Like drug resistance testing in other infectious disease surveillance systems, testing diagnostic specimens for HIV drug resistance and HIV-1 subtype surveillance is not experimental and does not require informed consent. Project areas must notify individuals that a HIV DR test may be performed on the diagnostic specimen.

Genotyping results and information from the HIV surveillance case report will be used to make population-based estimates of the prevalence of HIV drug resistance and HIV-1 subtypes among individuals newly diagnosed with HIV. Prevalence estimates will also be made for relevant demographic groups and HIV exposure categories. In areas performing variant, atypical and resistant HIV surveillance and HIV incidence surveillance, evaluation of recent HIV infection using a testing history and STARHS (Serologic Testing Algorithm for Recent HIV Seroconversion) will be collected as part of HIV surveillance for most newly diagnosed individuals. HIV incidence results in combination with the sequencing result, testing history data, and clinical information about disease progression at diagnosis will be used for population-based HIV estimates of the incidence of transmitted HIV drug resistance and HIV-1 subtypes. HIV sequence information may also be used to track the spread and clustering of atypical HIV strains of interest nationally.

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For newly diagnosed individuals whose specimens are amplified and genotyped successfully, an individual hard copy report of results will be made available by the health department to a provider designated by the individual.

1.3 Participating Surveillance Areas

Listed below are the areas funded as of April 2004 to participate in variant, atypical, and resistant HIV surveillance (including sites that participated in the antiretroviral drug resistance testing (ARVDRT) evaluation project).

1. Chicago Department of Public Health
2. Colorado Department of Public Health and Environment
3. District of Columbia Department of Health
4. Florida Department of Health
5. Illinois Department of Public Health
6. Indiana State Department of Health
7. Louisiana Office of Public Health
8. Maryland Department of Health and Mental Hygiene
9. Massachusetts Department of Public Health
10. Michigan Department of Public Health
11. Mississippi State Department of Health
12. New Jersey Department of Health and Senior Services
13. New York City Department of Health and Mental Hygiene
14. New York State Department of Health
15. North Carolina Department of Health
16. Pennsylvania Department of Health
17. Puerto Rico Department of Health
18. Seattle and King County Public Health
19. South Carolina Department of Health
20. Texas Department of State Health Services
21. Virginia Department of Health
22. Washington State Department of Health

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2.0 Introduction

2.1 Background

The Centers for Disease Control and Prevention (CDC) is responsible for maintaining a national surveillance system that provides data on the HIV/AIDS epidemic that can be used for national, state, and local public health HIV/AIDS prevention program planning and evaluation. Clinical and laboratory testing information data items have been incorporated into HIV/AIDS surveillance based on their utility on a population basis in characterizing the HIV epidemic or triggering particular public health action. HIV genetic sequence data based on the *pol* gene has now been incorporated into HIV/AIDS surveillance to evaluate the distribution of HIV-1 subtypes and mutations associated with HIV drug resistance among individuals newly diagnosed with HIV and the subset of recently infected persons.

In the late 1990s, several new nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), and protease inhibitors (PI) were approved for treating HIV infection in the United States. These newer drugs, combined with the NRTIs already available, provide clinicians with a variety of choices for initiating and changing antiretroviral treatment for patients infected with HIV-1. A panel representing international expertise in antiretroviral research and HIV patient care convened by the International AIDS Society – USA [13] and a Public Health Service interagency work group with expert consultation [9] have continually updated recommendations for prophylaxis or therapy that, for specific purposes, include all of the antiretroviral drugs currently approved by the FDA and in use in the US, and for HIV drug resistance testing.

The therapeutic purposes of antiretroviral drugs include prophylaxis after known occupational exposure (post-exposure prophylaxis), vertical transmission prophylaxis, treatment of primary infection (four to seven weeks after infection), initial treatment from early (little or no immunological damage) to late infection (substantial immunological damage), and changes in treatment regimens depending on virological and immunological response.[10,11,4,9,6,13] Clinical trials are being performed to evaluate pre-exposure prophylaxis with antiretroviral

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drugs. Studies have demonstrated that HIV drug resistance results (both genotype and phenotype) can be used to predict clinical outcome and to guide drug treatment choices.[6]

CDC is currently working with state and local health departments to integrate VARHS into routine HIV core surveillance similar to the way tuberculosis molecular surveillance was incorporated into tuberculosis surveillance. Like other public health surveillance activities, CDC's human subject protection process determined that the implementation of variant, atypical, and resistant HIV surveillance is not research (Appendix A).

2.2 Justification and Surveillance Usefulness

Studies have shown that *pol* gene sequencing results indicating the presence of mutations known to be associated with HIV drug resistance predict phenotypic sensitivity to antiretroviral drugs and clinical response.[6,9,13] VARHS supports the evaluation of HIV drug resistance (HIVDR) and factors associated with resistance in persons newly diagnosed with HIV in participating areas. Previous surveys have been based on convenience samples; VARHS is the first large surveillance system in the US designed to evaluate all persons diagnosed in participating sites in successive years. Representative sampling and ongoing collection of data through routine surveillance will provide information on trends in transmission of HIVDR. VARHS will determine the distribution of viral genotypes among persons newly diagnosed with HIV. Analyses will support evaluation of first-line HIV antiretroviral drug treatment and prophylaxis strategies in participating geographic areas by providing information to clinicians, pharmaceutical researchers, and public health authorities making treatment recommendations and developing new treatments. Information on the distribution of HIV-1 subtypes in the U.S. and in specific geographic areas will also be provided by VARHS, and will support selection of diagnostic and clinical tests appropriate for use with various HIV-1 subtypes, and the development of vaccines. Finally, phylogenetic analysis of the sequences generated by VARHS will allow investigation of the spread or clustering of atypical strains of interest, and contribute to analyses of evolution of HIV in the U.S. and worldwide.

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2.3 Objectives

1. Incorporate surveillance of transmitted strains of variant, atypical, and resistant HIV into routine HIV surveillance activities by:
    a. amplifying and sequencing relevant regions of the HIV *pol* gene from remnant HIV diagnostic specimens to evaluate mutations associated with HIV drug resistance and HIV-1 subtypes among all persons newly diagnosed with HIV
    b. evaluating mutations associated with resistance and HIV-1 subtype in the subset of diagnostic specimens with evidence of recent infection by laboratory testing using the serologic testing algorithm for recent HIV seroconversion (STARHS) or another CDC-approved method

2. Provide HIV drug resistance data and HIV-1 subtype data to assist local HIV prevention and treatment program planning and evaluation.

2.4 Implementing Variant, Atypical, and Resistant HIV Surveillance Guidance

This guidance is designed to provide assistance to HIV/AIDS core surveillance areas on implementing variant, atypical, and resistant HIV surveillance (VARHS). Guidance is provided on the design of the surveillance system, the identification of cases for testing, specimen collection and transport for HIV genetic sequencing and other HIV drug resistance tests, data management, confidentiality and security procedures, and personnel procedures. The appendices and references include supporting documentation such as a non-research determination by CDC, VARHS flow charts, specimen handling and shipping procedures, and guidance on the data elements to be used in evaluating HIV drug resistance and HIV-1 subtype prevalence nationally and in sub-populations.

VARHS will generally be implemented in areas already performing HIV incidence surveillance. It is recommended that HIV incidence surveillance procedures be in place before VARHS implementation is planned in detail. In some circumstances, simultaneous implementation of both types of surveillance may be suitable, but the default is for VARHS implementation to follow the implementation of HIV incidence surveillance. Areas should consult their CDC HIV incidence surveillance epidemiologist and the VARHS project officer about the appropriate time to plan and implement VARHS. In addition, prior to VARHS implementation, a site visit must

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be conducted by CDC. Sites should not begin collecting samples for VARHS until they have been approved to begin implementation by the CDC VARHS Project Officer.

At the end of selected sections of this document, a task box, like the one shown below, titled "VARHS Implementation Task" will provide guidance on the specific task that the surveillance area will need to address in order to implement variant, atypical, and resistant HIV surveillance. A description of the procedures to be used in an area to address the task should be included as part of the area-specific version of this guidance which may be submitted to CDC by the VARHS coordinator. Completion of the tasks is a key consideration in the successful implementation of VARHS.

SAMPLE VARHS Implementation Task

Variant, atypical, and resistant HIV surveillance areas should complete each implementation task appearing at the end of selected sections in this document.

3.0 Variant, Atypical, and Resistant HIV Surveillance Methods: Population and Design

3.1 Inclusion Criteria

- Specimens from all newly diagnosed HIV cases tested confidentially and eligible to be reported to the HIV case surveillance system are included in VARHS.

3.2 Exclusion Criteria

- Any case that has had a documented positive HIV test >3 months (before the specimen collected for VARHS) is excluded from VARHS.
- Any case with a previous specimen successfully sequenced for VARHS is excluded from HIV sequencing of an additional specimen in VARHS
- Any case known to have had previous exposure to antiretroviral drugs (before collection of the specimen for VARHS).

3.3 Surveillance Design

Variant, atypical, and resistant HIV surveillance is an extension of the existing national population-based HIV/AIDS case surveillance system. With over 20 years experience with case

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surveillance, state and local health department partners and CDC will use the case surveillance infrastructure to collect the information necessary to estimate the prevalence of transmitted HIV drug resistance and HIV-1 subtypes. In addition to data collected in the current case surveillance system, variant, atypical, and resistant HIV surveillance requires an aliquot of the remnant blood specimen made from an HIV diagnostic test or a follow-up test such as a confirmatory test made within three months of the original HIV diagnosis (Appendices 2 and 3).

3.4 Obtaining Eligible HIV-Positive Specimens

To minimize the possibility that a newly diagnosed individual might begin taking antiretroviral drugs before a specimen is obtained, HIV genetic sequencing for VARHS must be performed on an HIV-positive specimen collected at HIV diagnosis or from a follow-up HIV diagnostic blood draw no more than three months after HIV diagnosis. If volume and logistics permit, a remnant specimen for VARHS will be obtained from all eligible confirmed HIV-positive diagnostic specimens. A follow-up specimen drawn no more than three months from HIV diagnosis may also be used. Specimen types suitable for VARHS include serum, plasma, and blood. The use of dried fluid spots (DFS) for VARHS is currently being evaluated as an alternative specimen collection type and is a separately funded activity; areas that are not funded for this evaluation should not collect DFS specimens. In each surveillance area, laboratories that could potentially participate in VARHS will be identified from a review of local HIV surveillance data and laboratory licensing records.

In practice, VARHS will usually begin in public health laboratories working closely with the health department. Clinical facilities with their own HIV diagnostic laboratories may also be recruited for participation in VARHS. National commercial reference laboratories and other private laboratories where HIV diagnostic or clinical testing is performed can also participate in VARHS if resources are available to allow remnant specimens to be processed within the time frames described in the sections below.

The default practice for VARHS is that eligible specimens tested at or shipped to the central public health laboratory or laboratories in the area are shipped by the central laboratory for HIV

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VARHS testing. However, selected laboratories may ship eligible specimens for VARHS directly if the health department determines that the procedure will save resources and labor.

No funds are currently available from CDC to reimburse commercial reference laboratories for VARHS specimen handling costs on a national basis. The need for, and use of, reimbursement to local commercial and other private laboratories will be determined by each surveillance area and made available by the area as resources allow. The mechanism and type of reimbursement, if any, will be established locally, based on local policies. Shipping costs associated with sending specimens from state public health laboratories to the genotyping laboratory should be budgeted in the cooperative agreements CDC has with each participating area.

VARHS Implementation Task 3.4.A

Variant, atypical, and resistant HIV surveillance areas should identify laboratories required to report HIV positive tests to their HIV/AIDS surveillance system, the total number of new HIV positive diagnoses made annually in each laboratory, and the number of HIV positive specimens suitable for VARHS (plasma, serum, or blood) from which new HIV diagnoses are made annually in each laboratory.

3.5 Determining Eligibility and Obtaining and Handling VARHS Specimen Aliquots

Specimen handling and transport procedures should be decided by the public health laboratory and blood-drawing sites. If necessary, procedures can be modified when new aspects of a surveillance system are instituted. Sections under 3.5 describe tube types, transport times, and processing times that are optimal for VARHS. Decision-makers should take these factors into account when considering local procedures. Decisions on specimen handling and transport should be made primarily to optimize HIV diagnostic testing and the best use of local resources for major public health priorities; obtaining optimal specimens for VARHS has a lower priority.

One or more central public health laboratories will generally process and ship VARHS specimens to the genotyping laboratory. The project area VARHS coordinator may also agree that some VARHS specimens may be processed and shipped directly from selected non-public-

health laboratories if fewer resources and less labor are required for direct shipment and provided standard procedures are followed. These agreements should be discussed with the CDC project officer. Detailed shipping procedures for serum and plasma specimens can be found in Appendix D.

Since the use of dried fluid spots (DFS) for HIV genetic sequencing is still uncommon and is being evaluated by a limited number of public health departments as of July 2006, DFS handling procedures are not included in the main body of this guidance or in the VARHS shipping procedures appendix (Appendix D).

3.5.1. Tube type for HIV diagnostic specimens

Decision on tube type used for HIV diagnostic blood draws and follow-up specimens should be made on the basis of local diagnostic and surveillance needs and available resources. If changes are being considered to current practice, it should be noted that to ensure sufficient volume for additional HIV surveillance uses including VARHS, the HIV diagnostic blood draw would be at least eight-ml (optimal volume is ten-ml), drawn into a red-top Vacutainer clot tube or Serum Separator tube (SST). Eight- or ten-ml tubes with anticoagulant, or Plasma Separator tubes (PST), are suitable for diagnostic or follow-up specimens from which remnant plasma will be aliquoted for VARHS.

3.5.2. Specimen handling

After the blood draw and prior to serum or plasma separation, it is optimal to store the tube of blood at room temperature. The blood draw and specimen transport should be timed so that specimens arrive at the HIV testing laboratory and are processed (separated, aliquoted, and frozen) within 96 hours from the draw. Specimens processed up to 96 hours after the blood draw are still likely to be amplifiable for genetic sequencing. Specimens processed after that period may have a reduced likelihood of amplification, but should still be sent for VARHS.

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3.5.3. Serum and plasma processing

During separation, it is recommended both for the purposes of HIV testing and for VARHS that the specimens be centrifuged to remove red blood cells and prevent hemolysis. (Successful HIV amplification for sequencing is less likely with hemolysed specimens.) After separation of the serum, samples will optimally be maintained constantly at refrigeration temperature (4 degrees C) or on ice until samples are EIA tested and eligible aliquots are frozen for potential use in VARHS.

3.5.4. Diagnostic and clinical testing and freezing of serum or plasma aliquots

To maximize chances for successful amplification for genetic sequencing, HIV diagnostic testing or other relevant clinical testing will optimally begin immediately after centrifugation. Sera or plasma should be kept on the bench at room temperature for as short a time as possible before being returned to the refrigerator or placed on ice. If volume appears sufficient for the purposes of all basic laboratory tests and other local priorities such as archiving, for HIV incidence surveillance, and for VARHS, a one-ml aliquot from all EIA reactive samples will be frozen at –70 degrees C as soon as possible following the first reactive EIA. At this point, the aliquot is still considered a HIV diagnostic specimen; it will not be defined as a VARHS specimen until the specimen is confirmed as HIV positive, and until it is clear that the needs for serum for all higher priority laboratory tests, including diagnostic HIV testing and HIV incidence testing, have been fulfilled. Aliquots frozen as potential VARHS specimens should be thawed at any time if needed for higher priority tests. The freeze-thaw cycle will not affect the HIV diagnostic test results.

Optimally, the –70 degrees C freeze will occur within 96 hours of the blood draw. Preliminary data from four public health departments in CDC's ARVDRT pilot evaluation suggests that sera frozen within 96 hours of the blood draw have a great than 90% chance of having HIV amplified for HIV genetic sequencing. However, specimens frozen beyond 96 hours may still be sent for HIV genetic sequencing.

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Once frozen, specimens for genotyping should not be thawed until they reach the genotyping laboratory. A freeze-thaw cycle will reduce the chance of successful amplification for genotyping.

3.5.5. Determining eligibility/ handling of specimens

When specimens have been confirmed as HIV-positive by Western blot or any other method acceptable to the Department of Health, all HIV-negative specimens should be handled according to standard laboratory procedures. The VARHS coordinator will identify which of the remaining confirmed positive frozen aliquots are eligible for VARHS by matching information with the laboratory, HARS, or other HIV surveillance databases. Aliquots associated with individuals found to be diagnosed with HIV greater than three months previously, or who have specimens already tested as part of VARHS from another site, are not eligible for VARHS and should be handled according to standard laboratory procedures. Frozen aliquots from specimens yielding indeterminate or negative Western blot results will be handled according to standard laboratory procedures.

3.5.6. Cryovials and Aliquots

Cryovials for the sera or plasma aliquoted for VARHS should be two ml in size, polypropylene, with screw caps and external threads. If labels will not be not used, the tube should have a writing area. After the VARHS ID is generated locally, the cryovials should be labeled with the appropriate permanent markers or pre-typed labels. Labels that will stick on frozen tubes can be supplied at no cost from CDC, or the VARHS ID may be written directly onto the appropriate writing area with permanent marker.

Ideally, one ml per specimen is to be aliquoted for HIV genetic sequencing to be sent to the CDC-contracted Stanford University laboratory or the laboratory contracted by the local health department. When the volume is limited, priority is given first to the laboratory's standard operating procedures for HIV diagnostic and clinical testing and serum archiving, second to HIV incidence surveillance activities, and third to VARHS. If serum volume is insufficient to meet all these requirements, basic diagnostic and clinical

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and archiving needs should be met first, HIV incidence surveillance needs second, HIV genetic sequencing for VARHS third, and any site-specific VARHS back-up specimen needs last. If less than one ml is available for genetic sequencing when all other needs have been met, the specimen should still be sent for sequencing.

3.5.7. Specimen information to be recorded in VARHS specimen log or database

The diagnostic testing laboratory should maintain a VARHS specimen tracking log or database to provide information for evaluation if problems in amplification for genetic sequencing, specimen mix-up, or specimen contamination occur. Recommended elements of information are listed in Appendix E. A MS-Access database is supplied by CDC for data entry of this information.

Information may be recorded first on individual lab slips, specimen labels, or on batch slips. Batch slips may be used for initial recording of information applicable to batches of specimens, such as blood draw site, lists of patient identification numbers for specimens transported in a batch, time/date of receipt in the diagnostic laboratory, lab accession number range for a batch, time/date of centrifugation, time/date of separation, time/date of first positive EIA, time/date of aliquoting, time/date aliquots were frozen. All or some of this information may also be captured from in-house laboratory databases. Information will be transferred to the log or database for each individual specimen that is confirmed as HIV positive and ***not*** identified as ***in***eligible. Laboratory or Health Department personnel may work with CDC to develop methods of information transfer to minimize duplicate recording of information.

3.5.8. Shipment to the VARHS genotyping laboratory

For persons not previously reported to HARS/eHARS with a diagnostic date > 3 months earlier than the blood draw, not otherwise found to have a previous positive specimen > 3 months earlier than the blood draw, and not found to have a previous specimen successfully sequenced in VARHS, surveillance staff will compile a list of specimens to be packaged and shipped by the state or local public health laboratory to the genotyping

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laboratory. Specimen ID numbers should be recorded on the specimen manifest; a copy of the manifest should be kept by the VARHS coordinator.

Shipments to the genotyping laboratory should take place at least monthly. Specimens will be handled, packaged, and shipped according to the CDC VARHS laboratory shipping protocol (Appendix D). Specimens shipped as diagnostic specimens and using dry ice for packing must follow the procedures for packing and shipping specimens using dry ice (Appendix D).

VARHS Implementation Task 3.5.A

Variant, atypical, and resistant HIV surveillance areas should include a detailed laboratory procedures component in the local version of this guidance. Procedures described should include information on obtaining and processing specimens, determining eligibility, recording specimen tracking variables for local use, storing specimens, and shipping specimens. All procedures should be developed by the VARHS coordinator in consultation with participating laboratories.

VARHS Implementation Task 3.5.B

Variant, atypical, and resistant HIV surveillance areas should identify the laboratories that will transport specimens to a central public health laboratory in the area for VARHS shipping, and the laboratories, if any, that will ship specimens directly to the genotyping laboratory. The local version of this guidance should include descriptions of the procedures for the VARHS coordinator to receive specimen tracking information monthly, to receive shipping manifests whenever shipments are made, and to communicate at least quarterly with laboratories making the shipments.

3.6 Returning VARHS Results to Individuals

HIV genetic sequencing is often performed for clinical purposes for patients receiving treatment for HIV, and clinicians who treat patients for HIV are familiar with the formats in which results are reported for individual patients. Individual VARHS results will be made available in such a format. Because interpretation of results requires familiarity and training, VARHS results are not returned directly to individuals, but to their providers.

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When newly diagnosed HIV-positive clients return for post-test counseling or follow-up, they should receive a brief explanation of VARHS. Counselors should instruct clients on how to designate a provider to receive VARHS results if they wish to do so, either at that time or later. Clients will also be informed that the information gathered through VARHS will be used to help understand transmission of HIV and the transmission of drug resistant strains in the local geographic area. A hard-copy report similar to clinical HIV drug resistance testing reports with which physicians are familiar will be available to the Health Department from the genotyping laboratory no more than one month after the specimen is received in the genotyping laboratory. The counselor should inform the client of the time period before results will be sent to the provider from the Health Department.

If the blood draw that produced a VARHS remnant specimen was performed at a clinical site to which a participant is returning for medical consultation or care, the health department may arrange for the VARHS individual report to be returned directly to the participant's provider at that clinical site.

VARHS Implementation Task 3.6.A

Arrangements should be described in detail in local variant, atypical, and resistant HIV surveillance guidance for clients to identify a provider to whom the client's VARHS report should be sent. The arrangements should include a method for the client to designate a provider at the time of the encounter or at a later time (up to five years is suggested). Methods for designating a provider used in pilot areas include a telephone number that can be called or a card that can be sent to the Health Department.

3.7 Required Data Elements

Appendix E outlines the minimum set of data elements and the purpose of each element required for evaluating HIV drug resistance and HIV-1 subtype prevalence in the population and in subgroups within the population. Appendix E also describes the recommended specimen tracking elements that allow evaluation of potential or actual problems with HIV amplification for genetic sequencing, contamination, or specimen duplication.

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3.7.1. Demographic and clinical data

No demographic or clinical data are collected specifically for VARHS. Relevant demographic and clinical data are merged in from the main HIV/AIDS reporting system (HARS) database or equivalent. The demographic data used in the HIV drug resistance prevalence estimates include age, sex, race/ethnicity, region of origin, and exposure categories associated with HIV infection. The elements will allow for prevalence estimates of HIV drug resistance and HIV-1 subtypes among persons newly diagnosed with HIV to be made in major subgroups nationally, and also locally if numbers are sufficient. These elements will also allow weighting of estimates to take into account the characteristics of newly diagnosed persons in the area not included in VARHS.

3.7.2. HIV incidence data and related data items for calculation of the incidence of transmitted HIV drug resistance

Measures of transmitted HIV drug resistance and HIV-1 subtypes in a specific year will focus on the population recently infected with HIV and diagnosed in that year. HIV incidence surveillance data (results from a test using the STARHS algorithm and assay type) and date of the last negative HIV test, if available in the HIV surveillance system, are the key elements for this estimate. CD4 and viral load counts, and dates of occurrence of opportunistic infections and other AIDS-defining conditions, may also be used for modeling to estimate incidence of transmitted variant and resistant strains of HIV in past years. Demographic and clinical data from HARS will be used to weight these estimates.

3.7.3. Data used for VARHS eligibility determination

HARS and other surveillance databases will serve as the primary means of screening for eligibility by date of first positive HIV test and for previous use of ARV drugs. Matching of specimen information with HIV surveillance databases will be attempted to evaluate whether the participant was reported to the HIV surveillance systems with a positive HIV test more than three months before the relevant blood draw. Matching with routine laboratory surveillance databases containing HIV test information may also be possible to evaluate whether a participant has had a previous positive result greater than three

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months before the current specimen was drawn. However, shipment of specimens for VARHS should not be delayed for more than one month for the purposes of such evaluation, given the commitment to make reports available to providers in "real time" (if possible, within six weeks of the HIV diagnostic test or other blood draw).

Information on dates of HIV diagnostic test results and dates of prescription of antiretroviral drugs may not be available in HIV/AIDS surveillance reports until after VARHS specimens are shipped. Once these data become available, the results may define an individual case as VARHS-ineligible after HIV genetic sequencing is performed for VARHS. Persons diagnosed with HIV more than three months before the blood draw for VARHS, or receiving antiretroviral drugs before the blood draw for VARHS, will be excluded from the VARHS analysis.

It should be noted that, in contrast to HIV incidence estimates, persons diagnosed with AIDS and HIV simultaneously are not excluded from the estimate of HIV drug resistance prevalence or HIV-1 subtype prevalence among persons newly diagnosed with HIV.

3.7.4 Laboratory data

The VARHS database includes laboratory tracking information described in Appendix D.

The VAHRS database contains information on whether HIV could be amplified from each specimen. Stanford University lab or the local genotyping laboratory will transmit information on amplification to the Health Department and to CDC. For specimens from which HIV was successfully amplified and genotyped, the genotyping laboratory will transmit the complete sequence of the protease region, and at least the first 240 codons of the reverse transcriptase (RT) region, both as nucleotides and amino acids. The laboratory will also transmit a separate list of all mutations (associated with HIVDR and not associated with HIVDR) in any strain that differs from the reference strain used at the laboratory. The conversion of the sequence information into HIV drug resistance and

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subtype variables in the VARHS database by a CDC program is described in subsequent sections.

Hard copy laboratory reports that will be accessible to the health care provider of the client's choosing will be generated by the genotyping laboratory and sent to the Health Department. The Health Department will act as a repository for these hard copy resistance testing reports for a locally specified period of time from the diagnostic HIV test date.

VARHS Implementation Task 3.7.A

Variant, Atypical, and Resistant HIV Surveillance areas should review Appendix 5 and review the percentage of HIV reports that record HIV/AIDS surveillance elements used for analysis in VARHS. Because all the demographic and clinical data elements used are key elements for general HIV surveillance, areas may wish to explore methods to increase reporting of these elements. For instance, some pilot areas have added specific elements such as country of birth to their counseling and testing system laboratory request forms.

4.0 Confidentiality and Security of Variant, Atypical, and Resistant HIV Surveillance Data

Only data that are part of, or are being incorporated into, the routine HIV/AIDS surveillance system will be used. The only identifying information held in local public health departments will be information routinely held in the HIV/AIDS surveillance system or their equivalent. This information is governed by the U.S. Department of Health and Human Service's (DHHS) manual on security and confidentiality.[2] Policies and procedures, based on these guidelines and local laws, are already in place at state and local health departments and are used to secure hard copy and electronic information to protect the confidentiality of persons reported as having HIV infection. Additionally, laboratory staff that is responsible for the transmission and/or receipt of specimen shipping manifests and/or result reports must be trained on the DHHS Security and Confidentiality guidelines for HIV/AIDS surveillance data. These measures will be extended to protect the VARHS information held locally. Access by surveillance staff to information in HARS and VARHS data will be governed by the same security and confidentiality requirements. Under these guidelines, information that could identify an

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individual (e.g., name, address, ZIP code) will not be included in the data set that is transmitted from local surveillance areas to CDC.

HIV testing is a medical procedure. Therefore, policies and procedures are in place to protect the confidentiality of tested individuals and their medical records. VARHS will be performed only on specimens that have tested positive for HIV or specimens used for follow-up of a confirmed HIV positive result. All information related to variant, atypical, and resistant HIV surveillance will be subject to the same confidentiality and medical record protections as those for HIV-positive status.

VARHS Implementation Task 4.0.A

Variant, atypical, and resistant HIV surveillance areas should review their confidentiality requirements and draft specific procedures for handling variant, atypical, and resistant HIV data if needed or add VARHS components to the existing protocol.

5.0 Data Handling and Analysis

5.1 Data Management

All data will be considered part of routine HIV surveillance data. Data will be held to the standards of security and confidentiality for HIV/AIDS surveillance outlined in the U.S. Department of Health and Human Services manual and will take place at local health departments and CDC.[2] Data entry and management will take place at state or local health departments by using HARS and software developed by CDC or software that is compatible with CDC software. Surveillance data and laboratory tracking data will be merged locally into the local VARHS database provided by CDC. A program is available from CDC to merge information from HARS into the VARHS database, which will be updated when HARS is replaced by the eHARS document-based data entry system for HIV/AIDS surveillance. It is planned that the data management system that will in turn replace eHARS in the future will include the HIV *pol* gene sequence used for VARHS, and regularly updated programs to interpret the sequence and place the information into the main database. Once this system is deployed it will be able to accommodate all data fields required for variant, atypical, and

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resistant HIV surveillance. During the period when HARS and eHARS are in use, the VARHS database will remain a stand-alone adjunct system to HARS and eHARS, capable of merging core HIV/AIDS surveillance variables with HIV drug resistance and HIV-1 subtype surveillance information for analysis purposes.

From the VARHS database, a subset of HARS data for VARHS, and selected specimen tracking variables, will be transmitted to CDC over the Secure Data Network (SDN) on a monthly basis. Data transmitted to CDC will not include personal identifiers and will be encrypted and password protected.

VARHS Implementation Task 5.1.A

Variant, atypical, and resistant HIV surveillance areas should review their protocol for handling and storing data in secure locations and outline how VARHS data will be stored and secured. Personnel with access to the data should receive training on security and confidentiality procedures and should sign a confidentiality statement outlining the procedures and consequences for violating the guidelines.

VARHS Implementation Task 5.1.B

Variant, atypical, and resistant HIV surveillance coordinators should include in their local guidance the procedures for merging HARS, specimen tracking, and genotyping data into the VARHS database, and for transmitting data to CDC. The frequency with which data will be transmitted to CDC should be included. Persons transmitting VARHS data must apply for and be approved for a Secure Data Network certificate from CDC for transmission of VARHS data, or have the transmission of VARHS data added as an approved activity to an existing SDN certificate.

5.2 Data entry and merging of data

The VARHS database is a Microsoft Access database supplied by CDC with tables for laboratory tracking, demographic and clinical data, HIV incidence data, and HIV drug resistance and subtyping data. An additional table is available for local data entry, for which fields can be created locally. All data except identification numbers, laboratory tracking data, and data

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entered into the local table are merged into the VARHS database electronically and do not require manual data entry.

A VARHS identification number will be assigned to each specimen sent for genotyping and used for merging HIV genetic sequencing information into the VARHS database. The variant, atypical, and resistant HIV surveillance resistance identification number (VARHS ID) is a 14 digit number. It should be assigned as follows:

- Digits 1-4: The four digits representing the FIPS code of the project area
- Digits 5-8: The four digits representing the site (site number) where the blood draw was performed
- Digits 9-10: The last two digits of the year
- Digits 11-14: The four digit sequence number as assigned by the local health department

The VARHS database includes functions to allow areas to enter their FIPS (Federal Information Processing Standard, http://www.census.gov/geo/www/fips/fips.html) code only once, and to create a menu of blood drawing sites and their codes. The VARHS ID will be created automatically in the VARHS database when a minimal amount of information is entered for each specimen. The VARHS ID number should be recorded on the cryovial used for aliquoting serum or plasma before transport (after the specimen is confirmed as HIV seropositive). Electronic genetic sequence information will be sent back encrypted from the genotyping laboratory identified only by the VARHS ID number and merged into the database. Specimen tracking information will also be recorded using this number. The specimen accession number may also be entered into the database for local use.

The HARS state case number (STATENO), when assigned, is entered into the VARHS database for the purpose of merging in relevant variables from HARS.

Additional information for the use of local HIV surveillance staff, for the purposes of returning results or for eligibility determination, may be recorded in a local table in the Access database.

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5.3 Data handling, encryption, and transfer

Electronic VARHS data will be sent encrypted and password protected to the Health Department from the genotyping laboratory in the form of a text file representing the HIV *pol* gene sequence attached to the relevant VARHS identification number. In the future, CDC may provide a regularly-updated program to interpret this sequence and incorporate information on individual mutations of interest, level of resistance to each antiretroviral drug in common use, and HIV-1 subtype, into the "resistance person-view" table of the VARHS Access database. Additional programs are provided by CDC to export a SAS file to be used for local analysis, and to export a subset of non-identifying variables to be transferred to CDC.

Encryption software will be used for receipt of files from the genotyping laboratory and CDC. Areas receiving genotyping data from the Stanford University laboratory must purchase "Pretty Good Privacy" (PGP) software with at least 128-bit encryption in order to receive and send encrypted HIV genetic sequencing data. PGP Personal Desktop edition is suitable; a perpetual license is recommended. Data transferred electronically from a local genotyping laboratory must be encrypted using PGP or equivalent encryption software. PGP encryption keys must be exchanged between the genotyping laboratory and data transfer personnel at the health department. Data will be encrypted and transmitted from the health department to CDC through the SDN already in use for HIV/AIDS reporting. Either the SEAL encryption software used traditionally for HARS data transfer or PGP encryption software may be used for transfer of data to CDC through the SDN. Data sent from CDC to VARHS areas for the purposes of data quality assurance will be encrypted using PGP software and transferred through the SDN. PGP encryption keys must be exchanged between CDC and the health department.

VARHS Implementation Task 5.3.A

At least one month before specimen collection starts, variant, atypical and resistant HIV surveillance areas should purchase and install PGP encryption software with at least 128-bit encryption capacity. Encryption keys should be exchanged with the genotyping laboratory and with the VARHS data managers and the laboratory liaison at CDC before the first specimen shipment.

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5.4 Data Analysis

Nationally and locally, the overall prevalence of resistance to at least one antiretroviral drug among individuals newly diagnosed with HIV, and among the subset of individuals recently infected with HIV, should be reported annually. The prevalence of resistance to individual ARV drugs and categories of commonly used ARV drugs (currently nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors) among these two groups will also be reported, as well as the prevalence of HIV-1 subtypes.

The data will be stratified by factors such as demographic or exposure category factors for subpopulation analyses at the national and local levels. If the sampling procedure has sufficient statistical power, this stratification will allow comparisons among different geographic areas and different exposure categories. Results will be extrapolated to those who did not have specimens tested in VARHS.

Additional modeling of HIV drug resistance transmission may be performed using clinical and HIV incidence information to approximate times of infection on a population basis. Furthermore, in areas where anonymously tested specimens confirmed as HIV positive were collected for VARHS, a separate analysis will be performed for these specimens.

5.5 Data Dissemination

It is expected that analyses, interpretation, and dissemination of VARHS data will be the primary responsibility of CDC with the appropriate contributions from surveillance areas. Results from the aggregate CDC database will be analyzed regularly and feedback provided to areas. Aggregate results will also be published by CDC once a sufficient number of areas are participating. Area-specific analyses will be conducted at the discretion of participating areas. As appropriate, results will be presented at conferences and published in peer reviewed journals. The number of representative authors from areas and CDC will be determined for each presentation or paper.

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VARHS Implementation Task 5.5.A

Variant, atypical and resistant HIV surveillance areas should include in the local version of these guidelines a description of the proposed plan for reporting and dissemination, data elements to be disseminated, and the process for data dissemination.

6.0 Variant, Atypical and Resistant HIV Surveillance Responsibilities

Implementation of variant, atypical, and resistant HIV surveillance requires personnel with specific skills and dedicated time to integrate VARHS into the existing core HIV/AIDS surveillance system effectively. Generally, personnel who work primarily on HIV incidence surveillance or core HIV/AIDS surveillance will develop work plans to integrate VARHS into core HIV/AIDS surveillance in selected sites in coordination with their other responsibilities. CDC has identified functions considered essential to the implementation and maintenance of surveillance of variant, atypical, and resistance HIV. Individuals with VARHS responsibilities should have an understanding of HIV surveillance, HIV incidence surveillance, and HIV drug resistance surveillance, good communication skills, a basic understanding of the functioning of HIV diagnostic laboratories and their relationship to the public health system, good communication skills, and enthusiasm. Staff members with VARHS responsibilities should work closely with CDC, other states, local HIV diagnostic and clinical sites, private providers, and laboratories.

CDC recommends that persons be identified to perform the following functions: (1) coordination of variant, atypical, and resistant HIV surveillance, (2) VARHS epidemiological oversight and data analysis, (3) liaison between the health department and HIV diagnostic laboratories and the genotyping laboratory, (4) liaison between participating HIV diagnostic laboratories and the health department and genotyping laboratory, and (5) data management. These responsibilities of these staff members are described below.

6.1 Variant, Atypical and Resistant HIV Surveillance Coordination

- Provide overall management of VARHS
- Serve as the primary point of contact for CDC on VARHS

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- Work with surveillance epidemiologists, the HIV incidence coordinator, and laboratory liaison to the development of the area-specific procedures for and implementation of variant, atypical, and resistant HIV surveillance
- Directly manage or oversee the system for determining eligibility of specimens for VARHS
- Collaborate with the HIV diagnostic laboratory liaison(s) on developing specimen tracking and specimen transfer procedures
- Liaise with the genotyping laboratory to develop procedures for shipment of specimens and receipt of data
- Oversee data collection processes
    - Describe the process and identify personnel involved in data collection and merging of data into the VARHS database
- Work with individuals providing epidemiological oversight to develop procedures for
    - Data entry and quality assessment
    - Data editing and file correction
    - Data transfer procedures
    - Preparation of monthly reports
    - Security and confidentiality procedures
- Develop and manage the system for returning VARHS results to providers identified by newly diagnosed individuals
- Participate in CDC site visits, trainings, and workshops

6.2 Epidemiological Oversight

- Plan and implement integration of VARHS activities with HIV core surveillance and HIV incidence surveillance activities
- Develop a VARHS analysis plan
- Develop systems to ensure data quality, analyze local VARHS data and produce reports
- Develop presentations for local clinical and diagnostic sites and laboratories to explain variant, atypical, and resistant HIV surveillance
- Participate in data dissemination activities
    - Collaborate with stakeholders to determine data needs and frequency of reporting
    - Identify results and surveillance issues for review and dissemination
    - Develop a data dissemination plan in collaboration with person coordinating VARHS and CDC
- Participate in CDC site visits, trainings, and workshops

6.3 Laboratory liaison from the health department

This function will often be performed by the person with VARHS coordination responsibility

- Act as the liaison between the public health department and laboratories from which specimens are being shipped
- Oversee transfer of specimen tracking data from laboratories to the VARHS database at the health department

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- In collaboration with liaisons based at participating laboratories, develop local procedures for processing and shipping of specimens to the genotyping laboratory
- In collaboration with liaisons based at participating laboratories, develop quality control procedures outlined for preparing specimens
- Develop and oversee procedures to maintain security and confidentiality of specimens
- Participate in CDC site visits, trainings, and workshops

6.4 Laboratory liaison based at a participating HIV diagnostic laboratory

- Liaise with the person coordinating VARHS and the health department laboratory liaison to develop the laboratory-specific plan for processing, storing, determining eligibility, tracking, and shipping specimens to the genotyping laboratory
- Oversee preparation and shipping of VARHS specimens to the genotyping laboratory
- Monitor quality control procedures outlined for preparing VARHS specimens
- Record specimen tracking data in the log or database

6.5 Data Management

- Assist the person coordinating VARHS activities with daily management of VARHS data
- Serve as subject matter expert on VARHS data elements and data management programs
    - Apply to receive certification to send HIV drug resistance data through the CDC Secure Data Network (SDN) or to add the resistance component to an existing certificate
    - Identify at least one back-up person to receive CDC SDN certificate, and take responsibility for maintaining and updating a list of persons with certification and ensuring CDC is informed of changes
    - Conduct data quality assessments
- Conduct data management
    - With CDC data managers, modify CDC's generic data management programs for use at the local area level
    - Run programs to merge data into the VARHS database regularly
    - Develop and implement edit checks and conduct data cleaning.
    - Perform data export and transfer to CDC
    - Receive genotyping data from the genotyping laboratory and run programs to merge these data into the local database
    - Run programs to export the local SAS analysis database
    - Collaborate with persons working on VARHS and other area surveillance and prevention staff, as needed, on data cleaning, data entry, and data set preparation
    - Prepare data sets for local analysis
- Maintain security and confidentiality of data.
- Participate in CDC site visits, trainings, and workshops

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VARHS Implementation Task 6.0.A

Variant, atypical, and resistant HIV surveillance areas should describe the responsibilities for planning and implementation of VARHS locally, and the duties and time to be spent on VARHS for each staff member who will be assigned these responsibilities.

7.0 Public Health Benefit

VARHS will determine the distribution of viral genotypes among persons newly diagnosed with HIV, supporting efforts to characterize and track the HIV epidemic nationally in the U.S. Analyses will support evaluation of first-line HIV antiretroviral drug treatment strategies nationally in participating geographic areas, and provide information useful to research scientists developing new antiretroviral drugs. Strategies for use of specific drugs in HIV pre- and post-exposure HIV prophylaxis will be enhanced by HIV drug resistance surveillance information.

VARHS will support evaluation of the utility of baseline clinical HIV drug resistance testing in particular geographic areas. Current Department of Health and Human Services guidelines for treatment of HIV infection suggest that testing performed before treatment begins may be clinically useful up to three years after seroconversion. Given that many mutations appear to remain detectable for at least this period of time, the guidelines go on to state, "….Using resistance testing…in patients with chronic HIV infection is less straightforward…It may be reasonable to consider such testing…when there is a significant probability that the patient was infected with a drug-resistant virus…A recent study suggested that baseline testing may be cost-effective when the prevalence of drug resistance in the relevant drug-naïve population is > 5%, but such data are infrequently available."[12] This International AIDS Society-U.S.A. recommends HIV drug resistance testing for all recently infected persons, and adds "It is often difficult to ascertain how long an individual has been infected, and consideration should be given to HIV drug resistance testing when the duration is uncertain and the expected regional prevalence of resistance is $\geq$5%."[13] Both sets of guidelines refer to an analyses that suggests the HIV drug resistance testing is cost-effective in drug-naïve persons if the regional prevalence of resistance is $\geq$5%.[12] VARHS will supply an estimate of the prevalence of resistance both in chronically and recently infected persons newly diagnosed with HIV, providing support for

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clinical decision-making whether baseline clinical testing is likely to be cost-effective before treatment is started.

Studies have demonstrated that the HIV *pol* gene sequence can be used to evaluate HIV-1 subtypes (and also HIV-2 subtypes, although the rarity of HIV-2 in the U.S. makes it unlikely that such an evaluation will be required). A high prevalence of HIV-1 subtypes other than subtype B in a geographic area has implications for appropriate selection of HIV diagnostic and clinical tests both for populations and individuals.[1] VARHS will provide public health and clinical personnel with prevalence estimates for non-B HIV-1 strains circulating in particular geographic areas. In addition, if prevalence of HIV-1 non-B subtypes is shown to be increasing, this finding could have implications for vaccine studies. Also, should specific mutations associated with drug resistance be shown to be associated with some non-B subtypes, this could have implications for treatment guidelines.

In surveillance of other organisms, such as *M. tuberculosis*, molecular surveillance has allowed identification of atypical strains of special interest.[7,8] Although no such strains have currently been identified for HIV, routine surveillance based on routine sequencing of the HIV *pol* gene will also allow phylogenetic analyses to follow the spread of atypical HIV strains of interest through geographic areas and within particular subgroups, supporting evaluation and targeting of prevention strategies. HIV genetic sequencing surveillance data collected over period of years will also contribute to analyses of the evolution of HIV within the U.S. and worldwide.

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Appendix A. National Center for HIV, STD, and TB Prevention's Non-research Determination for HIV Variant, Atypical, and Resistant HIV Surveillance

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.
- X**B.** 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**

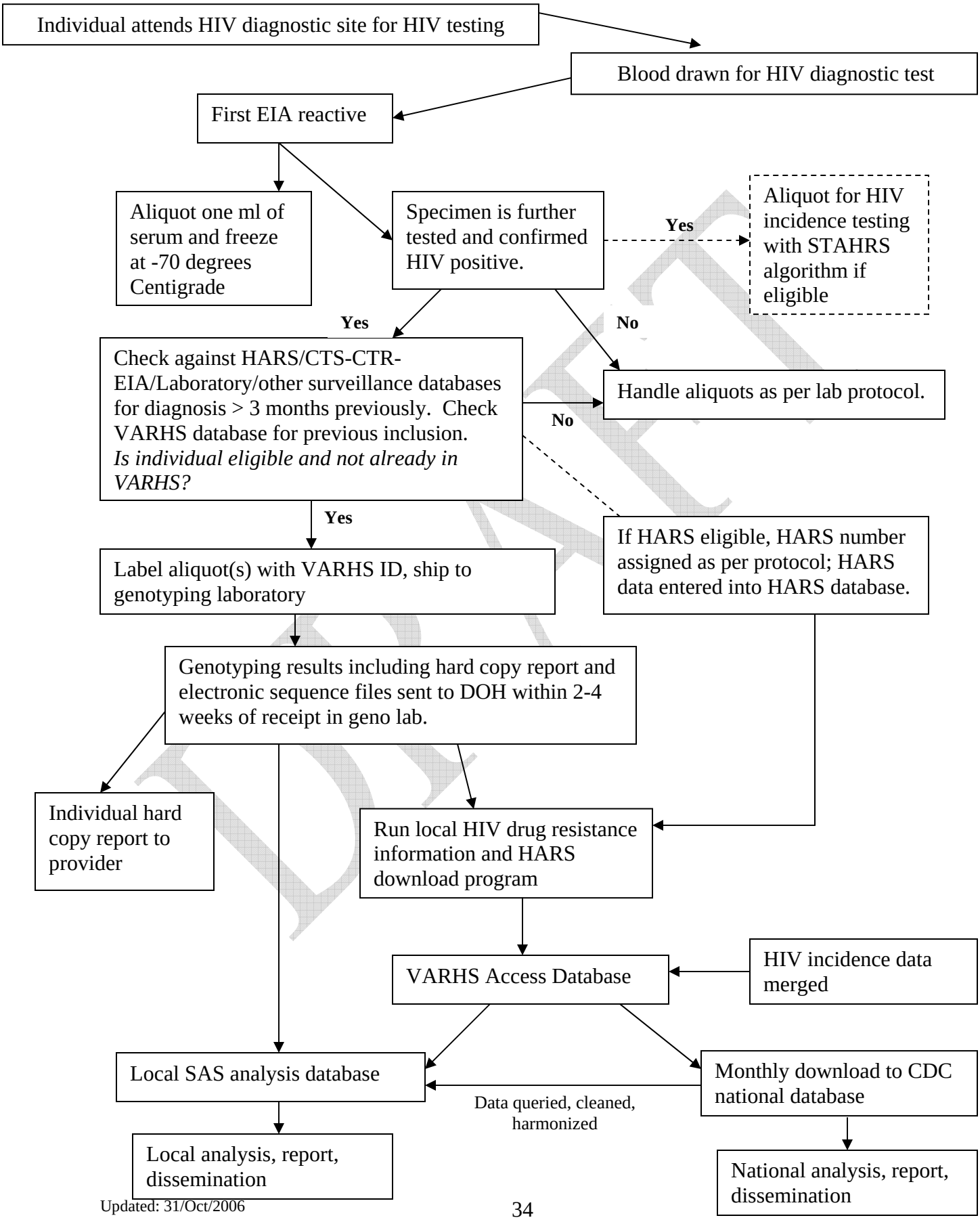
or

___**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 — Date
Associate Director for Science
National Center for HIV, STD, and TB Prevention

Appendix B. Epidemiologic Flow Chart for Variant, Atypical, and Resistant HIV Surveillance



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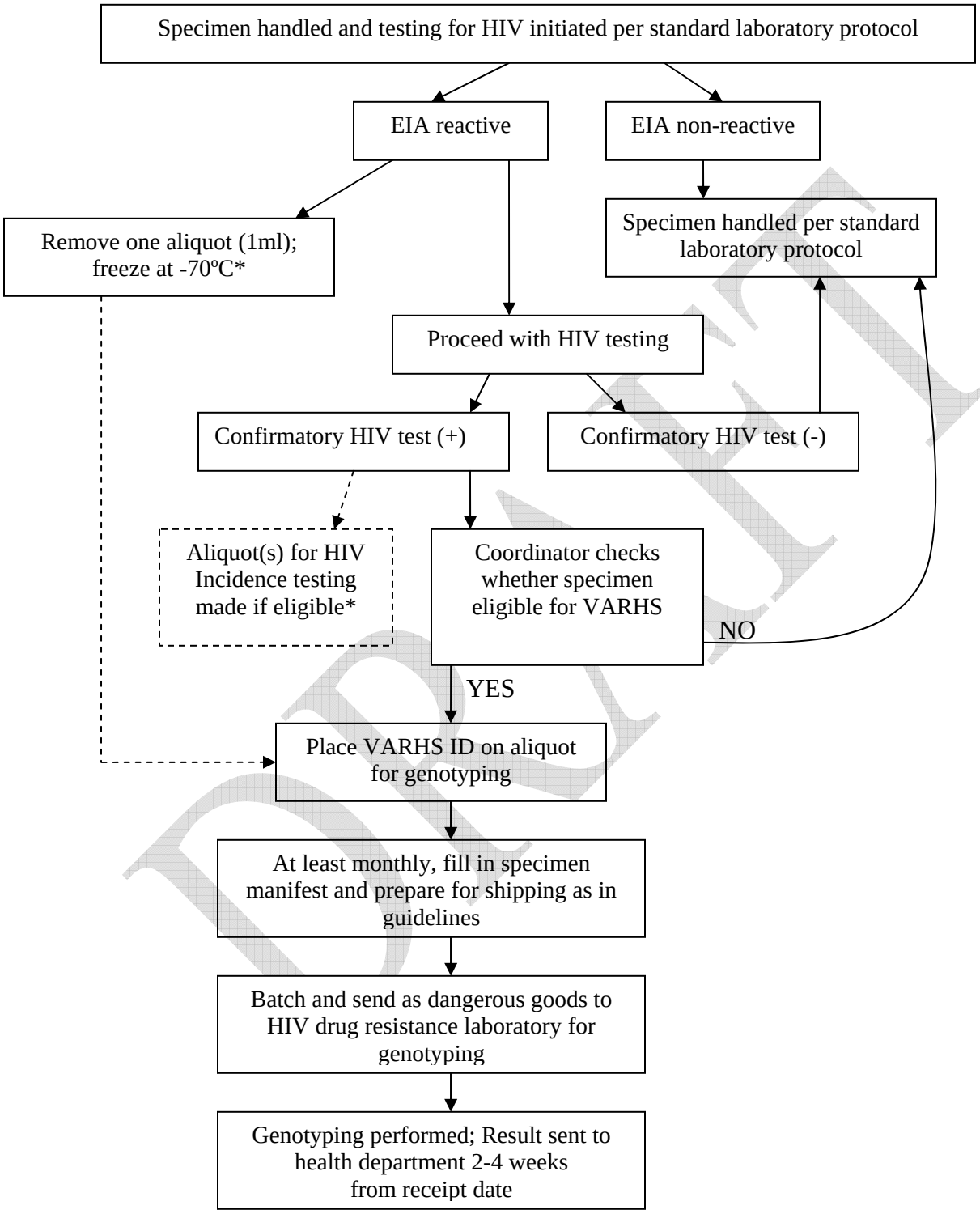
Appendix C: VARHS Operational Laboratory Flow Chart



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* Priorities if specimen volume is limited:
1. HIV diagnostic testing- all aliquots remain available for diagnostic testing until confirmation is completed
2. HIV incidence testing using STARHS
3. HIV drug resistance genotyping
4. HIV drug resistance testing back-up (if applicable)

Appendix D
Guidelines for the Processing, Storage and Shipment of Variant, Atypical and Resistant HIV Surveillance (VARHS) Specimens to Genotyping Labs for Antiretroviral Drug Resistance Testing

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HIV Incidence and Case Surveillance Branch
Division of HIV/AIDS Prevention
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention

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1.0 Purpose

This standard operating procedure describes the methods for the handling, storage, and shipment of Variant, Atypical, and Resistant HIV surveillance (VARHS) serum and/or plasma specimens that will be tested for HIV antiretroviral drug resistance and HIV-1 subtyping.

2.0 Introduction

Serum or plasma from HIV diagnostic specimens is to be collected and frozen at minus 70 degrees Centigrade. For the purposes of resistance testing, the serum is to ideally be separated within 48 hours of the blood draw and frozen within 96 hours of the blood draw. Frozen serum or plasma will be shipped to a CDC designated testing laboratory for genotype analysis.

NOTE: Back-up specimens will no longer be sent to the CDC Serum Bank. Project areas may elect to store a "back-up" aliquot for use in the event that something happens to the original aliquot sent to the lab or if a specimen needs to be re-tested for any reason.

3.0 The Setting and Personnel Required for Specimen Processing

3.1 Centrifugation, aliquoting, and shipping should be performed at or under the auspices of a laboratory that is CLIA certified for handling HIV+ specimens.

3.2 All personnel handling specimens should receive blood borne pathogens training.

3.2.1 See OSHA's Occupational Exposure to Bloodborne Pathogens Standard: http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=10051.

3.3 Personnel handling or processing specimens should have the appropriate laboratory training in the relevant laboratory techniques for handling HIV+ specimens and for performing the specific tasks required.

3.4 The setting in which centrifugation, aliquoting, and shipping occurs should meet Biosafety level 2 specifications required by the U.S. Department of Health and Human Services for handling of specimens containing HIV (http://www.cdc.gov/od/ohs/biosfty/bmbl4/bmbl4s2.htm).

4.0 Materials

4.1 The following materials are required for the collection and shipment of VARHS specimens:

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4.1.1 Cryogenic vials: 1.5 to 2 ml with screw cap, external threads, O-ring, and made of polypropylene

4.1.2 Freezer labels that will remain on the tubes upon freezing. Many cryogenic vials have a label area printed on them that is suitable for writing with a permanent marker. This is acceptable in place of labels.

4.1.3 Cardboard storage boxes for cryogenic vials: 81 spaces/box

4.1.4 Low temperature freezer: - 70° Centigrade

4.1.4.1 If not already in practice, it is recommended that a daily temperature log be kept to ensure that the freezer is operating properly.

4.1.4.2 The freezer should be housed in a location with proper ventilation to avoid overheating and freezer failure.

4.1.4.3 Staff must be certain there is adequate space in the - 70° C freezer to house VARHS specimens.

4.1.5 A supply of dry ice in pellet form

4.1.6 Saf-T-Pak (http://www.saftpak.com) STP 320 insulated shipping containers certified to ship frozen diagnostic specimens (i.e., HIV+ sera and dry ice)

4.1.7 Shipping courier air bills

4.1.8 Materials for shipper packing (Refer to Section 6.2.4.1)

5.0 Specimen Collection and Processing

5.1 All processing of specimens should be done by personnel qualified to handle HIV+ specimens under the auspices of a laboratory equipped for the handling of HIV+ specimens (http://www.cdc.gov/od/ohs/biosfty/bmbl4/bmbl4s2.htm).

5.2 As soon as possible after separation, the serum should be aliquoted from the collection tube to the corresponding vial (1 ml per cryogenic vial is optimal).

5.3 If sufficient serum appears to be available for all diagnostic needs and HIV incidence testing, one 1-ml (optimal volume) aliquot should be made for HIV drug resistance testing. This aliquot should be shipped to Stanford University or to the locally-contracted genotyping laboratory. Project areas may elect to store a

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"back-up" aliquot for use in the event that something happens to the original aliquot sent to the lab or if a specimen needs to be re-tested for any reason.

5.4 Place the aliquots in cardboard boxes for cryogenic vials in a - 70° C freezer. Optimally, the - 70° C freeze will occur within 96 hours of the blood draw.

5.5 Sera aliquoted and frozen as potential specimens for HIV drug resistance testing remain HIV diagnostic specimens until all HIV diagnostic tests and any other basic laboratory tests have been completed. If additional serum is needed for diagnostic testing or HIV incidence testing, sera aliquoted for potential HIV drug resistance testing should be thawed and used for those purposes. If a back-up specimen was made, this specimen should be used first. If more volume is required, the specimen for the genotyping laboratory may also be used.

5.6 After a positive HIV confirmatory test, or at the time determined by the standard laboratory procedures, each cryogenic vial is labeled with the appropriate VARHS Specimen ID. The VARHS ID is a 14-digit number that is assigned to each specimen sent for genotyping.

5.6.1 The 14-digit VARHS Specimen ID consists of the following:

5.6.1.1 The four-digit ***Project Area*** (digits 1-4), which corresponds to the FIPS code of the project area (state or city).
5.6.1.2 The four-digit ***Site Number*** (digits 5-8) where the blood draw or finger-stick was performed.
5.6.1.3 The last two digits of the ***blood draw year*** (digits 9-10).
5.6.1.4 The four-digit ***Sequence Number*** (digits 11-14) assigned by the health department as planned locally.

5.7 Every specimen that is eligible for VARHS should be entered into a specimen handling and processing log or a database. Each project area is expected to develop its own log or database, or use the specimen tracking database provided by CDC. In addition, each project area is responsible for ensuring that all information is logged for each specimen before the specimen is shipped.

6.0 Shipping

6.1 Preliminary planning for shipping to Stanford University genotyping laboratory

6.1.1 Specimens for genotypic resistance testing should be sent to the Stanford University laboratory. All specimens should be shipped as diagnostic specimens using International Air Transport Association (IATA) Packing Instructions 650. Dry ice will be included with each shipment using IATA Packing Instructions 904.

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6.1.2 Because shipping specimens involves using dry ice, shipping personnel must be trained and certified to ship dangerous goods. See Appendix D-1 for a list of companies that provide training.

6.1.3 Establish contact with the point person at the Stanford University laboratory.
6.1.3.1 Stanford Virology Main Lab: (650) 725-7165
6.1.3.2 Mary Arroyo: (650) 725-4146

6.1.4 A "test" shipment must be sent prior to the first shipment of VARHS specimens to assure that all procedures are in place. The test shipment should exactly duplicate a real shipment (i.e., ship frozen liquid in cryogenic vials on dry ice) and only needs to be sent once. See the procedures outlined in sections 6.1.5 – 6.1.8 below.

6.1.4.1 The purpose of the test shipment is to familiarize the sender with the shipment notification process and the diagnostic specimen and dry ice shipping process. Shipping frozen water on dry ice without the infectious substance labels will accomplish the purpose of the shipment.

6.1.5 Arrange for the preparation of the "test" and the initial shipment to be overseen by laboratory staff experienced in the shipment of comparable specimens.

6.1.6 Notify Stanford lab that the "test" shipment is on the way by calling the main lab at (650) 725-7165 or by email without emailing or faxing the specimen manifest.

6.1.6.1 In the call/email, please include the number of samples being shipped and the Fed Ex tracking #, if applicable. ***Remember, per CDC's Security and Confidentiality Guidelines for HIV Surveillance, do not email or fax the specimen manifest, but continue to include the manifest with the shipment.***

6.1.7 Ensure that adequate STP 320 shipping containers or equivalent are available. The Stanford laboratory will return these to the shipping lab, as these are expensive shippers and need to be re-used.

6.1.8 Ensure that an adequate supply of shipping courier air bills is available.

6.2 Packing procedures for shipment to Stanford University laboratory

6.2.1 Specimens must be shipped on the same day that they are packed. Plan to begin the packing process early enough to make the last shipping courier

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pick-up of the day. ***Packing and shipping should only be done Monday through Wednesday. Never pack and ship the week of Thanksgiving, Christmas, New Year's, or July 4th.***

6.2.2 The shipping laboratory should read and walk through all of these steps prior to starting the preparation of the actual shipment in order to be familiar with what is required.

6.2.3 Put on gloves and a laboratory coat.

6.2.4 Bring the STP 320 shipper that is to be used for the shipment and other materials needed for packing the specimens into the area where the shipment is being prepared.

6.2.4.1 If the shipper is new and being used for the first time, check to be sure that it includes the following items:

6.2.4.1.1 2 sheets of bubble wrap
6.2.4.1.2 2 STP 710 or equivalent certified secondary containers
6.2.4.1.3 2 250-ml absorbent strips
6.2.4.1.4 Class 9 label and dry ice quantity label
6.2.4.1.5 Other hazard and handling labels
6.2.4.1.6 1 instruction sheet

6.2.5 For a diagram of the above contents, refer to the Saf-T-Pak catalog (http://www.saftpak.com). Use only what is needed of the above contents for each individual shipment. Save left over supplies for future shipments.

6.2.6 If the STP 320 shipper is being re-used, the labels will already be in place on the outer cardboard container.

6.2.7 Ensure that adequate supplies of the other materials listed in 6.2.4.1 are on hand.

6.2.8 Prepare three copies of the shipping manifest (Appendix D-2). On the manifest, list the specimen project number on each vial to be shipped, the specimen draw date, and the specimen freeze date. ***Note: The freeze date entered here should be the last freeze date for the aliquot being shipped.*** Indicate (circle) whether the specimens are serum or plasma. Bring the copy of the manifest that is going to be shipped into the area in which the shipment is being prepared.

6.2.8.1 Copy 1 of the shipping manifest should be included in the shipment to the Stanford laboratory
6.2.8.2 Copy 2 of the shipping manifest should be sent to CDC (Refer to Section 6.3.2)

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6.2.8.3 Copy 3 of the shipping manifest should be kept by the project area's VARHS Coordinator or the laboratory sending the samples to the Stanford laboratory

6.2.9 Prepare the shipping courier air bill (Appendix D-3) that Stanford will use to send the shipper back for re-use. Fill in the air bill with the shipping laboratory's complete return address, Stanford's address, and the billing number. The air bill should be stapled to the shipping box return form. Bring the copy of the air bill that is going to be shipped into the area in which the shipment is being prepared.

6.2.10 If dry ice is in another location which requires leaving the area in which the shipment is being prepared, use a separate container to bring the dry ice that is needed for shipping back into the shipping area at this time.

6.2.11 Go to the freezer and remove the entire 2-inch freezer box containing the specimens to be sent.

6.2.12 Bring the specimens to the area in which the shipment is being prepared. ***Please remember that these specimens are to remain frozen at all times and therefore should not be removed from a -70° C environment for more than a few minutes.***

6.2.13 Re-check the screw-cap lids on the specimen vials and tighten if necessary.

6.2.14 Place the freezer box containing the specimens to be sent into the secondary leak-proof container and make sure the samples are surrounded by bubble wrap and absorbent strips. The vials should not move around or rattle inside the vessel.

6.2.15 Place the secondary vessel into the inner box and place the inner box into the polystyrene cooler.

6.2.16 Pack pelleted dry ice in the shipper and around the inner box. The STP320 shipper will hold ~8 kg of dry ice (~10lbs) and if packed completely, will keep the contents frozen for greater than 80 hours.

6.2.17 ***Do not*** put dry ice inside the inner box.

6.2.18 Place the lid on the polystyrene cooler.

6.2.19 Place one copy of the VARHS shipping manifest on top of the shipping box return form with the air bill that Stanford lab will use to recycle the shipper the shipping lab, fold in half and place on top of the polystyrene lid.

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6.2.20 Fold over the top flaps and seal the shipping container with clear shipping tape.

6.2.21 The outer box must have a mark in the form of a square set at an angle of 45° (diamond shaped). The mark must be at least 2 inches by 2 inches and include the UN 3373 designation. The proper shipping name "Diagnostic Specimens" must be marked on the outer package adjacent to the diamond shaped mark. Labels can be purchased to place on the outer box that fulfills this requirement.

6.2.22 Apply the Class 9 Hazard Label over the lower diamond shaped outline on the box.

6.2.23 Apply the net quantity dry ice label to the outlined area adjacent to the Class 9 Hazard Label. Write the approximate amount (in kg) of dry ice used to pack the container.

6.2.24 Prepare the shipping courier paper work as directed by the shipping training and certification course, and select the overnight shipping option.

6.2.25 If the aforementioned steps are not completed prior to the last shipping courier pick-up, unpack the specimens and place them back in the - 70° C freezer and begin the process again on the next appropriate day.

6.3 Procedures for Shipment to Stanford University laboratory

6.3.1 Ship only Monday through Wednesday. Never ship the week of Thanksgiving, Christmas, New Year's, July 4th, or major local holidays.

6.3.2 Send the second copy of the specimen manifest to Richard Kline at CDC via the SDN (preferred) or by US mail. On the manifest, indicate the date that the specimens were shipping to Stanford. ***Do not email or fax the specimen manifest to the CDC or to Stanford lab.***

6.3.2.1 Mailing Address:
Attn: Richard Kline
Centers for Disease Control and Prevention
1600 Clifton Rd. NE. MS-E-47
Atlanta, GA. 30333
Phone: 404-639-4958

6.3.3 Keep the third copy of the specimen manifest.

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6.3.4 Notify Stanford lab that a shipment is on the way by calling the main lab at (650) 725-7165 or by email without emailing or faxing the specimen manifest.

6.3.4.1 In the call/email, please include the number of samples being shipped and the Fed Ex tracking #, if applicable. ***Remember, do not email or fax the specimen manifest, but continue to include the manifest with the shipment.***

6.3.5 Track the shipment using the 10-12 digit FedEx tracking number listed on the air bill. This can be done via the website www.fedex.com or by calling 1-800-GO-FEDEX.

6.3.5.1 If a problem is identified, please notify:
Stanford Main Lab: (650) 725-7165 and
Richard Kline: (404) 639-4958

6.3.6 The shipping laboratory will receive acknowledgement for successful receipt of shipment from the Stanford laboratory within 48 hours via the agreed upon system. If the shipping lab does not receive this notification, the Stanford Lab should be contacted.

6.4 Preliminary planning for shipping to a locally-contracted genotyping laboratory

6.4.1 Follow the procedures listed in section 6.1 above, substituting the locally-contracted laboratory's contact information with Stanford's contacts in sections 6.1.3 and 6.1.6.

6.5 Packing procedures for shipment to a locally-contracted genotyping laboratory

6.5.1 Follow the procedures listed in section 6.2 above substituting local procedures wherever applicable and the locally-contracted laboratory for the Stanford laboratory.

6.6 Procedures for Shipment from the processing laboratory to a locally-contracted genotyping laboratory

6.6.1 Follow the procedures listed in section 6.3 above substituting local procedures wherever applicable and the locally-contracted laboratory for the Stanford laboratory.

6.7 Procedures for local transport from the processing laboratory to a locally-contracted genotyping laboratory

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6.7.1 Follow the procedures listed in 6.2.1 – 6.2.20 above or substitute local procedures as discussed with Richard Kline at CDC to ensure that specimens remain frozen during transport and until ready for genotyping at the genotyping laboratory.

6.7.1.1 Always include a copy of the shipping manifest in the shipment.

6.7.2 Whenever specimens are transported, send a copy of the specimen manifest to Richard Kline at CDC via the SDN (preferred) or by US mail. On the manifest, indicate the date that the specimens were shipping to the genotyping lab. ***Do not email or fax the specimen manifest to the CDC or the genotyping laboratory.***

6.7.2.1 Mailing Address:
Attn: Richard Kline
Centers for Disease Control and Prevention
1600 Clifton Rd. NE. MS-E-47
Atlanta, GA. 30333
Phone: 404-639-4958

6.7.3 Transport specimens only Monday through Thursday, unless local guidelines specify otherwise. If local HIV surveillance or laboratory staff are not personally handling the transport, do not transport specimens during the weeks of Thanksgiving, Christmas, New Year's, July 4th, or major local holidays.

6.7.4 Track the shipment through the FedEx or other courier's tracking system.

6.7.4.1 If there are problems with the transfer, please notify:
Richard Kline: (404) 639-4958 and
The appropriate personnel at the genotyping laboratory

6.7.4.2 Develop an acknowledgement system so that the genotyping laboratory informs the shipping laboratory when the shipment has arrived.

6.8 Local Transfer from the processing area to the genotyping area within one laboratory (where the HIV diagnostic testing and genotyping for HIV drug resistance surveillance are performed within the same laboratory).

6.8.1 If HIV testing and genotyping are performed in the same laboratory, and diagnostic testing is complete and aliquots are identified as VARHS specimens, please complete the following:

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6.8.1.1 Send a copy of the specimen manifest (Appendix D-2) to Richard Kline at CDC via the SDN (preferred) or by US mail. On the manifest, indicate the date that the specimens were shipping to the genotyping lab. ***Do not email or fax the specimen manifest to the CDC or the genotyping laboratory.***

6.8.1.1.1 Mailing Address:
Attn: Richard Kline
Centers for Disease Control and Prevention
1600 Clifton Rd. NE. MS-E-47
Atlanta, GA. 30333
Phone: 404-639-4958

6.8.2 Ideally, the initial freezing of specimens should be done in a freezer convenient to the genotyping laboratory, so that transfer of frozen specimens will not be necessary.

6.8.3 If frozen specimens are to be transferred from a freezer in one area to a freezer in another area, a biohazard bag, cooler, and dry ice or cool-packs should be ready before the specimens are removed from the freezer. Specimens should be kept in their storage box and placed in the biohazard bag. The bag should be placed in the cooler with dry ice or freezer bags and transported as quickly as possible to the other freezer.

6.8.4 If there are problems with the transfer, please notify:
Richard Kline: (404) 639-4958 and
The appropriate personnel at the genotyping laboratory

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APPENDIX D-1

TRAINING AND CERTIFICATION FOR SHIPPING INFECTIOUS SUBSTANCES

These are some companies that provide training for dangerous goods shipping. The Centers for Disease Control and Prevention does not endorse any particular company.

1. **FedEx:**
    - 1-800-GO-FEDEX
    - 3 day IATA based training
    - Covers all hazardous materials
    - Cost is ~$550

2. **Saf-T-Pak**
    - 1-800-814-7484
    - Specifically for infectious and diagnostic substances, and dry ice
    - 3 options: One day seminar, on-site programs, or interactive CD (can be completed in 3-5 hours)
    - Certificate is valid for 2 years or until regulations change
    - Cost is ~$250

3. **Viking Packaging (Oklahoma)**
    - 1-800-788-8525, Contact: David Weilert
    - Seminars monthly in Tulsa@ ~ $300 per person
    - Covers all nine classes of hazardous materials
    - Covers shipping under IATA
    - Certificate good for 2 years
    - Will do group classes in local area @ ~$3,000 plus travel costs

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APPENDIX D-2

CDC VARHS GENOTYPING MANIFEST

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Stanford Hospital and Clinics
300 Pasteur Drive
Stanford, CA 94035

CDC VARHS Genotyping Manifest

Clinical Microbiology/Virology H1526
(650) 723-6671
Directors: Steven Foung, MD / EJ Baron, PhD

Date specimens sent to Stanford: _____

Link project number (VARHS ID number)	**Draw Date**	**Freeze Date**	**Serum or Plasma** (CIRCLE)	**Volume** (if < 1ml)	**Stanford Lab number** (STANFORD USE)
			Serum or Plasma		
			Serum or Plasma		
			Serum or Plasma		
			Serum or Plasma		
			Serum or Plasma		
			Serum or Plasma		
			Serum or Plasma		
			Serum or Plasma		
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			Serum or Plasma		
			Serum or Plasma		
			Serum or Plasma		
			Serum or Plasma		
			Serum or Plasma		
			Serum or Plasma		
			Serum or Plasma		

Shipping Instructions:
1) Call Stanford Virology Lab (650) 725-7165 when package is sent (keep a record of tracking number)
2) Complete this manifest form and include a copy with the specimens
3) Package and ship on Monday, Tuesday or Wednesday only
4) Shipping Address: Virology Laboratory Specimen Processing
Stanford Hospital and Clinics
820 Quarry Road RM H1537A
Palo Alto, CA 94304

Mail hard copy of the report to:
Attn: _____
Location _____
Street Address _____
City _____
State _____ Zip code _____

Contact person name and phone number: _____ ( ) __ __ __ - __ __ __ __

Stanford Virology Test Code: AVRT

(for office use only)
Billing done:_____
Original: Box # _____
Extract: Box # _____
Product: Box #_____

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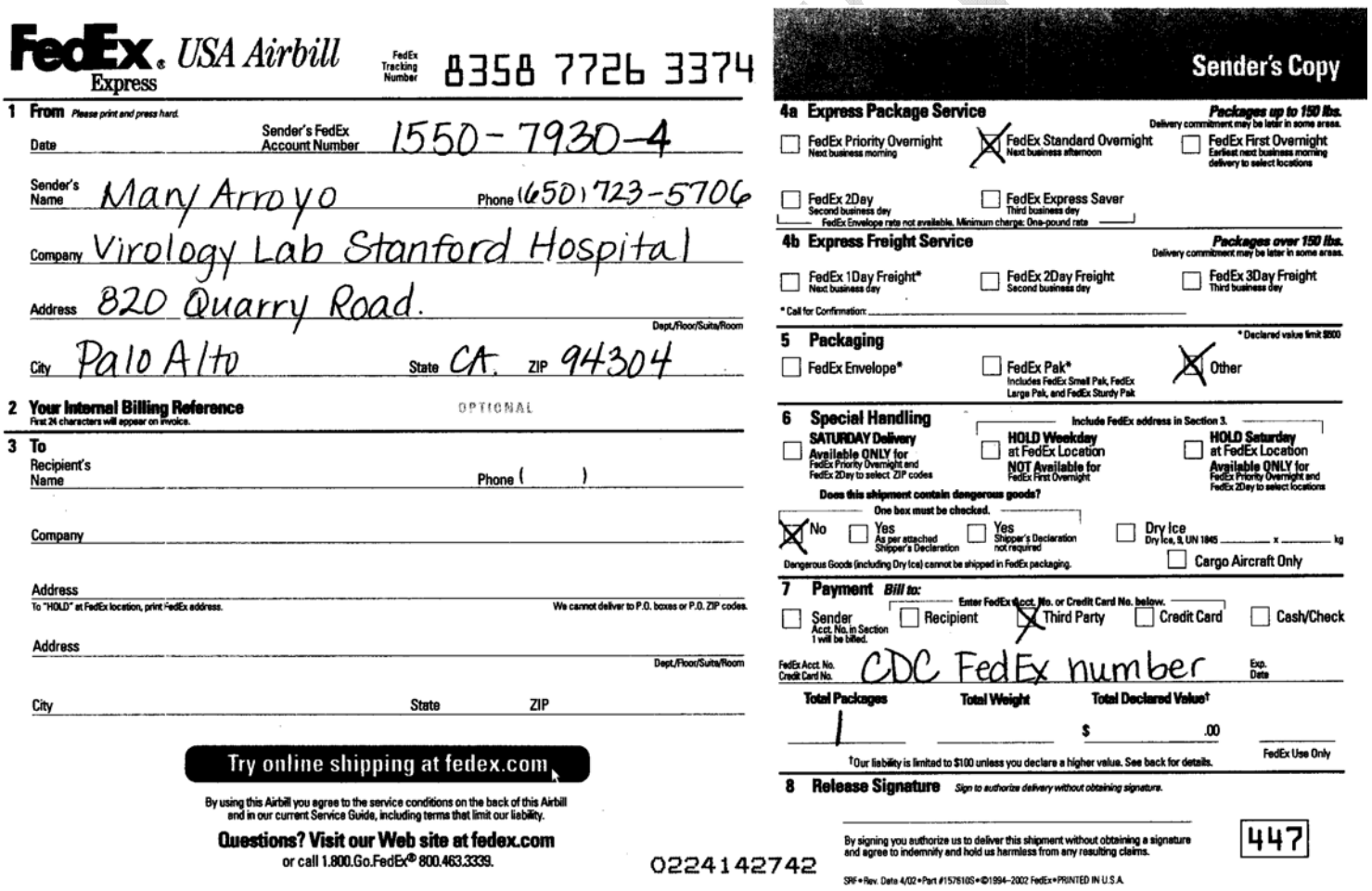
APPENDIX D-3

STANFORD SHIPPING BOX RETURN

Sender: Attach return FedEx air bill. All sections must be filled out, except for the date which will be completed at Stanford. See example below.

Stanford Virology Receiving Desk: Give the empty shipping box, packing materials, and return FedEx air bill to Hina in Virology for return to sender.



FedEx Express USA Airbill — FedEx Tracking Number 8358 7726 3374

1 From (Please print and press hard.)
Date
Sender's FedEx Account Number 1550-7930-4
Sender's Name Mary Arroyo Phone (650) 723-5706
Company Virology Lab Stanford Hospital
Address 820 Quarry Road. Dept./Floor/Suite/Room
City Palo Alto State CA ZIP 94304

2 Your Internal Billing Reference (First 24 characters will appear on invoice.) OPTIONAL

3 To
Recipient's Name Phone ( )
Company
Address (To "HOLD" at FedEx location, print FedEx address. We cannot deliver to P.O. boxes or P.O. ZIP codes.)
Address Dept./Floor/Suite/Room
City State ZIP

Try online shipping at fedex.com

By using this Airbill you agree to the service conditions on the back of this Airbill and in our current Service Guide, including terms that limit our liability.

Questions? Visit our Web site at fedex.com or call 1.800.Go.FedEx® 800.463.3339.

0224142742

Sender's Copy

4a Express Package Service (Packages up to 150 lbs. Delivery commitment may be later in some areas.)
☐ FedEx Priority Overnight — Next business morning
☒ FedEx Standard Overnight — Next business afternoon
☐ FedEx First Overnight — Earliest next business morning delivery to select locations
☐ FedEx 2Day — Second business day
☐ FedEx Express Saver — Third business day
FedEx Envelope rate not available. Minimum charge: One-pound rate

4b Express Freight Service (Packages over 150 lbs. Delivery commitment may be later in some areas.)
☐ FedEx 1Day Freight* — Next business day
☐ FedEx 2Day Freight — Second business day
☐ FedEx 3Day Freight — Third business day
* Call for Confirmation:

5 Packaging (* Declared value limit $500)
☐ FedEx Envelope*
☐ FedEx Pak* — Includes FedEx Small Pak, FedEx Large Pak, and FedEx Sturdy Pak
☒ Other

6 Special Handling (Include FedEx address in Section 3.)
☐ SATURDAY Delivery — Available ONLY for FedEx Priority Overnight and FedEx 2Day to select ZIP codes
☐ HOLD Weekday at FedEx Location — NOT Available for FedEx First Overnight
☐ HOLD Saturday at FedEx Location — Available ONLY for FedEx Priority Overnight and FedEx 2Day to select locations

Does this shipment contain dangerous goods? (One box must be checked.)
☒ No
☐ Yes — As per attached Shipper's Declaration
☐ Yes — Shipper's Declaration not required
☐ Dry Ice — Dry Ice, 9, UN 1845 ____ x ____ kg
Dangerous Goods (including Dry Ice) cannot be shipped in FedEx packaging.
☐ Cargo Aircraft Only

7 Payment Bill to: (Enter FedEx Acct. No. or Credit Card No. below.)
☐ Sender — Acct. No. in Section 1 will be billed.
☐ Recipient
☒ Third Party
☐ Credit Card
☐ Cash/Check
FedEx Acct. No. / Credit Card No. CDC FedEx number Exp. Date

Total Packages: 1 Total Weight: Total Declared Value†: $ .00
†Our liability is limited to $100 unless you declare a higher value. See back for details.
FedEx Use Only

8 Release Signature (Sign to authorize delivery without obtaining signature.)
By signing you authorize us to deliver this shipment without obtaining a signature and agree to indemnify and hold us harmless from any resulting claims.

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Appendix E. Uses for VARHS Data Elements

Table 1

The following data elements are used for estimations of the national prevalence and incidence of transmitted HIV drug resistance and distribution of HIV-1 subtypes and for making estimates for major subpopulations.

Data Element	HIV drug resistance Prevalence	HIV drug resistance incidence	HIV-1 subtype distributions
Demographic Data			
Age	X	X	X
Sex	X	X	X
Race/ethnicity	X	X	X
Exposure category for HIV infection	X	X	X
Country of origin	X	X	X
Current residence	X	X	X
State of residence at the first HIV positive test	X	X	X
Laboratory Data			
STARHS result		X	
STARHS assay type		X	
HIV pol gene genetic sequence	X	X	X
HIV drug resistance phenotyping results	X	X	X
Mutation-specific assays	X	X	X
Previous HIV Testing Data			
Date of first HIV test specimen		X	
Date of first positive HIV test specimen		X	
Reason for first positive HIV test		X	
First positive HIV test performed	X	X	
Date of last documented negative HIV test		X	
Clinical Data			
AIDS diagnosis date		X	
Available CD4 counts		X	
Dates of CD4 counts		X	
Available viral loads		X	
Dates of viral loads		X	
Recent/current use of antiretroviral agents	X	X	
Antiretroviral agents used	X	X	
Timing of antiretroviral use	X	X	
Date(s) of opportunistic infection diagnosis		X	

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Table 2. Evaluation of Laboratory Tracking Data

The following laboratory data elements are used for local tracking of specimens, evaluating problems with amplification of HIV for genotyping, supporting plans to optimize specimen handling processes for surveillance purposes, and evaluating problems with contamination

	Tracking	Amplification	Handling processes	Contamination
VARHS ID	X	X	X	X
Accession number	X			X
Site of blood draw	X	X	X	
Tube type	X	X	X	X
Date and time of blood draw	X	X	X	
Date and time of separation	X	X	X	X
Date and time of freeze	X	X	X	
Volume aliquoted, if < 1 ml	X	X		

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