CLINICAL AND LABORATORY STANDARDS INSTITUTE®

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M53-A

Criteria for Laboratory Testing and Diagnosis of Human Immunodeficiency Virus Infection; Approved Guideline

This document provides guidance for laboratorians performing human immunodeficiency virus testing and for the interpretation of results by health care providers in advanced diagnostic laboratories.

A guideline for global application developed through the Clinical and Laboratory Standards Institute consensus process.

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For further information on committee participation or to submit comments, contact CLSI.

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Criteria for Laboratory Testing and Diagnosis of Human Immunodeficiency Virus Infection; Approved Guideline

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Abstract

The accurate diagnosis of human immunodeficiency virus (HIV) infection is essential for limiting the spread of infection and for the appropriate clinical management of persons infected with HIV. Over the past several years, numerous tests and testing strategies have been developed and are used by laboratorians and clinicians to diagnose HIV infection. CLSI document M53-A, *Criteria for Laboratory Testing and Diagnosis of Human Immunodeficiency Virus Infection; Approved Guideline*, provides an extensive review of existing laboratory methods commonly used to test for HIV infection. This guideline also offers recommendations for how to best use and interpret these tests accurately and effectively to diagnose HIV infection.

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Foreword

Since the advent of human immunodeficiency virus (HIV) testing, laboratory-based methods have undergone tremendous change. The routine use of nucleic acid tests, the introduction of antigen-antibody combination tests, and the widespread implementation of rapid testing methods, including the use of different specimen types, have changed the way HIV infection is diagnosed. Although these tests may offer improved sensitivity, specificity, and more rapid turnaround times, clinicians and laboratorians are asked to determine which tests to perform and how to best interpret the results.

There is increasing momentum to establish universal routine testing programs for HIV infection in order to limit the spread of infection and to identify individuals who may benefit from earlier initiation of antiviral therapy. In 2006, the Centers for Disease Control and Prevention issued a recommendation for routine HIV screening of all patients in the health care setting.[1] Concurrent with these recommendations, laboratorians and clinicians have used a number of new tests and testing strategies to diagnose HIV infection. Although there is an increased demand to use these tests, adequate consensus guidelines have not been proposed to assist in the appropriate use and interpretation of these tests and testing strategies.

This guideline was developed to provide an extensive review of existing laboratory methods commonly used to test for HIV infection and offer recommendations for how to best use and interpret these tests to accurately establish the diagnosis of HIV infection and effectively report these results to health care providers. This guideline is intended for use in the diagnosis of HIV-1 and HIV-2 infection in advanced diagnostic laboratories and point-of-care settings, and may not be applicable in resource-limited settings.

Key Words

Algorithms, differentiation testing, enzyme immunoassay, HIV initial testing, HIV supplemental testing, HIV-1, HIV-2, immunofluorescence assay, line immunoassay, nucleic acid testing, Western blot

Criteria for Laboratory Testing and Diagnosis of Human Immunodeficiency Virus Infection; Approved Guideline

1 Scope

This document provides an overview of the natural history and response to human immunodeficiency virus (HIV) infection, an in-depth review of initial and supplemental tests for the diagnosis of HIV infection, and initiation of a quality control (QC) program for HIV testing. This guideline also addresses special situations that commonly confound HIV testing, including the diagnosis of acute and recent HIV infection, initial and supplemental testing during pregnancy, labor and delivery, and newborn testing. Special attention is also given to testing for HIV-1, non-B subtype, and HIV-2 testing. In addition, diagnostic testing algorithms are provided to assist clinicians and laboratorians in the stepwise use of these tests, as well as a framework for additional testing and the interpretation of results. Furthermore, reporting criteria for commonly obtained test results are also provided.

This guideline is intended for use in the laboratory diagnosis of HIV infection in the health care setting, and does not address methods or strategies for screening the blood supply or organ or tissue donation. Furthermore, this guideline is not intended for use outside the clinical setting and does not address issues for diagnosing HIV from nonhuman material, environmental surfaces, or postmortem. Although some of the proposed tests and testing strategies may be universally applicable, the guidelines are primarily intended for advanced diagnostic laboratories, and may not address testing methods or strategies in more resource-limited settings.

2 Standard Precautions

Because it is often impossible to know what isolates or specimens might be infectious, all patient and laboratory specimens are treated as infectious and handled according to "standard precautions." Standard precautions are guidelines that combine the major features of "universal precautions and body substance isolation" practices. Standard precautions cover the transmission of all known infectious agents and thus are more comprehensive than universal precautions, which are intended to apply only to transmission of blood-borne pathogens. Standard and universal precaution guidelines are available from the Centers for Disease Control and Prevention (CDC).[2] For specific precautions for preventing the laboratory transmission of all known infectious agents from laboratory instruments and materials and for recommendations for the management of exposure to all known infectious diseases, refer to CLSI document M29.[3]

3 Terminology

3.1 A Note on Terminology

CLSI, as a global leader in standardization, is firmly committed to achieving global harmonization whenever possible. Harmonization is a process of recognizing, understanding, and explaining differences while taking steps to achieve worldwide uniformity. CLSI recognizes that medical conventions in the global metrological community have evolved differently in the United States, Europe, and elsewhere; that these differences are reflected in CLSI, International Organization for Standardization (ISO), and European Committee for Standardization (CEN) documents; and that legally required use of terms, regional usage, and different consensus timelines are all important considerations in the harmonization process. In light of this, CLSI's consensus process for development and revision of standards and guidelines focuses on harmonization of terms to facilitate the global application of standards and guidelines.

In M53-A, the term *diagnostic sensitivity* is combined with the term *clinical sensitivity*, because in Europe, the term "clinical" often refers to clinical studies of drugs under stringent conditions.

In order to align the usage of terminology in this document with that of ISO and CLSI document GP02,[4] the term *standard operating procedure (SOP)* has been replaced with the term *procedures/instructions*. For the sake of introduction and to avoid confusion, the document development committee has chosen to include the acronym for *standard operating procedure (SOP)* parenthetically where the term *procedures/instructions* appears in the text.

3.2 Definitions

acute HIV infection – the phase of infection that occurs between the time of first detection of HIV by virological assay (eg, RNA, DNA, or viral antigens) until the first detection of confirmed HIV-specific antibodies.

analytical sensitivity – quotient of the change in an indication and the corresponding change in the value of a quantity being measured (ISO 15193)[5]; **NOTE 1:** The term "analytical sensitivity" is not intended to be used as a synonym for "detection limit" (ISO 15193)[5]; **NOTE 2:** ISO/IEC Guide 99:2007[6] uses the term "sensitivity of a measuring system"; **NOTE 3:** The amount of measurand being detected by the measurement procedure at a given detection frequency. Also, see **seroconversion sensitivity.**

analytical specificity – ability of a measurement procedure to measure solely the measurand (ISO 17511)[7]; **NOTE 1:** It denotes freedom from interference by any element or compound other than the analyte; **NOTE 2:** Specificity has no numerical value in this context.

calibration (standards) – operation that, under specified conditions, in a first step, establishes a relation between the quantity values with measurement uncertainties provided by measurement standards and corresponding indications with associated measurement uncertainties and, in a second step, uses this information to establish a relation for obtaining a measurement result from an indication (ISO/IEC Guide 99)[6]; **NOTE:** According to the US Code of Federal Regulations, calibration is the process of testing and adjustment of an instrument, kit, or test system, to provide a known relationship between the measurement response and the value of the substance being measured by the test procedure (42 CFR 493.1218).[8]

CE marking – symbolizes the conformity of the product with the applicable Community requirements imposed on the manufacturer. The CE marking affixed to products is a declaration by the person responsible that the product conforms to all applicable Community provisions, and the appropriate conformity assessment procedures have been completed.[9]

chemiluminescent assay – an assay in which the signal is generated by a compound that emits light as the result of a chemical reaction.

clade – See **subtype.**

clinical sensitivity – the proportion of subjects with a well-defined clinical disorder whose test values are positive or exceed a defined decision limit (eg, a positive result and identification of the patients who have a disease); **NOTE 1:** "Diagnostic sensitivity" is used in Europe and "clinical sensitivity" is used in the United States; **NOTE 2:** Clinical sensitivity refers to the assay's ability to detect subjects with the condition or disease; **NOTE 3:** The clinical disorder must be defined by criteria independent of the test under consideration; **NOTE 4:** This term can also be defined as percent positivity in specimens in which the target measurand (analyte) is known to be present (ie, derived from subjects with disease). Also, see **seroconversion sensitivity.**

The Quality Management System Approach

Clinical and Laboratory Standards Institute (CLSI) subscribes to a quality management system approach in the development of standards and guidelines, which facilitates project management; defines a document structure via a template; and provides a process to identify needed documents. The approach is based on the model presented in CLSI document HS01—*A Quality Management System Model for Health Care.* The quality management system approach applies a core set of "quality system essentials" (QSEs), basic to any organization, to all operations in any health care service's path of workflow (ie, operational aspects that define how a particular product or service is provided). The QSEs provide the framework for delivery of any type of product or service, serving as a manager's guide. The QSEs are as follows:

Documents and Records	Equipment	Information Management	Process Improvement
Organization	Purchasing and Inventory	Occurrence Management	Customer Service
Personnel	Process Control	Assessments—External and Internal	Facilities and Safety

M53-A addresses the QSEs indicated by an "X." For a description of the other documents listed in the grid, please refer to the Related CLSI Reference Materials section on the following page.

Documents and Records	Organization	Personnel	Equipment	Purchasing and Inventory	Process Control	Information Management	Occurrence Management	Assessments—External and Internal	Process Improvement	Customer Service	Facilities and Safety
GP02		GP21			X C28 GP27 H18 MM13	GP02		GP27	GP27		M29

Adapted from CLSI document HS01—*A Quality Management System Model for Health Care.*

Path of Workflow

A path of workflow is the description of the necessary steps to deliver the particular product or service that the organization or entity provides. For example, CLSI document GP26—*Application of a Quality Management System Model for Laboratory Services* defines a clinical laboratory path of workflow, which consists of three sequential processes: preexamination, examination, and postexamination. All clinical laboratories follow these processes to deliver the laboratory's services, namely quality laboratory information.

M53-A addresses the clinical laboratory path of workflow steps indicated by an "X." For a description of the other documents listed in the grid, please refer to the Related CLSI Reference Materials section on the following page.

Preexamination				**Examination**			**Postexamination**	
Examination ordering	Sample collection	Sample transport	Sample receipt/processing	Examination	Results review and follow-up	Interpretation	Results reporting and archiving	Sample management
	MM13	H18 MM13	H18 MM13	H18	X	X	X	MM13

Adapted from CLSI document HS01—*A Quality Management System Model for Health Care.*

Related CLSI Reference Materials*

C28-A3c **Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline—Third Edition (2010).** This document contains guidelines for determining reference values and reference intervals for quantitative clinical laboratory tests.

GP02-A5 **Laboratory Documents: Development and Control; Approved Guideline—Fifth Edition (2006).** This document provides guidance on development, review, approval, management, and use of policy, process, and procedure documents in the medical laboratory community.

GP21-A3 **Training and Competence Assessment; Approved Guideline—Third Edition (2009).** This document provides background information and recommended processes for the development of training and competence assessment programs that meet quality and regulatory objectives.

GP27-A2 **Using Proficiency Testing to Improve the Clinical Laboratory; Approved Guideline—Second Edition (2007).** This guideline provides assistance to laboratories in using proficiency testing as a quality improvement tool.

H18-A4 **Procedures for the Handling and Processing of Blood Specimens for Common Laboratory Tests; Approved Guideline—Fourth Edition (2010).** This document includes criteria for preparing an optimal serum or plasma sample and for the devices used to process blood specimens.

M29-A3 **Protection of Laboratory Workers From Occupationally Acquired Infections; Approved Guideline—Third Edition (2005).** Based on US regulations, this document provides guidance on the risk of transmission of infectious agents by aerosols, droplets, blood, and body substances in a laboratory setting; specific precautions for preventing the laboratory transmission of microbial infection from laboratory instruments and materials; and recommendations for the management of exposure to infectious agents.

MM13-A **Collection, Transport, Preparation, and Storage of Specimens for Molecular Methods; Approved Guideline (2005).** This document provides guidance related to proper and safe biological specimen collection and nucleic acid isolation and purification. These topics include methods of collection, recommended storage and transport conditions, and available nucleic acid purification technologies for each specimen/nucleic acid type.

* CLSI documents are continually reviewed and revised through the CLSI consensus process; therefore, readers should refer to the most current editions.

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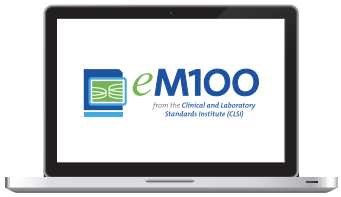

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